Differential diagnosis in nephrology

Dr. András Tislér

Department of Internal Medicine and Oncology

September 2022

SEMMELWEIS
UNIVERSITY 1769

Sándor Korányi
1866-1944

Renal signs, symptoms	Renal syndromes	Morphological diagnosis	? diagnosis	Etiological diagnosis
• **pain** • **hematuria** • **proteinuria** • **edema** • **GFR decrease** • **Hypertension** • **Immunological abnormality** • **Tubular dysfunction** • **Renal morpholo-gical change**	• Nephritis • Nephrosis • Nephritis • Rapidly progressive glomerulo-nephritis • Asymptomatic urinary abnormality • Acute kidney injury • Chronic kidney disease	• Minimal change nephropathy • Focal segmental glomerular sclerosis • Membranous nephropathy • Membranopro-liferative GN • Pauci immune - crescentic GN • Diabetic nephropathy • Amyloidosis • Acute tubular necrosis • ……..	• **?**	• **Poststrepto-coccal GN** • **SLE** • **Hepatitis C** • **Cryoglobuli-nemia** • **ANCA vasculitis** • **Goodpasture disease** • **Diabetic nephropathy** • **…** • **…**

Overview

- Differential diagnosis of the main renal symptoms
- Differential diagnosis of the main renal syndromes
- Case study

Pain

- Most renal diseases present insidiously without pain, frequently only with laboratory abnormalities

Differential diagnosis of lumbal pain

(? localization, intensity, type, radiation, aggravating – alleviating factors, accompanying signs)

- **Sudden onset, cramping**
  - Obstruction of the urinary tract (eg. stone, blood clot, papilla necrosis)
  - Usually unilateral, radiating downwards toward bladder, genitalia

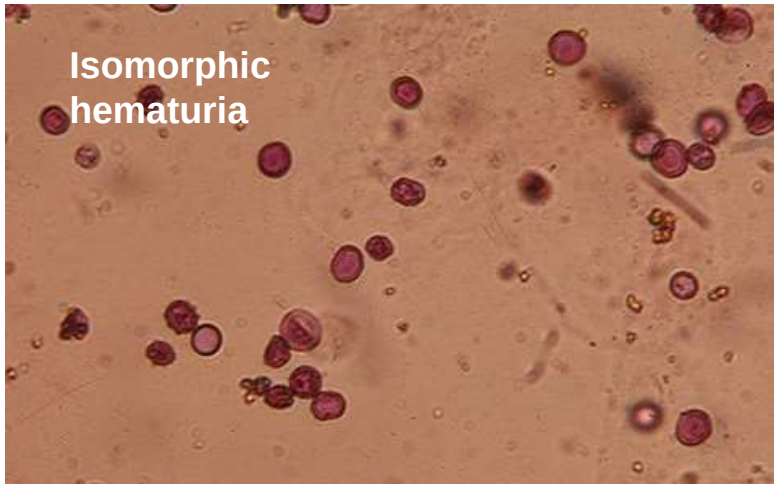
- **Blunt**
  - Unilateral: renal cyst infection/bleeding, tumor, renal infarct, renal vein thrombosis, with fever and UTI: pyelonephritis, abscess
  - Bilateral: interstitial nephritis, renal edema, glomerular diseases are usually not painful

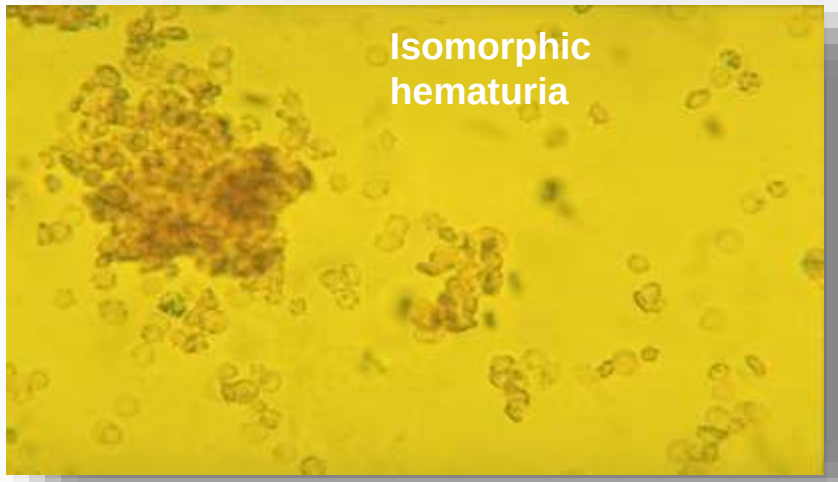
- **Dysuria, pollakisuria**
  - Lower UTI

- **Lumbal pain of extrarenal origin:**
  - Lumbar spine, muscles, neurological
  - Atypical: acute cholecystitis, pancreatic tumor, pancreatitis, colon neoplasm, spleen infarct

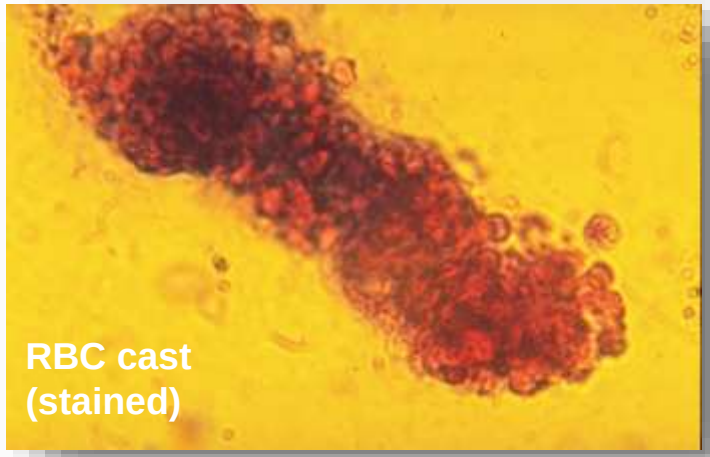
Hematuria

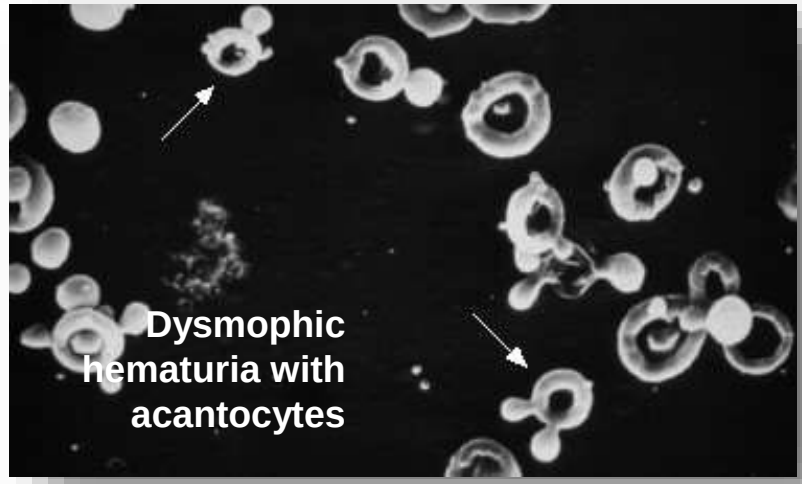
- **Healthy person: Dipstick negative, sediment < 3-4 RBC/high power field**
- **Macroscopic – suggests urological origin (but may be seen in IgA nephropathy)**
- **Microscopic – may be either urological or nephrological in origin**
- **Urology causes: Renal/uroepithelial tumor, stone, UTI (eg. cystitis), renal cyst rupture, papillary necrosis**
- **Nephrological : Glomerulonephritis, Alport-syndrome, thin basement membrane disease, acute interstitial nephritis**
- **Microscopic urinary sediment examination may help to differentiate:**
  - **Urolological: similar RBCs (isomorphic)**
  - **Nephrological: variable appearance of RBCs (dysmorphic) (eg. acantocyte – glomerular origin)**
  - **RBCs in casts suggest glomerular origin**


Isomorphic
hematuria

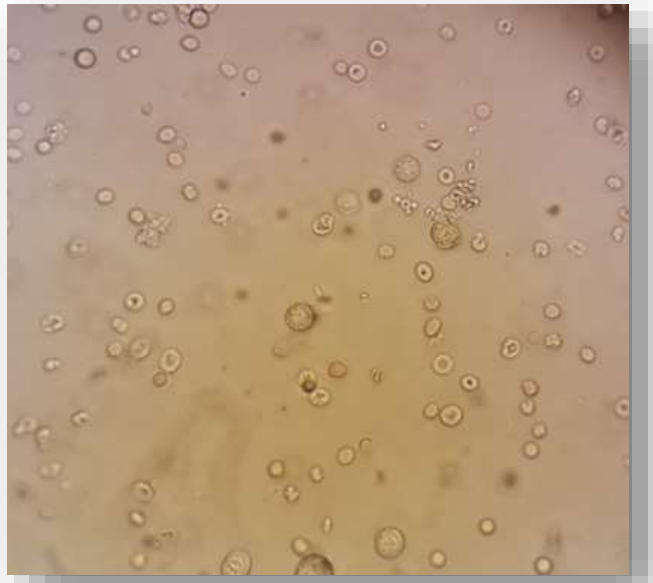

Isomorphic
hematuria

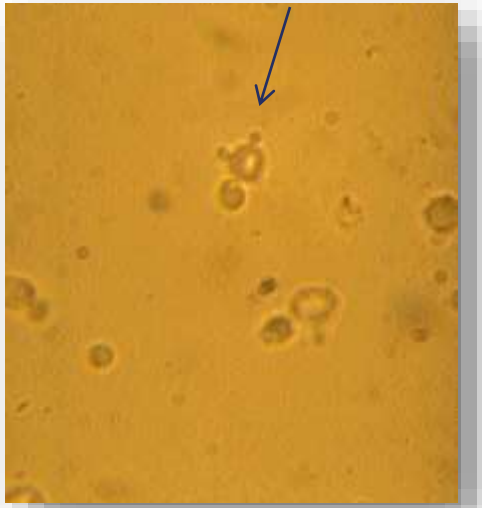

Dysmophic
hematuria with
acantocytes


RBC cast
(stained)

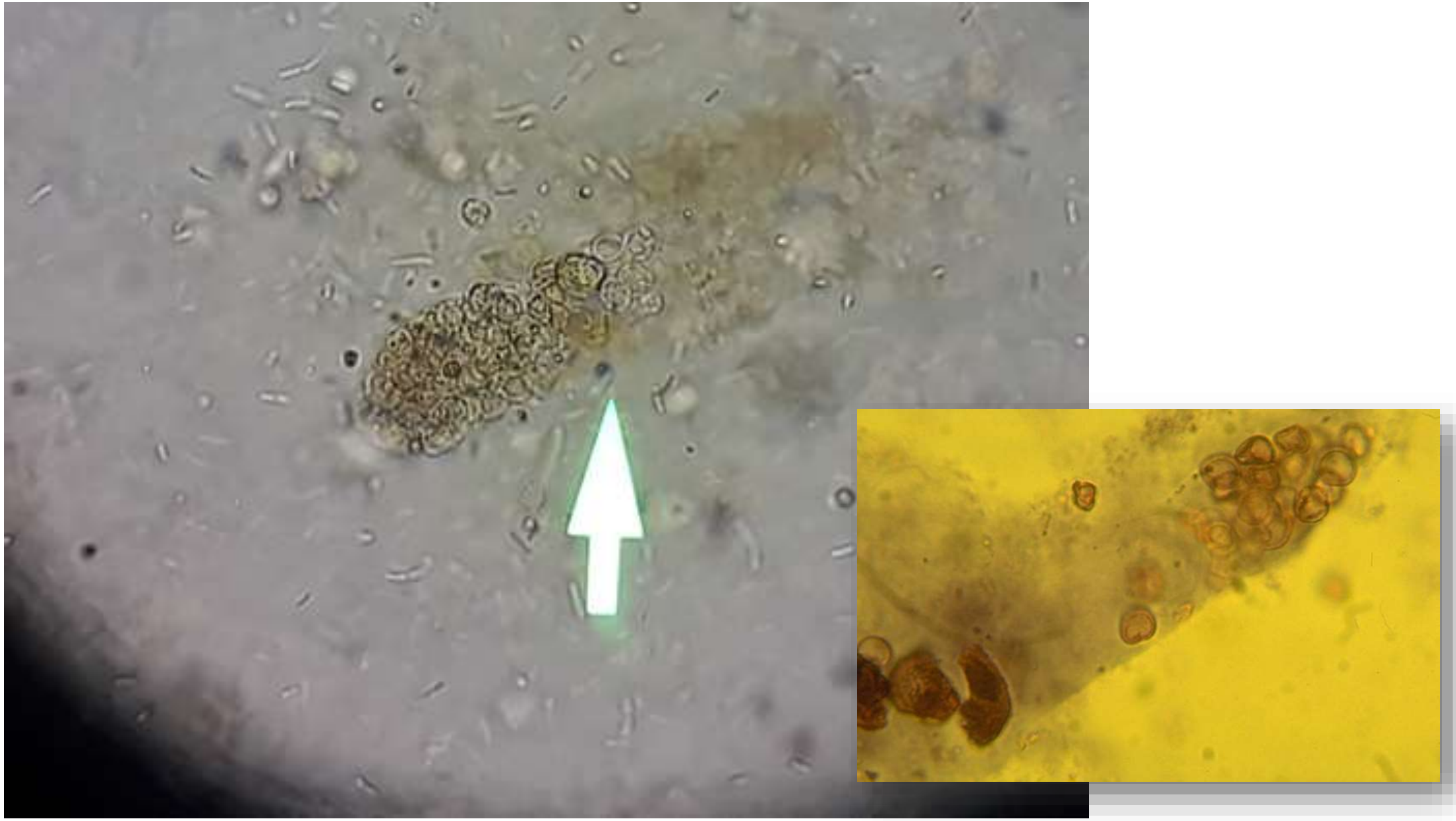

Dysmophic
hematuria with
acantocytes

Dysmorphic RBCs, acantocyte, RBC cast (nephritis)





RBC cast (nephritis)

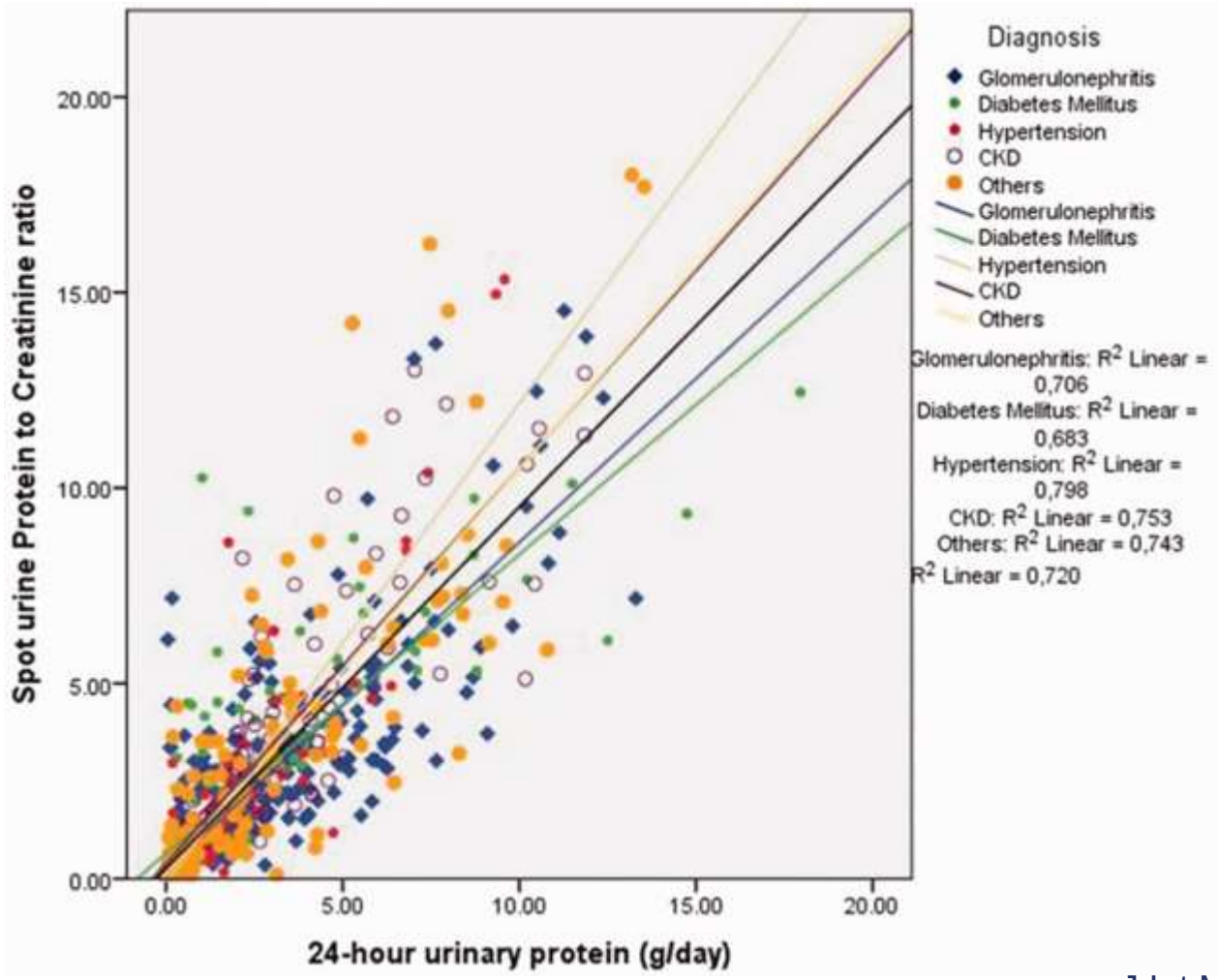


Proteinuria and albuminuria

- Normal protein excretion: up to 200 mg/day (20 mg/mmol)
  - Mainly Tamm-Horstfall protein (uromodulin) secreted in the loop of Henle
  - Also other proteins including filtered but not reabsorbed small amounts of albumin (max. 30 mg/day)
- Normal albuminuria <30mg/nap (<3mg/mmol)

- Determination
  - 24/h urine collection (mg/day)
  - Spot urine (or short collection) protein/creatinine ratio (mg/mmol)
    - **Normal 20 mg protein/mmol creatinine**
    - **Normal 3mg albumin/mmol creatinine**
    - **100 mg/mmol spot urine protein/creatinine corresponds to 1 g/day proteinuria**

Relationship betveen 24-hour proteinuria and spot urine protein to creatinine ratio



J Int Med Res. 2019 Mar; 47(3): 1179

Proteinuria, albuminuria

- Urine dipstick
  - Positive if urine albumine concetration >500mg/l
  - detects mainly albumin (may be false negative if the protin is not albumin – eg. Kappa chains)

- „clinically significant” proteinuria:
  - >500mg/day (>50mg/mmol creatinine)
  - Heralds poor renal prognosis
  - Treatment target is less than 500mg/day in most glomerular diseases

- Albuminuria
  - > 30mg/day (3 mg/mmol)
  - May suggest early diabetic nephropathy (previously called microalbuminuria)
  - >300mg/day corresponds to about 500mg/day proteinuria (previously called macroalbuminuria)

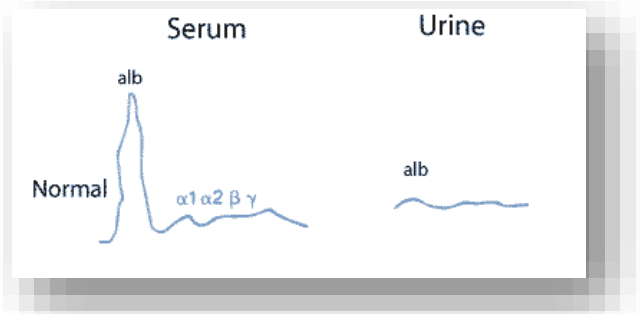
- „nephrotic” range proteinuria
  - >3-3.5g/day (0.3-0.35 g/mmol) that is accompanied with the nephrotic syndrome

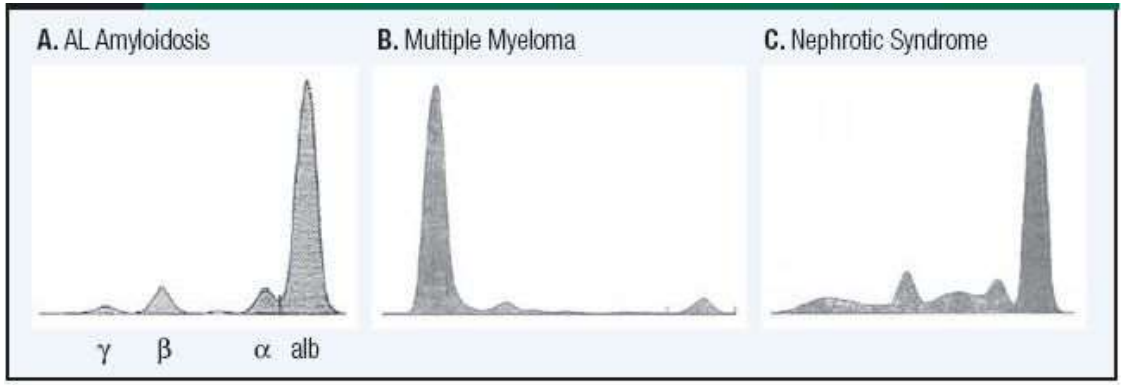
Differential diagnosis of proteinuria
>200mg/day or >20mg/mmol

- Spurious proteinuria (non-renal)
  - inaccurate sampling, blood in the urine, colpitis
- Functional
  - temporary: fever, intense physical exercise, venous congestion
  - Orthostatic proteinuria
- Glomerular: glomerulonephritis, glomerulopathy
  - Damaged glomerular filtration barrier spills albumin and variable amount of globulins in the primary filtrate (more severe damage more globulin)
- Tubular proteinuria
  - Damage to the proximal tubule leads to failure to reabsorb small molecular weight proteins (eg. Fanconi syndrome, interstitial nephritis)
- „overflow” proteinuria
  - High amount of small molecular weight protein in the serum is being filtered and overflows reabsorption (kappa/lambda light chains a.k.a. Bence-Jones proteinuria)

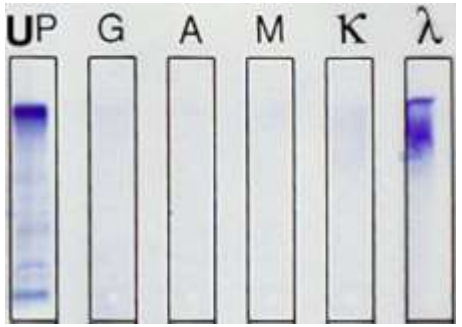
Characterisation of urinary proteins

- Urine electrophoresis





- Urine immunofixation



- Free kappa – lambda light chain measurement

Frequently used immunological tests in the diagnosis of renal diseases

Immunology marker	Significance
ANA (anti-nuclear antibody)	SLE, other systemic autoimmune disease
ANCA (anti-neutrophil cytoplasmic antibody)	Small vessel vasculitis (pauci-immune crescentic GN)
Anti-cardiolipin antibody, anti- beta-2 glycoprotein	Antiphospholipid syndrome
Anti-dsDNS antibody	SLE
Anti-GBM antibody	Goodpasture syndrome
SS-A, SS-B antibody	Sjögrens' syndrome, SLE
Anti-streptolysin antibody	Poststreptococcal glomerulonephritis
Complement 3, 4 decrease	SLE, cryoglobulinaemia
Anti-Scl70 antibody, Anti centromere antibody, anti RNA polymerase III	Systemic sclerosis,scleroderma renal crisis
Phospholipase A2 receptor antibody	Membranous nephropathy

Overview

- Differential diagnosis of the main renal symptoms
- Differential diagnosis of the main renal syndromes
- Case study

Renal signs, symptoms	Renal syndromes	Morphological diagnosis	Pathophysiologic diagnosis	Etiological diagnosis
• **pain** • **hematuria** • **proteinuria** • **edema** • **GFR decrease** • **Hypertension** • **Immunological abnormality** • **Tubular dysfunction** • **Renal morpholo-gical change**	• Nephritis • Nephrotic • Nephritic • Rapidly progressive glomerulo-nephritis • Asymptomatic urinary abnormality • Acute kidney injury • Chronic kidney disease	• Minimal change nephropathy • Focal segmental glomerular sclerosis • Membranous nephropathy • Membranopro-liferative GN • Pauci immune - crescentic GN • Diabetic nephropathy • Amyloidosis • Acute tubular necrosis • …….	• E.g. IgA nephropathy	• **Poststrepto-coccal GN** • **SLE** • **Hepatitis C** • **Cryoglobuli-nemia** • **ANCA vasculitis** • **Goodpasture disease** • **Diabetic nephropathy** • … • …

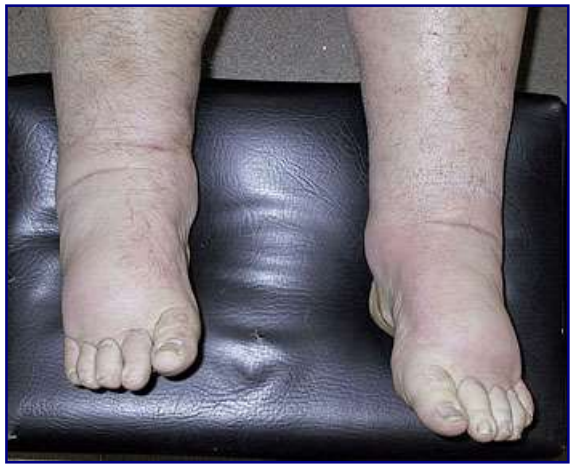
The „major” nephrology syndromes

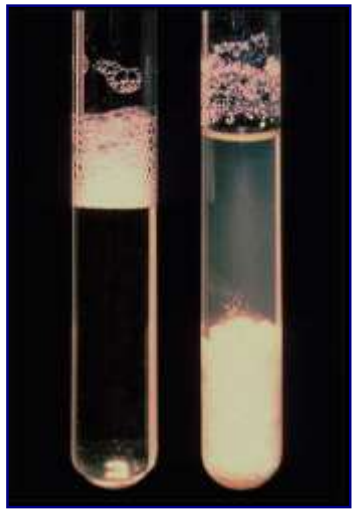
- Nephrosis
- Nephritis
  - Rapidly progressive glomerulonephritis (RPGN)
- Acute kidney injury
- Asymptomatic proteinuria and/or hematuria
- Chronic kidney disease

A given disesase may present with more than one syndrome (e.g. IgA nephropathy: usually asymptomatic urinary abnormality, but occasionall RPGN)

Nephrotic syndrome

- **Proteinuria (usually >3,5 g/day)**
- **Hypalbuminemia**
- **Edema**
- **Hyperlipoproteinemia**
- **Thromboembolic events**
- **GFR may be normal**





- **Further differentiation with immunserology and kidney biopsy**

Differential diagnosis of the nephrotic syndrome

- **Primary renal disease (no other organ involvement)**
  - **Primary membranous glomerulopathy (usually anti-PLA2 receptor antibody positive)**
  - **Minimal change nephropathy**
  - **Focal segmental glomerulosclerosis**

- **Renal manifestation of a systemic disease**
  - **Diabetic nephropathy**
  - **Amyloidosis**
  - **Secondary FSGS (congenital podocytopathy, HIV, extreme obesity, glomerular loss for an unrelated reason)**
  - **Secondary membranous glomerulopathy (lupus nephritis, malignancy, drugs, hepatitis B/C, syphilis, NSAIs, TNF- inhibitors)**

Nephritic syndrome

- **Hematuria**
- **Proteinuria**
- **Urinary casts**
- **Hypertension**
- **edema**
- **Oliguria**
- **Decreased GFR**

Differential diagnosis of the nephritic syndrome

Pathologically these are <u>proliferative</u> glomerulonephritides either with immune complex mediated or complement disregulation mechanisms

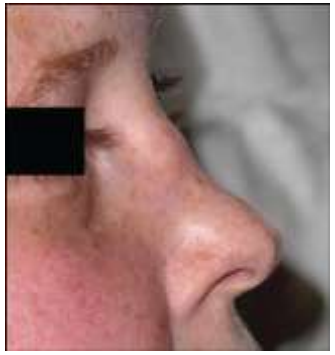
- **Proliferation in different parts of the glomerulus (mesangial, crescent, endocalpillary…)**

- **Poststreptococcalis glomerulonephritis**
- **Postinfectiosus glomerulonephritis**
  - **E.g. subacute endocarditis, abscess**
- **Membranoproliferative glomerulonephritis**
  - **Lupus nephritis, cryoglobulinemia, monoclonal immunglobulin deposition**
  - **„dens-deposit" disease, C3 glomerulonephritis**

Further tests towards morphologic/etiologic diagnosis: renal biopsy, immune serology, electrophoresis

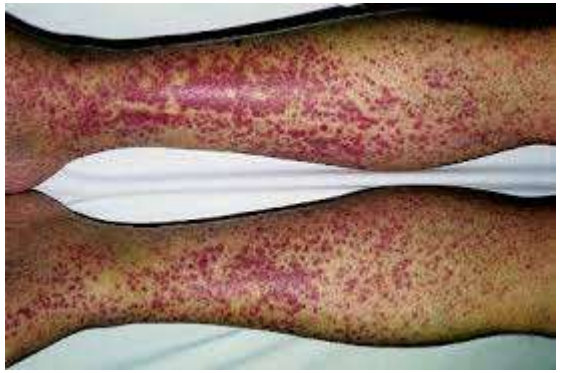
Rapidly progressive glomerulonephritis syndrome (RPGN)

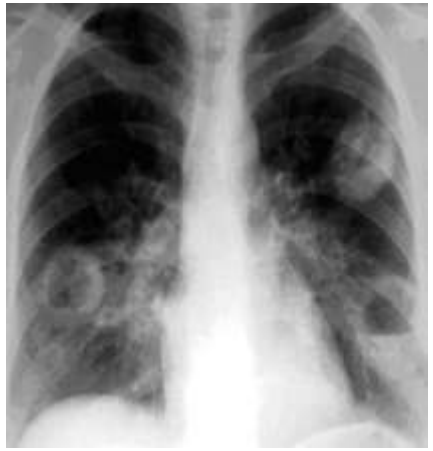
- Rapid worsening of kidney function (weeks-months)
- If untreated dismal prognosis



- Nephritic urinary findings
  - Glomerular hematuria, variable proteinuria
  - Cellular (RBC) casts

- Frequent systemic symptoms
  - vasculitis
  - Pulmonary (bleeding)
  - upper airway
  - Arthritis
  - Fever
  - Neuropathy





Rapidly progressive glomerulonephritis syndrome (RPGN)

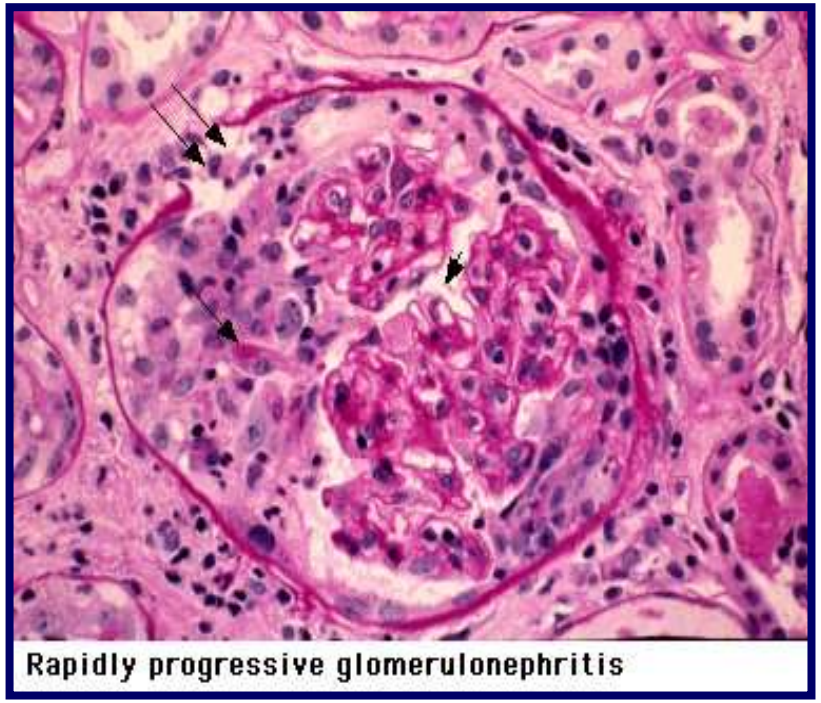
- Renal biopsy with immunfluorescein staining and serology are needed for further differentiation

- Light microscopy usually shows crescents with parietal cell proliferation (extracapillary proliferation)
  - Parietal cell proliferation
  - Glomerular tuft compression
  - Glomerular necrosis

- Further differentiation based

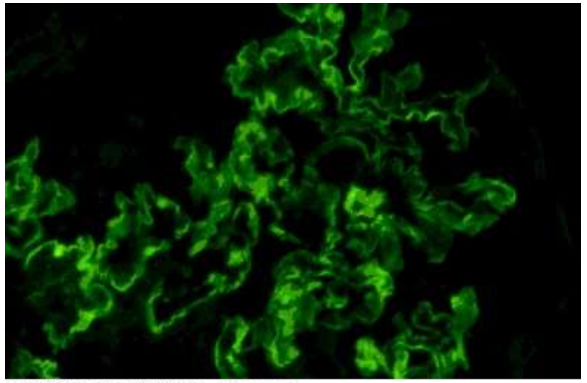
  on immunofluorescence

  microscopy findings and immunserology

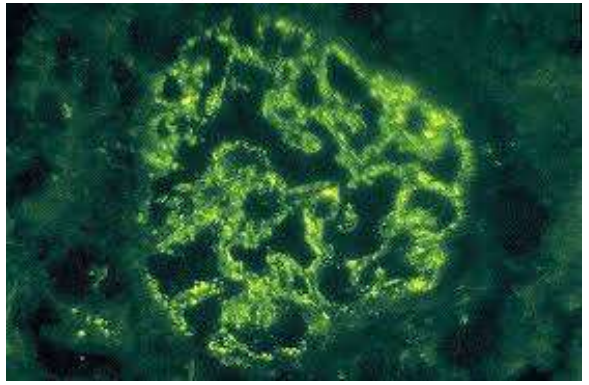

Rapidly progressive glomerulonephritis

Differentiation of crescent glomerulonephritis with RPGN

1. **Linear** immunglobulin deposition
- **Anti-GBM antibodies**
- Renal +/- pulmonary symptoms
- Goodpasture disease

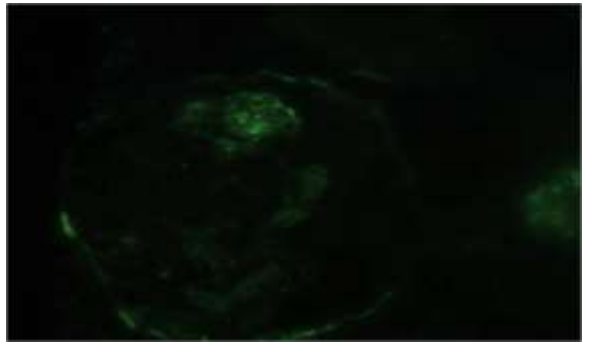

Anti-GBM antibody disease

2. **Granular** immunglobulin deposition
- These are immuncomplexes
- **eg. lupus nephritis, IgA nephropathy**

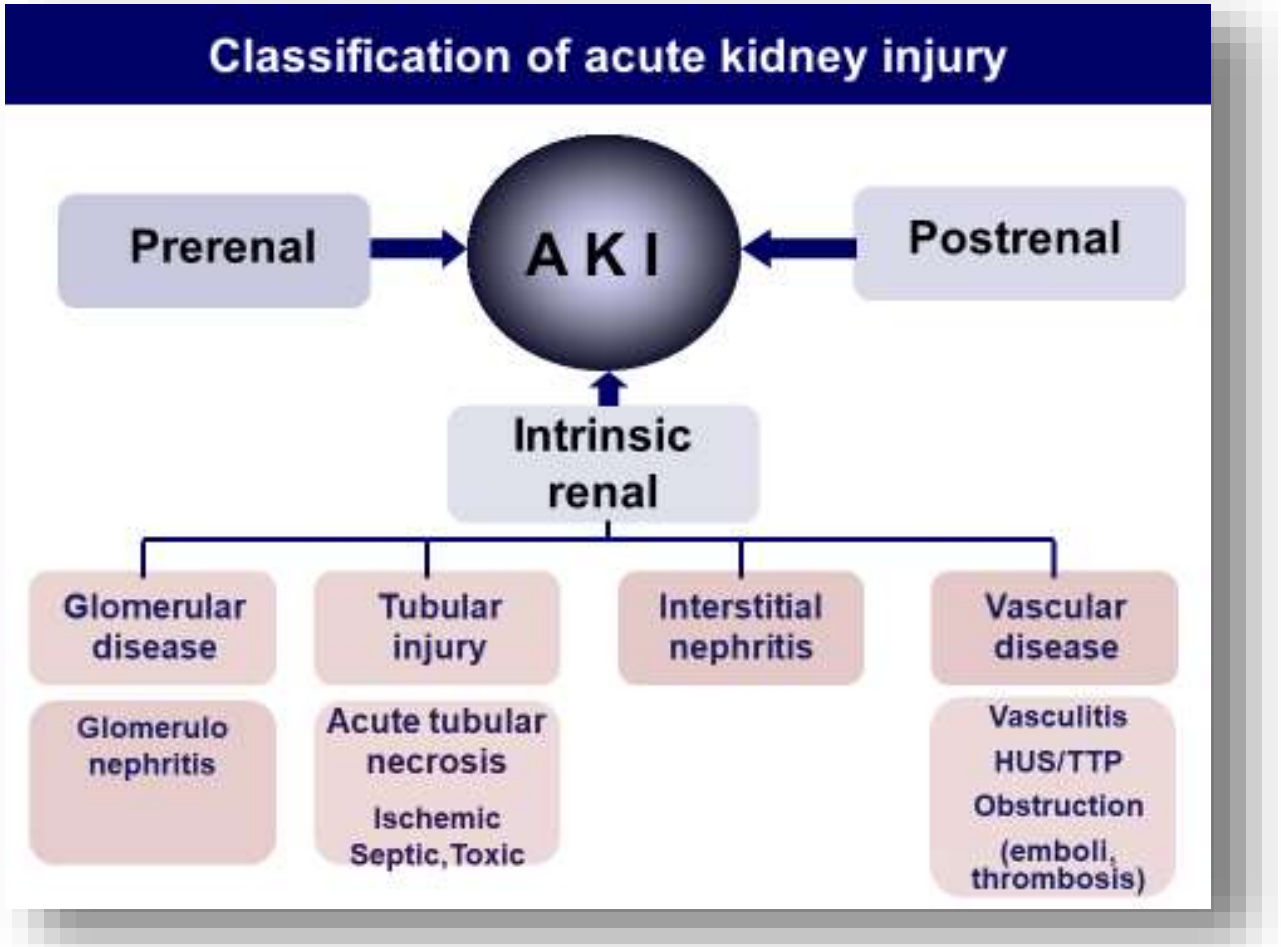


3. No immunglogulin deposition

„pauci”-immune = „hardly any”
- **These are ANCA vasculitides**
  - ***Granulomatosis with polyangitis (prviously Wegener gran)***
  - ***Microscopic polyangitis***
  - ***Eosinophil granulomatosis with polyangitis***



Differentiation of acute kidney injury (syndrome)



- Definition: decrease in GFR within hours to days
- Further differention: clinical picture, ultrasound, laboratory and urinalysis, occasionally renal biopsy

Indications for renal biopsy

- Nephrotic syndrome
- Nephritic syndrome
- RPGN
- Asymptomatic proteinuria in the 1-3g/day range (particulary if GFR declines or proteinuria increases)

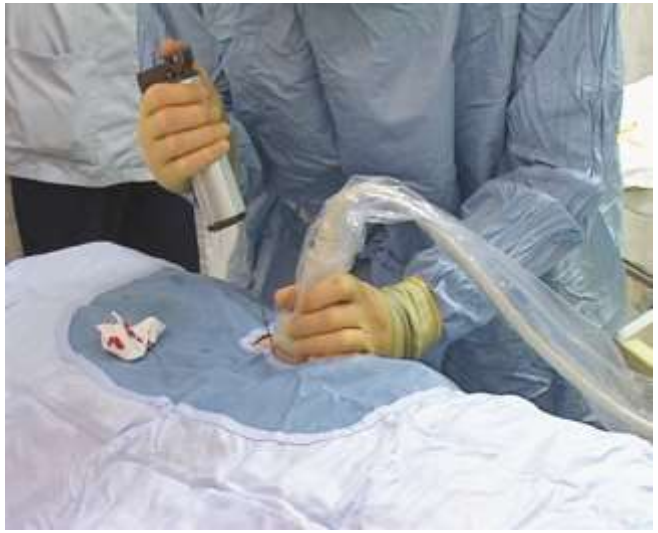
- Acute kidney injury (intrinsic)
  - If there is a suspicion that it is not caused by acute tubular necrosis
- Chronic kidney disease of unknown origin
  - But not if on ultrasound small, scarred kidneys
- Dysfunction of transplanted kidney

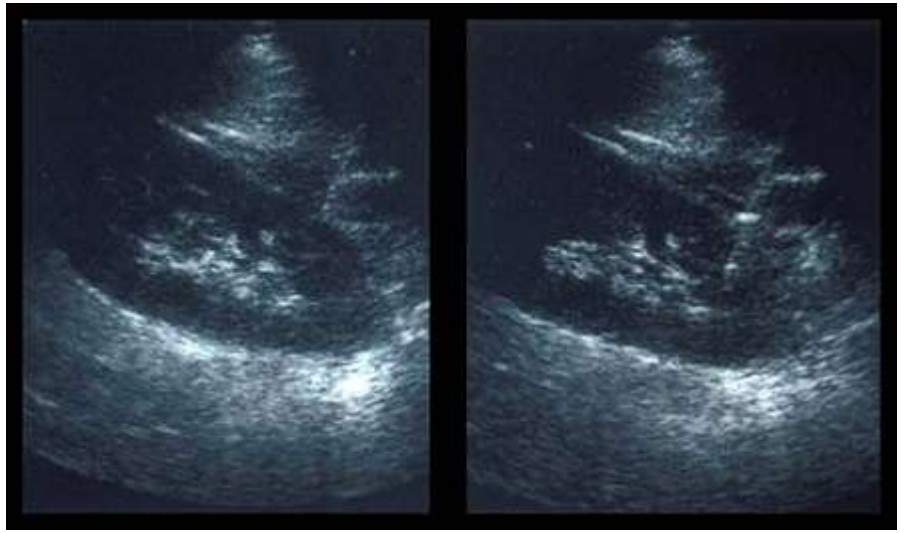
Contraindications to renal biopsy

- Uncooperative patient
- Single kidney
- Multiple renal cysts
- Renal neoplasm
- Acute pyelonephritis
- Uncontrolled bleeding diathesis
- Uncontrolled blood pressure (BP > 160/95 mmHg)

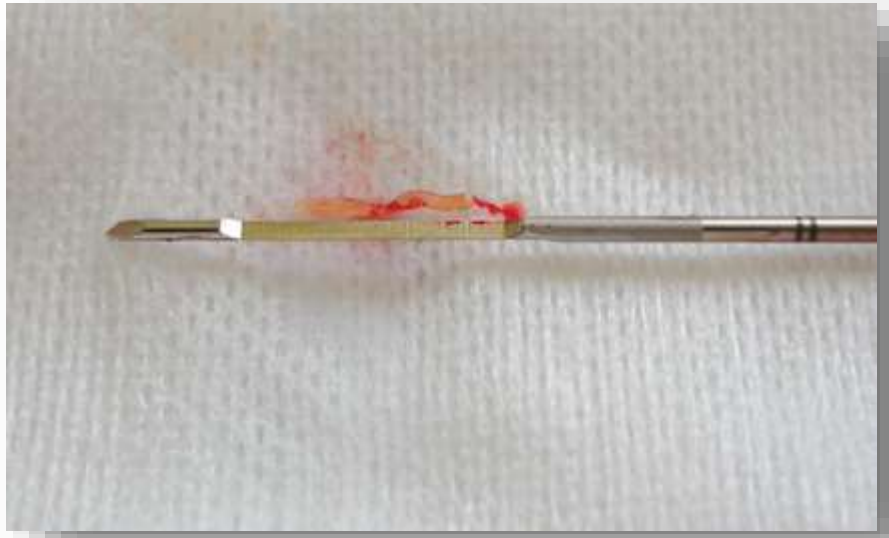
Renal biopsy

- Local anesthesia, ultrasoung guidence
- Evaluation by light – , immunfluorescent – and electron microscopy

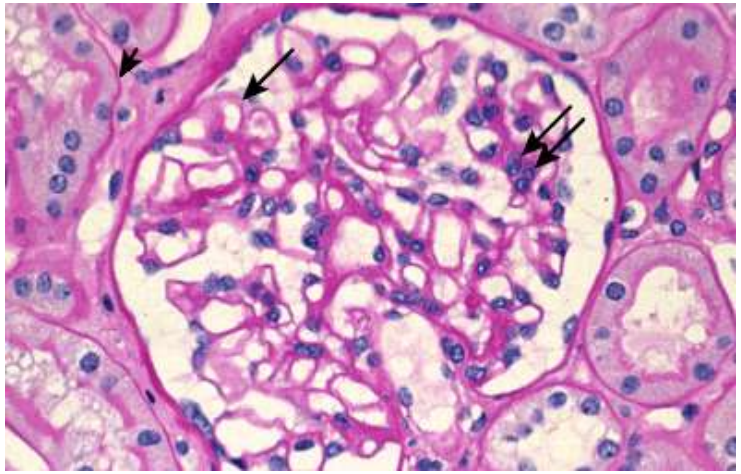




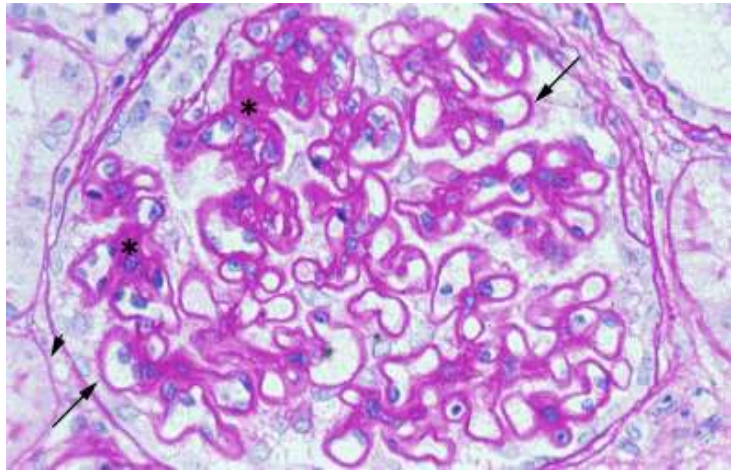
Renal biopsy sample



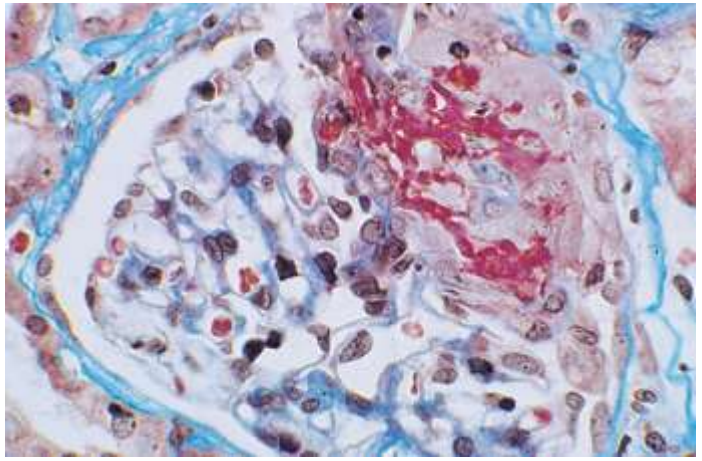
Evaluation of a biopsy sample: light microscopy



Normal glomerulus

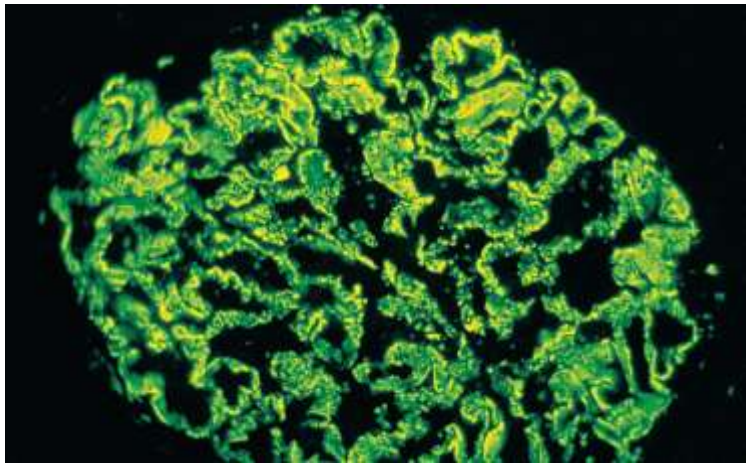


Membranosus nephropathy

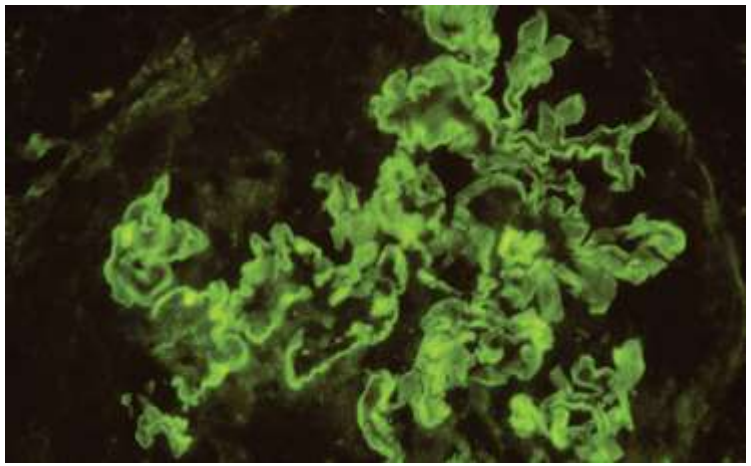


Crescent formation

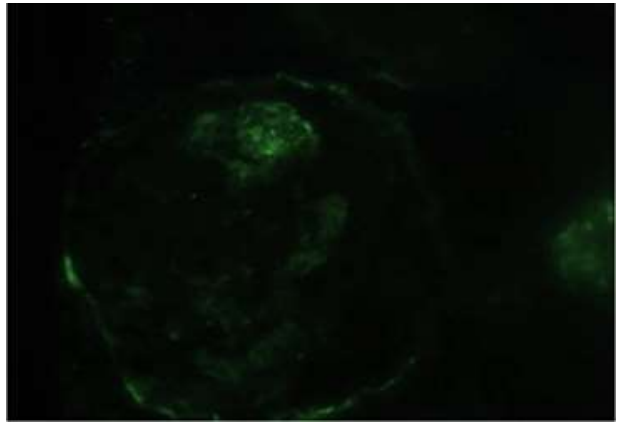
Evaluation of a biopsy sample: immunfluorescent microscopy



Granular pattern

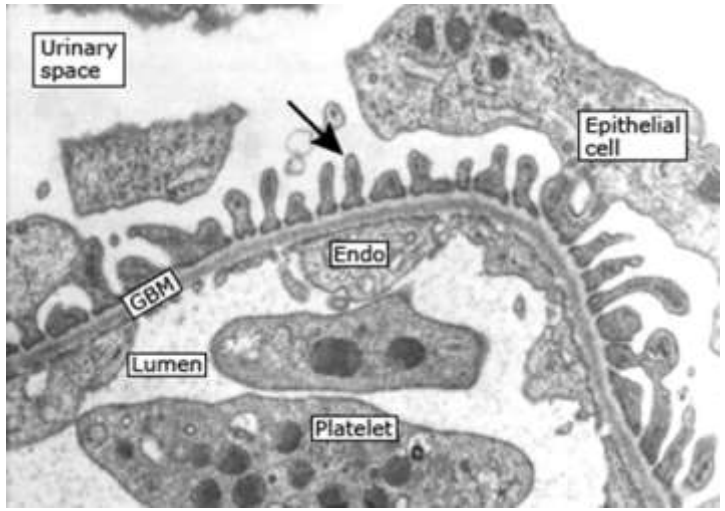


Linear pattern

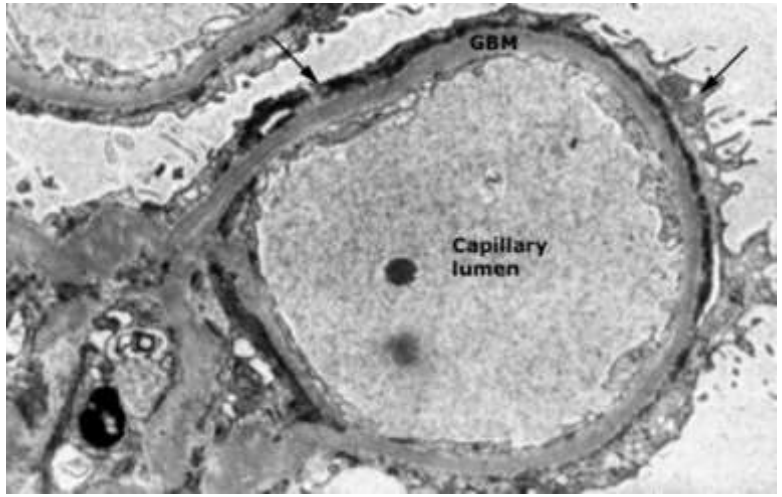


Pauci-immune pattern

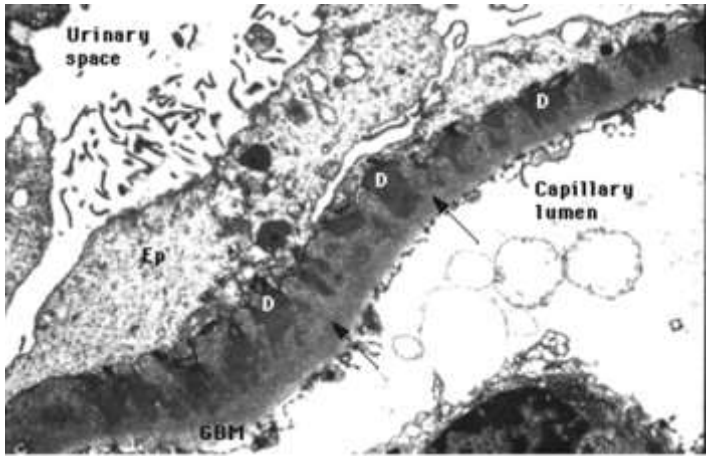
Evaluation of a biopsy sample: electron microscopy



Normal filtration barrier



Podocyte foot process effacement (MCN)



Subepithelial immune deposits in membranosus nephropathy

„Major” nephrology syndromes

- Nephrosis
- Nephritis
  - Rapidly progressive glomerulonephritis (RPGN)
- Acute kidney injury
- Asymptomatic proteinuria and/or hematuria
- Chronic kidney disease

Asymptomatic urinary abnormality

non-nephrotic proteinuria and/or hematuria w/o nephritic syndrome

- Asymptomatic proteinuria (usually 0,5-2g/day)
  - See causes of proteinuria above
  - Glomerular diseases eg.
    - **Early diabetic nephropathy**
    - **secondary FSGS**
    - **Hypertensive nephropathy**
- Asymptomatic microhematuria
  - See causes of hematuria above
  - Glomerular diseases eg.
    - **IgA nephropathy**
    - **Alport syndrome**
    - **Thin-basement membrane abnormality**

Further differentiation with renal biopsy is needed if proteinuria worsens, GFR decreases

Differential diagnosis of chronic kidney disease

- Signs and symptoms
  - Decreased GFR, variable progression
  - Usually small kidneys with echogenic parenchyma
  - Variable urinary abnormalities (depending on the original disease)
  - Complications according to the stages of CKD (hypertension, electrolyte-acid base alterations, anemia, cardiovascular diseases)

- Differential diagnosis
  - Usually not a diagnostic problem
  - the original kidney disease may not be identified (hypertension, diabetes, glomerulonephritis, tubulointerstitial nephritis…)
- To be done
  - Slow progression, prepare for renal replacement therapy
  - Prevent complications

Overview

- Definition and method of differential diagnosis
- Differential diagnosis of the main renal symptoms
  - Pain, hematuria, proteinuria
- Differential diagnosis of the main renal syndromes
  - Nephrosis
  - Nephritis
  - RPGN
  - Acute kidney injury
  - Asymptomatic urinary abnormalities
  - Chronic kidney disease
- Case study

Case

- 72 y/o female admitted with a creatinine of 734umol/l and edema
- Hx: Hypertension, 1 year ago right breast cancer operation followed by hormone and cytotoxic therapy – no metastases
- PE: weak, frail, ++ edema, pulmonary rales, no abdominal, skin, joint changes
- Laboratory: Hb 98g/l, wbc 14G/l, plt 110G/l LDH 580 U/l, CRP 40mg/dl, urea 26mmol/l, norm LFT, K 5,1mmol/l, pH 7,35, urine ++ proteinuria +++ blood, cellular casts, chest Xray: congestion

- Differential diagnostic questions, issues
  - Acute (nephritic)-subacute (RPGN) - chronic kidney disease ?
  - Cause? – several possibilities (GN?, HUS? RPGN? Drug induced?…)
  - Should dialysis be commenced?
- To-be-done at this stage: previous laboratory? UH, urinary sediment, reticulocyte? haptoglobin?

Case cont’d

- Creatinine and urine 1 year ago normal, 6 months ago 210umol/l with hematuria, 3 months ago 282umol/l and mild anemia
- UH: normal sized kidney, norm parenchyma echogenic, no obstruction
- Urinary sediment: dysmorphic glomerular haematuria, RBC casts, proteinuria 182mg/mmol
- Haptoglobin normal

- Syndrome diagnosis: RPGN, no HUS, no obstruction
- Differential diagnosis
  - Anti-GBM disease? Immuncomplex GN?, ANCA vasculitis?

- To be done:
  - renal biopsy
  - immunology (anti-GBM, ANA, anti-dsDNS, ANCA antibodies

Case cont’d

- Kidney biopsy
  - Crescentic, diffuse glomerulonephritis with necrosis and fibrosis
  - Immunfluorescence: pauci-immune
- Serology:
  - anti GBM neg, ANA poz, cryoglobulin neg, anti-dsDNS neg, cANCA neg, pANCA poz 1:160, anti-proteinase 3 norm, anti myeloperoxidase 280u/l (norm <20)

- Diagnosis: microscopic polyangitis without pulmonary involvement

- To be done:
  - Plasma exchange
  - Immunsuppression: steroid, cyclophosphamid, rituximab
  - Hemodialysis if needed

Overview

- Definition and method of differential diagnosis
- Differential diagnosis of the main renal symptoms
  - Pain, hematuria, proteinuria
- Differential diagnosis of the main renal syndromes
  - Nephritis
  - RPGN
  - Nephrosis
  - Asymptomatic urinary abnormalities
  - Acute kidney injury
  - Chronic kidney disease
- Case study