GLOMERULAR DISEASES

seminar

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Glomerular diseases #1 (62-year-old man – December, 2013)

Reason for admission: Laboratory investigations performed in a local lab revealed impaired renal function.

Signs and symptoms: The patient has been complaining about migratory joint pain for 2 weeks. His left ankle became swollen. He experiences some stiffness in his fingers in the morning. Pain is usually absent in the morning and appears in the afternoon. Indomethacin (NSAID) suppository relieved pain. He had a febrile episode 2 months ago, (a supposed urinary tract infection), for which he recieved antibiotics . He became afebrile and the fever has not returned. Recently, he has had dyspnea on exertion (he can climb one flight of stairs). He has had constipation since his operation (05.2013). His stool is not black or bloody, and he has not had diarrhea. His appetite has been decreased for a month, and he underwent upper endoscopy because of heartburn. His weight decreased by 4-5 kgs in the past 2 months. He consumes 2 L of fluid daily. He has no dysuria, and his urine did not appear bloody. Passing urine is easy, urine flow is continuous. He has no incontinence. Nycturia: 2x. His legs are not swollen.

Glomerular diseases #1 (62-year-old man – December, 2013)

Past medical history: traumatic PTX (1984)

- Pneumonia with abscess formation in the upper lobe of the right lung (01.2007)
- Pneumonia with abscess formation in the upper lobe of the right lung (03.2013) - (Augmentin and Levofloxacin treatment). Chest CT scan: in the upper lobe of the right lung there is a inhomogenous structure of 5x4,5 cm size, with irregular contour. Summary: in the right apex , the size of the pathologic stucture is unchanged. It may correspond with inflammation, aspergillosis, structure of mycotic origin, or a tumor . Bronchoscopy: intact trachea and bifurcation. The width of the carina is normal. Orifices of the main bronchi are visible. No direct or indirect signs of a tumor . The mucous membrane of the right upper lobe is slightly hyperemic and fragile, there is some mucopurulent discharge. Culture, ZN negative.
- 05.2013. right upper lobectomy. Histology: morphologic changes correspond with a granulomatous inflammation due to bronchiectasis and consequent infection.

Glomerular diseases #1 (62-year-old man – December, 2013)

Physical investigation (details): Radial pulse: 70/min, regular, equal. Blood pressure: 168/89 mmHg (left), 170/96 mmHg (right).
Slightly anemic appearance.
Lymph nodes: not palpable.
Edema: not visible/palpable.
Lungs: alterations corresponding to the right upper lobectomy.

Laboratory:

- WBC: 8.6 Giga/L; L-NEU: 69.3 %; Hemoglobin: 95 g/L; MCV: 77.8 fL; THRCY: 450 Giga/L;
- PCO2: 29.6 Hgmm; PO2: 84 Hgmm; pH:7.33; bicarb: 15.2 mmol/L;
- Glu: 4.8 mmol/L; Trigliceride: 1.63 mmol/L; Cholesterol: 5.5 mmol/L; Urate: 645 umol/L
- T.bilirubin: 8.3 umol/L; LDH: 310 U/L; GOT: 8 U/L; GPT: 4 U/L; GGT: 24 U/L;
- CN: 25.9 mmol/L; Creatinine: 751 umol/L; eGFR: 6.0 ml/min/1.73 m2;
- Na: 133 mmol/L; K 5.6 mmol/L; Ca: 2.35 mmol/L; PO4: 2.19 mmol/L; Mg: 0.68 mmol/L;
- Total protein: 72.5 g/L; Albumin: 34.9 g/L;
- CRP: 64 mg/L; ESR: 111 mm/h;
- Urine SG: 1010 g/cm3; pH: 5.5; Prot: 2+; blood: 3+; sediment: RBC 49/HPF ; WBC: 6/HPF

Glomerular diseases #1 (62-year-old man – December, 2013)

Imaging:

Chest X-ray: St.p. right upper lobectomy. There is some fluid in the left lateral sinus. Focal patchy infiltrates can be seen in the parahilar regions bilaterally and also the right basal area. Some right-sided linear densities are present. The right hemidiaphragm is elevated by 3 fingers. The size of the heart is normal.
Summary: bilateral infiltrates. Some right-sided pleural fluid.

Renal ultrasound: The position, size and structure of the kidneys are normal. The urinary collecting system in the renal sinus is not visible. The parenchyma is homogenous without any distinct masses. Urinary bladder and the surrounding region is without any abnormalities.

Glomerular diseases #1 (62-year-old man – December, 2013)

Elements of the clinical picture:

- low eGFR – previously normal values √
- hematuria √
- proteinuria √
- hypalbuminemia -
- edema -
- high blood pressure √
- systemic signs: fever, joint pain, weight loss √

Clinical syndrome:

Acute nephritis?
Rapid progressive glomerulonephritis?
Hematuria + proteinuria -> chronic nephritis?
Nephrotic syndrome?
Asymptomatic urinary abnormalities (isolated hematuria / proteinuria)?

Expected histologic abnormalities:

proliferative vs. non-proliferative changes by light microscopy?

Glomerular diseases #1 (62-year-old man – December, 2013)

RPGN – Which diseases should be considered?

- SLE
- ANCA-associated vasculitis
- Goodpasture-syndrome
- Cryoglobulinemia
- IgA nephropathy
- Postinfectious GN

Diagnostic steps

Laboratory:	C3 and C4	C3: 1.58 g/L; C4: 0.43 g/L
	ANA screen, anti ds-DNA	ANA1: slightly pos 1:40; ANA2: negative 1:160
	ANCA – anti-MPO és anti-PR3	aMPO: 3 U; aPR3: 234 U
	anti-GBM	aGBM: 1 U/mL
	ASO	-

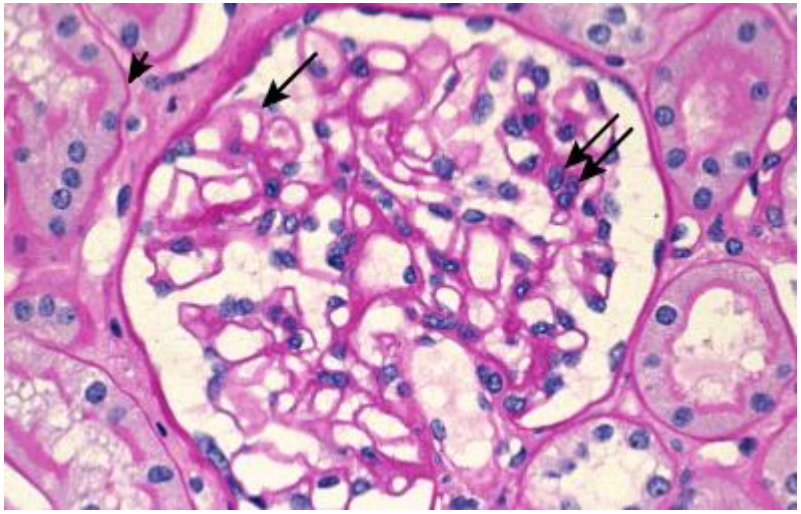
Glomerular diseases #1 (62-year-old man – December, 2013)

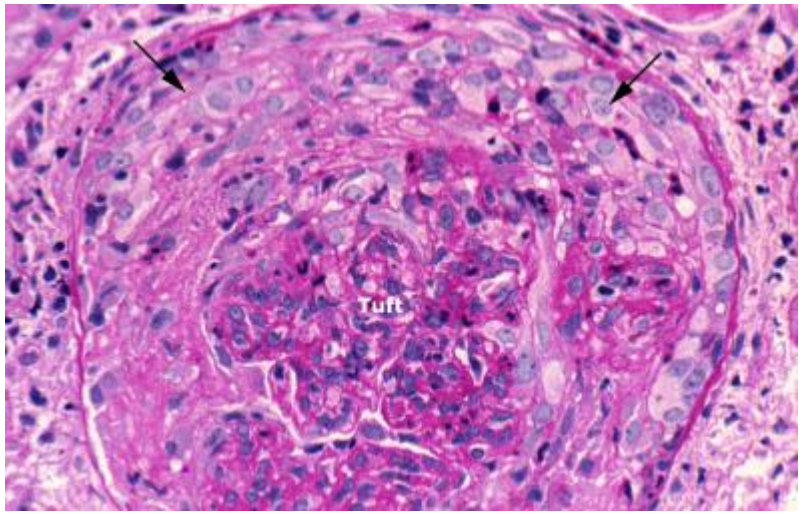
Diagnostic steps

Renal biopsy

Light microscopy – proliferative changes

Which cells may proliferate?
- endocapillary (endothel, neutrophil granulocytes)
- mesangial (mesangium)
- mesangio-capillary (mainly mesangium, spreading to the endothel side of the basement membrane)
- extracapillary (crescent formation) (epithel cells of the Bowman capsule)





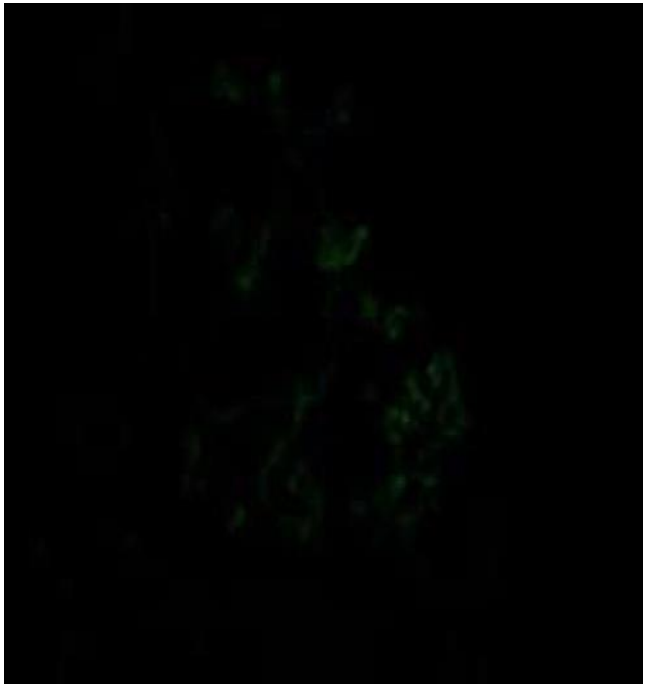
Glomerular diseases #1 (62-year-old man – December, 2013)

Diagnostic steps

Renal biopsy

Immunofluorescence (IgG, IgA, IgM, light chains, C3, C1q)

Pattern type?
- linear
- granular
- pauci-immun



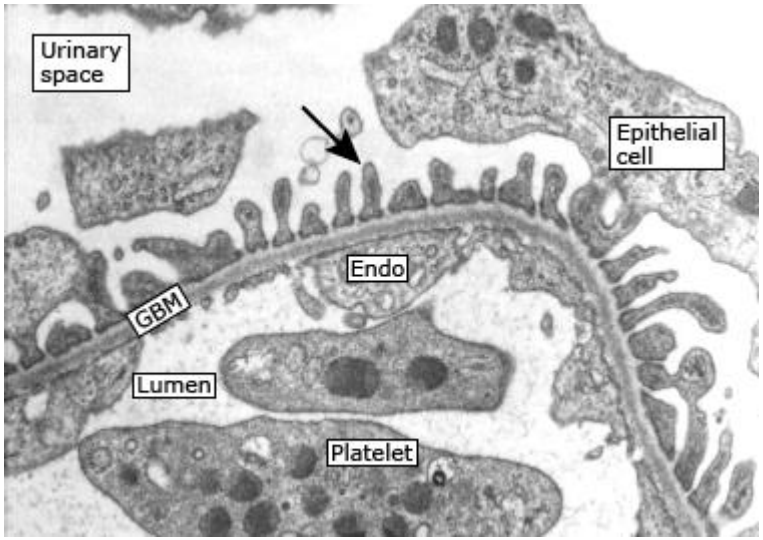
Glomerular diseases #1 (62-year-old man – December, 2013)

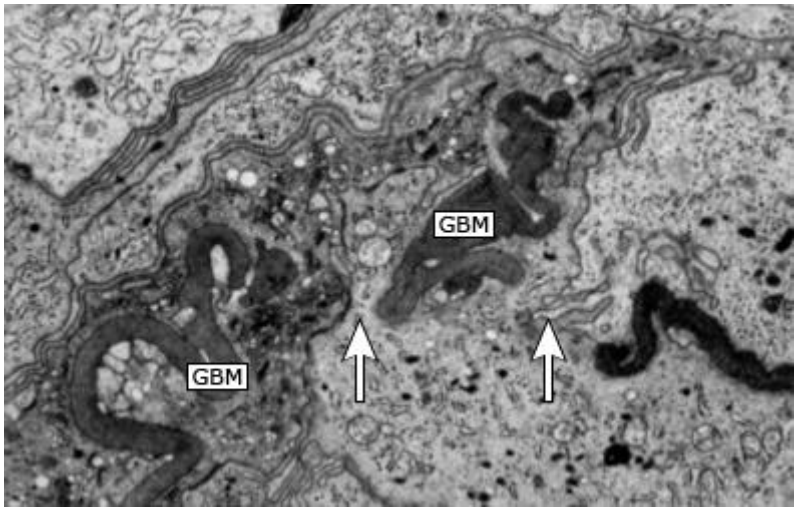
Diagnostic steps

Renal biopsy

Electron microscopy

- the condition of the basement membrane
- immune complexes





Glomerular diseases #1 (62-year-old man – December, 2013)

Do we need renal biopsy in this case for the diagnosis?

Pros:
„gold standard" – diagnosis is confirmed by histology
active inflammation vs. chronic fibrosis – efficacy of the therapy

Cons:
diagnosis is set based on clinical opicture + laboratory findings
therapy is needed rapidly without any waste of time

In this patient treatment was initiated WITHOUT renal biopsy.

Glomerular diseases #1 (62-year-old man – December, 2013)

Therapeutic options

Immunosuppression:

Induction

corticosteroid + cyclophosphamide
methylprednisolon 500 mg iv. for 3 days followed by 32 mg po. daily dose tapered down gradually in 5 months
cyclophosphamide iv. 800 mg in infusion, monthly pulses for 5 months
preventive uromitexan
obs. neutropenia – in case of fever, urgent laboratory evaluation!

Plasmapheresis

- 5 cycles

Supportive therapy: transfusion (6 packs of RBC)
hemodialysis (was not necessary)
antihypertensive treatment (amlodipin – a CCB)
PPI (preventive)
trimethoprim-sulfomethoxazol (Sumetrolim)

Glomerular diseases #1 (62-year-old man – December, 2013)

Results

2013.12. 1.	pulse cyclophosphamide (800mg) + 5xPE	Se creat: 723->337 umol/l aPR3: 324->54 U
2014.01. 2.	pulse cyclophosphamide (800mg)	Se creat: 258 umol/l
2014.02. 3.	pulse cyclophosphamide (800mg)	Se creat: 260 umol/l
2014.03. 4.	pulse cyclophosphamide (800mg)	Se creat: 252 umol/l
2014.04. 5.	pulse cyclophosphamide (800mg)	Se creat: 222 umol/l aPR3: 13 U

Headache did not recur, nasal congestion and ear plugging became less prominent. Afebrile. No loss of consciousness. No cough, dyspnea on exertion is unchanged. Good appetite. Body weight increased by 2-3 kg. No nausea or vomiting. Stool is regular, not bloody or black. Passing urine is painless, urine is not bloody, urine volume is normal. No swelling of the legs.
Home BP: 130-140 mmHg SBP.

Glomerular diseases #1 (62-year-old man – December, 2013)

Therapeutic options

Immunosuppression:

Maintenance treatment	azathioprine
	obs. liver function
	CAVE: allopurinol (Milurit)

Results

2014.04. 5. pulse cyclophosphamide (800mg)	Se creat: 222 umol/l.
	aPR3: 13 U
2014.05. azathioprine	Se creat: 292-320 umol/l
2014.07.	Se creat: 362 umol/l
	aPR3: 37 U

How to continue?

Glomerular diseases #1 (62-year-old man – December, 2013)

Questions: Active inflammation due to a relapse?
Progression of chronic kidney disease due to fibrosis?

Renal biopsy

Pros:

„gold standard" – diagnosis is confirmed by histology -
active inflammation vs. chronic fibrosis – efficacy of the therapy √

Cons:

diagnosis is set based on clinical opicture + laboratory findings -
therapy is needed rapidly without any waste of time -

Results of the renal biopsy

Immunofluorescence microscopy

In the frozen section 2 glomeruli showed global sclerosis, and one glomerulus had open capillary loops. Staining for C3 provided mild (+), granular reaction along the basement membrane, while staining for IgM and IgA provided even milder reaction at the same site.

Summary: Description correspondent with a pauci-immune GN

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Light microscopy

Two tissue samples were investigated that contained renal cortex. Totally 34 glomeruli were anayzed. Six glomeruli had maintained structure with signs of mild ischemic damage. One glomerulus displayed focal segmental glomerular sclerosis. The remaining 27 glomeruli demonstrated global sclerosis. A moderate-degree widening of the interstitium, and also moderate, focal chronic infiltration by inflammatory cells were also observed. Tubular atrophy was diffuse and overall. In the intima of the small vessels, segmental deposition of a PAS-positive material was demonstrated. Larger vessels were intact. Under polarized light, Congo-stain did not provide any apple-green birefringence.

Summary: No signs of immuncomplex glomerulonephritis could be observed. The tissue analyzed displays diffuse glomerular sclerosis accompanied by moderate-degree interstitial fibrosis, tubular atropy and signs of hypertensive damage in smal vessels.

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Electron microscopy

One glomerulus was studied in the ultra-thin section. Mesangial region and the number of cells were regular and capillary loops were open. Glomerular basal membrane had normal structure. Podocyte foot process effacement could be seen along 10% of the basement membrane. The cytoplasm of podocytes was rich in vacuola. The interstitium was wider than normal, with excessive accumulation of collagene fibers. Tubular basement membrane was extremely thick and creased, accompanied by the atrophy of tubular epithelium and a barely visible tubular lumen. In the interstitium, focal chronic infiltration of inflammatory cells could be observed. Immundeposits were not visible.

Summary: Electronmicroscopic evaluation confirms the findings demonstrated by light microscopy.

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Follow-up

2014.09. creat: 254
2015.01. creat: 238
2015.04. creat: 244
2015.06. creat: 204
2015.09. creat: 220
2015.12. creat: 213 – Azathioprine STOP.
2016.03. creat:220
2016.07. creat:200
2016.10. creat:210
2017.01. creat: 179 Alb:39, routine evaluation of anti-PR3:332. Urine: SG:1015, pH:6.0, prot:+, sediment: 3-4 RBC, 1-1 squamous cells.

The overall condition is fine. Afebrile. Subfebrility, cough and rinorrhea during the previous week. No bleeding from the respiratory tract. No loss of consciousness. Some cough with worsening dyspnea. Maintained appetite. Stable body weight (89.9 ->90.6 ->89.8 kg). No nausea or vomiting. Stool regular, not bloody or black, no need of laxatives. No dysuria, urine not bloody, normal urine volume (~1.5-2 L/day). No swelling of the legs. Occasional joint pain (shoulder pain mentioned 3 months before disappeared)
Home BP: SBP around 130 mmHg.

Glomerular diseases #1 (62-year-old man – December, 2013)

Follow-up

2017.01. creat: 179, routine evaluation of anti-PR3:332

Summary: increased immunological activity without clinical manifestation. Observation is needed.

2017.06. creat: 169, Alb: 43, Urine: SG:1020, pH:6.0, prot:+, sediment:1 RBC, 2-4 WBC

The overall condition is fine. Afebrile. No respiratory problems or ear plugging. No bleeding from the respiratory tract. No loss of consciousness. No cough, dyspnea of unchanged degree. Maintained appetite. Slightly decreased body weight (89.9 ->90.6 ->89.8 ->87.7kg). No nausea or vomiting. Stool regular, not bloody or black, no need of laxatives. No dysuria, urine not bloody, normal urine volume (~1.5-2 L/day). Some swelling of the legs. No joint pain recently.
Home BP: SBP around 130 mmHg.
Summary: There is not any active clinical manifestation of the disease. Further observatrion ios needed.

Glomerular diseases #1 (62-year-old man – December, 2013)

Follow-up

2017.11.
Afebrile. Progressive weakness. Migratory joint and muscle pain of variable degree for 2-3 weeks. No respiratory bleeding, no cough. Occasional ear plugging (not worse than before). Urine volume maintained, urine not bloody/darker than usual. No loss of consciousness. Dyspnea on exertion (unchanged severity). Somewhat worse appetite. Stable body weight (~ 88kg). Stool regular, not bloody or black, no need of laxatives. Some swelling of the legs.
Home blood pressure: 130-140 mmHg SBP

Laboratory: creat 315
alb:44
Urine: SG:1020, pH:6.0, prot.:++++, sediment:120-25 RBC. TP/creat: 417 mg/mmol
aPR3: 1434 (!)

Summary: Obvious immunologic and clinical relapse. Immunosupressive therapy is required.

Glomerular diseases #1 (62-year-old man – December, 2013)

Therapeutical options

Immunosupression:

Induction
corticosteroid + rituximab
methylprednisolon 500 mg iv. for 3 days followed by 32 mg po.
daily dose tapered down gradually in 5 months
rituximab iv. 800 mg pulses in infusion, weekly, for 4 weeks
paracetamol – antihistamine (Suprastin) prophylaxis

Plasmapheresis
recommended in case of
- need of dialysis / severe azotemia
- bleeding from the lower respiratory tract

was not performed in our case

Supportive therapy: antihypertensive treatment (amlodipin + carvedilol)
diuretics (furosemid)
PPI prophylaxis
osteoporosis prevention (viatmin D3- and Ca-supplementation)
trimethoprim-sulfomethoxazol (Sumetrolim)

Glomerular diseases #1 (62-year-old man – December, 2013)

Results

2018.01. creat: 488, aPR3: 122
2018.02. creat: 441, aPR3: 30
2018.04. creat: 437 - corticosteroid STOP, azathioprine START
2018.06. creat: 506, aPR3: 84
2018.07. creat:540
2018.08. creat: 525
2018.09. creat:541
2018.10. creat:522
2018.11. creat:510
2018.12. creat:543 aPR3:252
2019.01. creat:589

Weakness became less profound. Unchanged joint pain. Occasional headache. Afebrile. No cough, no bleeding from the respiratory tract. Variable appetite. Stable body weight (91.9 ->90.9 ->90.8kg). No nausea or vomiting. Stool regular, not bloody or black, no need of laxatives. Maintained urine volume, urine not bloody / darker. Some swelling of the legs.
Home BP: SBP around 120 mmHg.

Summary: St. V. chronic kidney disease, regular follow-up is necessary. Pre-dialysis condition, urgent dialysis treatment is not needed.
Peritoneal dialysis started in April, 2019.