New insights in the diagnosis and management of membranous nephropathy

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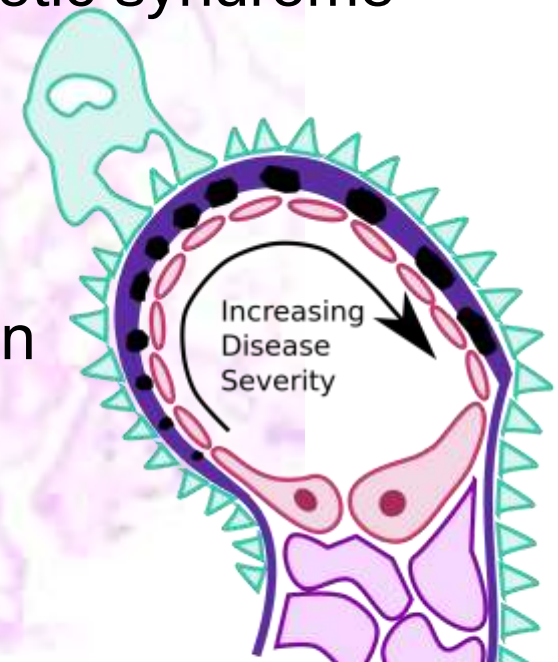
What we know about Membranous Nephropathy

- Antibody-mediated autoimmune glomerular disease
- Deposition of subepithelial immune complexes
- 1:100,000 per year, commoner in whites, males > females (unlike most autoimmune diseases)
- The commonest diagnosis in adults with nephrotic syndrome (~25%)
- Can lead to ESRF
- Clearly defined histology…
- …Wide variability in phenotype and progression

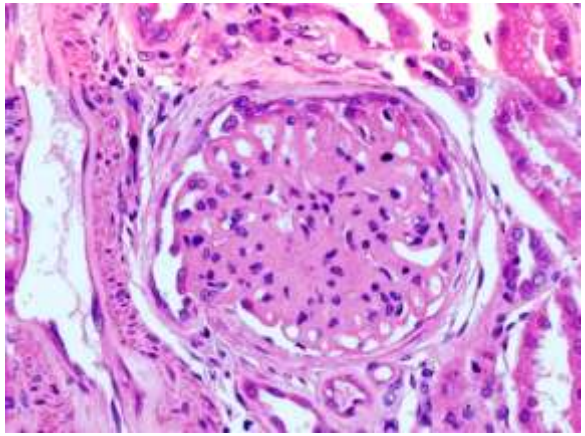


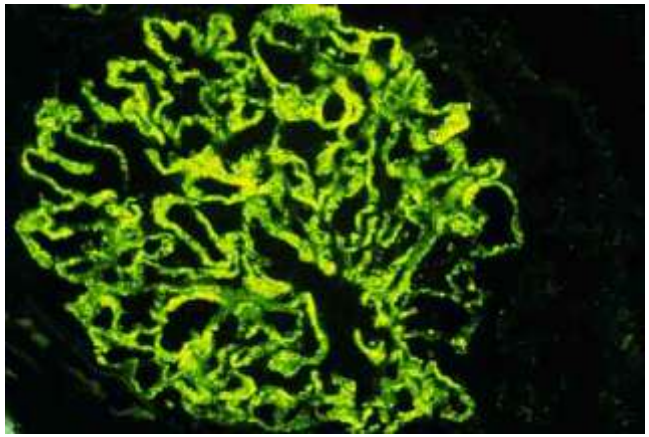
Membranous nephropathy, not nephritis

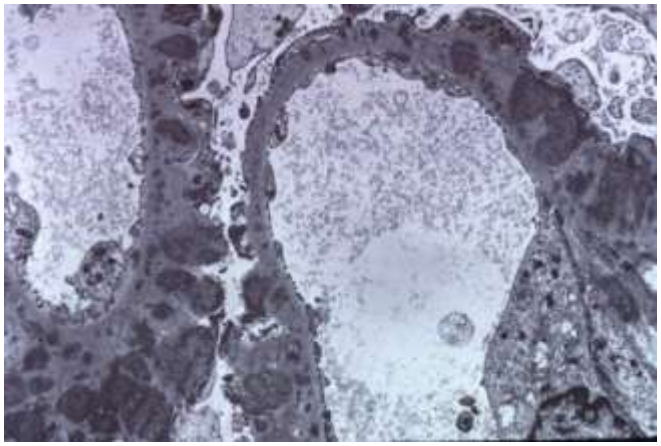
Glomerular deposits contain immunoglobulin (IgG) and complement (C3) components:

- C3 deposits – hence alternative pathway activation
- Not C1q (classical pathway)

  = Deposits without any sign of inflammation





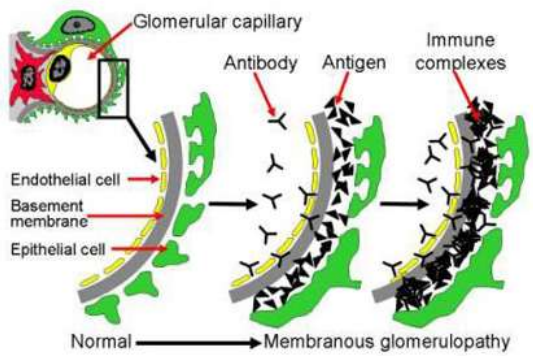


Is it primary or secondary MN?

- How to tell the difference
  - History, serology, IF for antibodies and look for specific antigen

- Primary (idiopathic) IgG_4
- Secondary IgG_1 IgG_2 IgG_3
  - hepatitis B (even if not active)
  - autoimmune diseases (esp lupus) **C1q C3 IgG IgM IgA**
  - Malignancies
  - Drugs: gold, penicillamine, captopril, NSAIDs

So what is the antigen?



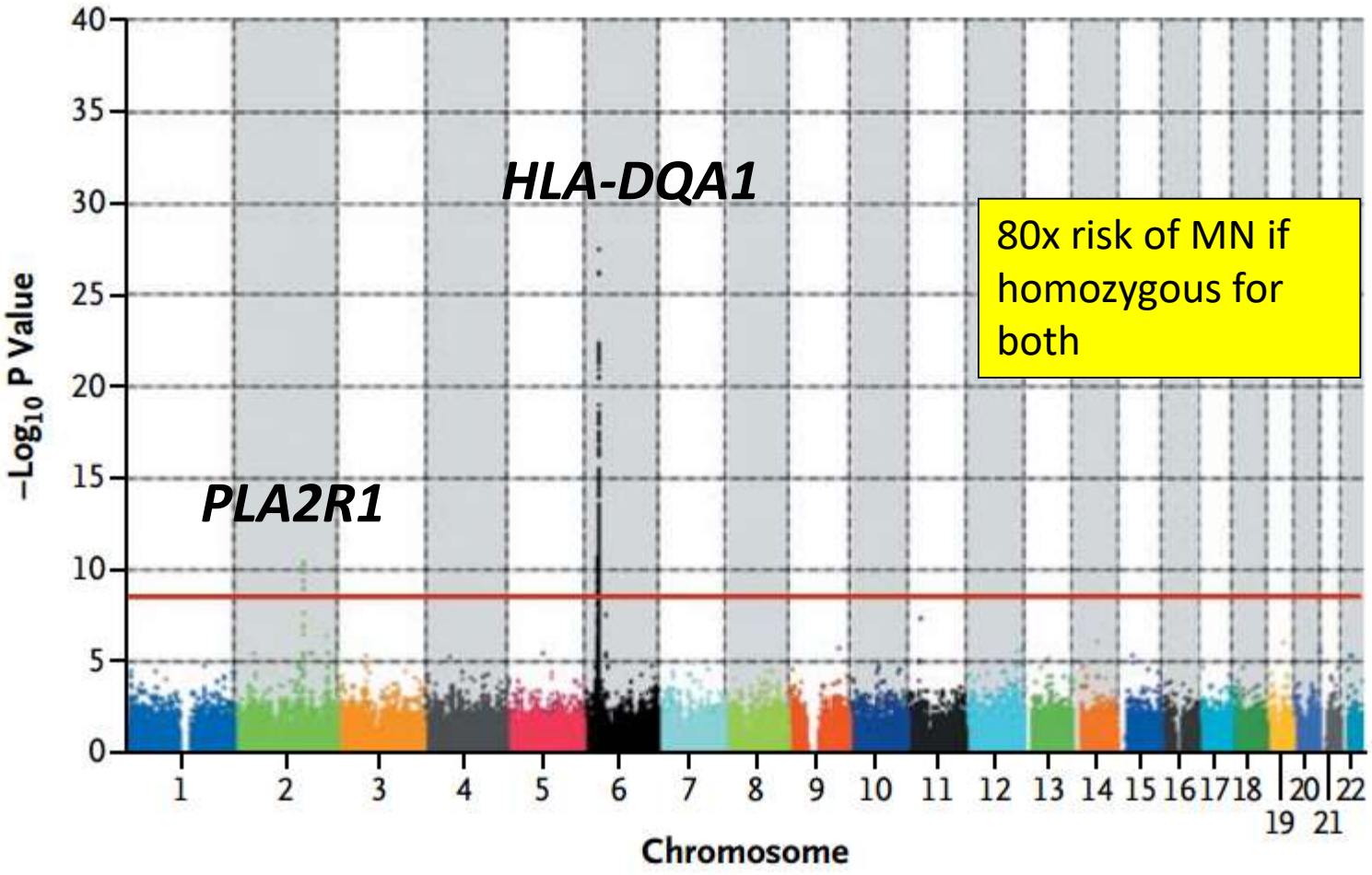
- In MN, immune complexes due to antibodies against podocyte antigens
- 1959 - Heymann nephritis: only in rats
- 2002 – Antigen: NEP
- 2009 – Antigen: PLA2R
- 2014 – Antigen: THSD7A

- All of these antigens are on podocytes

Neonatal MN = alloimmune
Mother makes anti-NEP IgG to NEP expressed in placenta

Adult MN = autoimmune
Beck et al 2009: Western blotting of patient's serum on normal glomeruli

Genetics independently confirms the association of PLA2R with MN



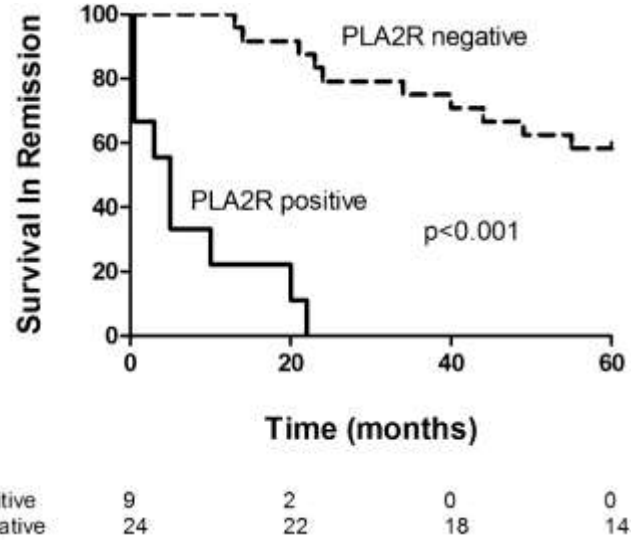
80x risk of MN if homozygous for both

Stanescu et al, NEJM 2011

These antibodies are clinically useful

- Anti PLA2R
  - specificity 95%; sensitivity 70-85% of adult MN patients
  - antibody status after immunosuppression predicts survival during remission
- Anti-THSD7A
  - 10% of PLA2R-negative adult MN patients

Bech et al CJASN 2014 (9) 1386



- Pathogenic antibodies
  - Recurrence after transplantation – within a week, hence antibody mediated
  - PLA2R is not expressed in mouse/rat/rabbit podocytes so can't do transfer experiments

Treatment: how to decide

- Are you sure it's not secondary MN?
- Will they spontaneously remit? (20-30%)
  - ACE/ARB if not nephrotic and not progressive
  - But 60% may progress to nephrotic syndrome (Hladunewich CJASN 2009)
  - Proteinuria >4g/d have 55% chance of ESRD at 10 years
- Will they be nephrotic for too long?
- Is the kidney worth saving?
  - Interstitial fibrosis/tubular atrophy or CKD 4-5

Immunosuppressive options for primary MN

Relapse rates

- Glucocorticoids alone don't work
- Glucocorticoid+cytotoxic – alternating monthly course **22-30%**
  - Very toxic; but may preserve renal function if already CKD
- CNIs (ciclosporin or tacrolimus) **40-70%**
  - >50% chance of relapse at 6 months if no maintenance treatment
  - Steroids not needed
- Mycophenolate doesn't work without steroids **90-100%**
- ACTH
- Rituximab **25-30%**
  - Dose/frequency and long-term effects unclear

Biopsy-proven primary MN

1. 69M, nephrotic (14 g/d, Alb 23 g/l), creatinine 125 umol/l. Previous angina. BP 148/90.

2. 56M, nephrotic (7 g/d, Alb 25 g/l), creatinine 88 umol/l, no chronic damage on biopsy.

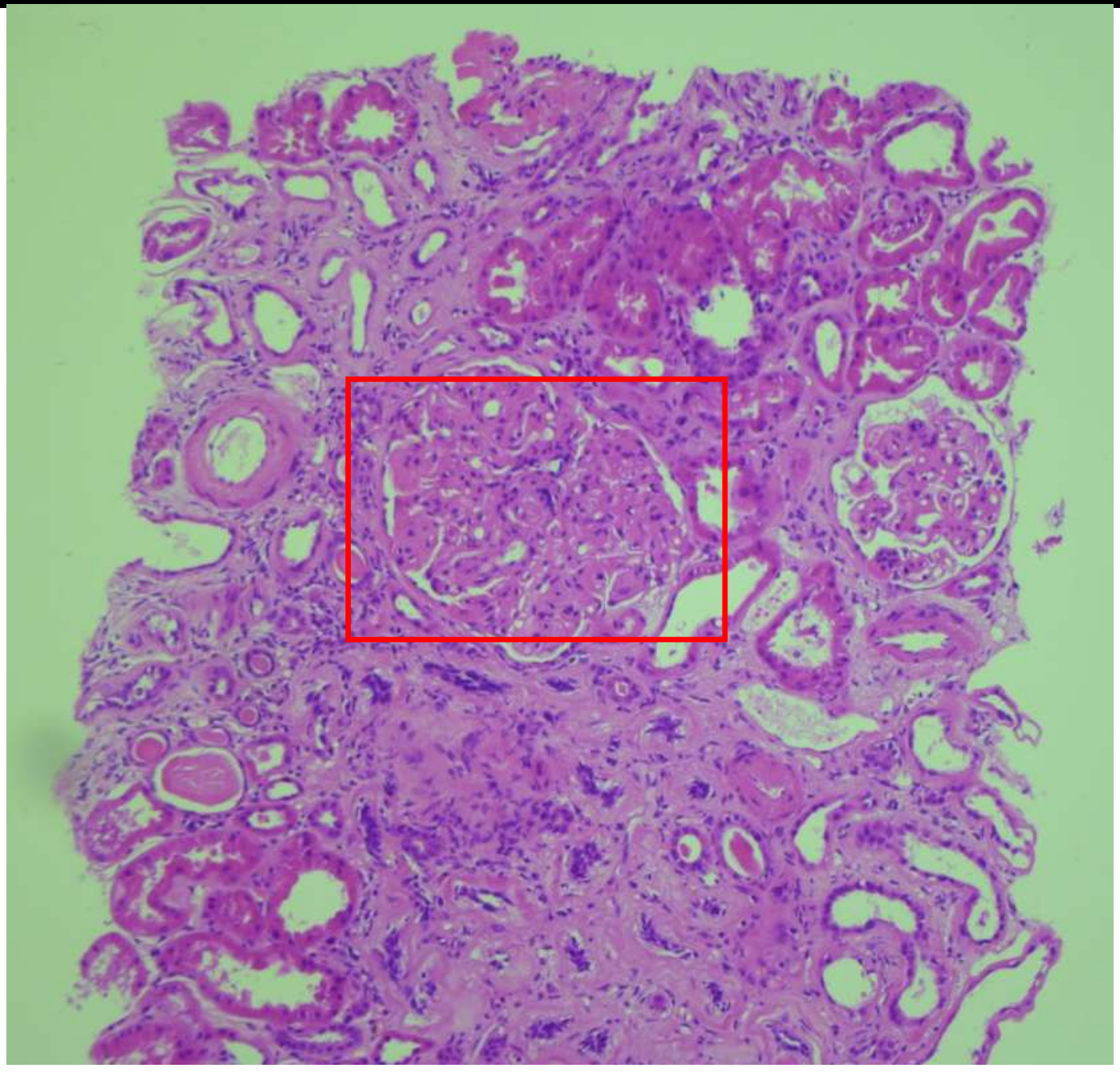
3. 77M, nephrotic (14 g/d, Alb 22 g/l), creatinine 157 umol/l May 2016, 234 umol/l Aug 2016, 292 umol/l Sept 2016. Type 2 DM 2006, no laser treatment. CABG x3 1999. Already on aspirin and losartan 100 mg daily.

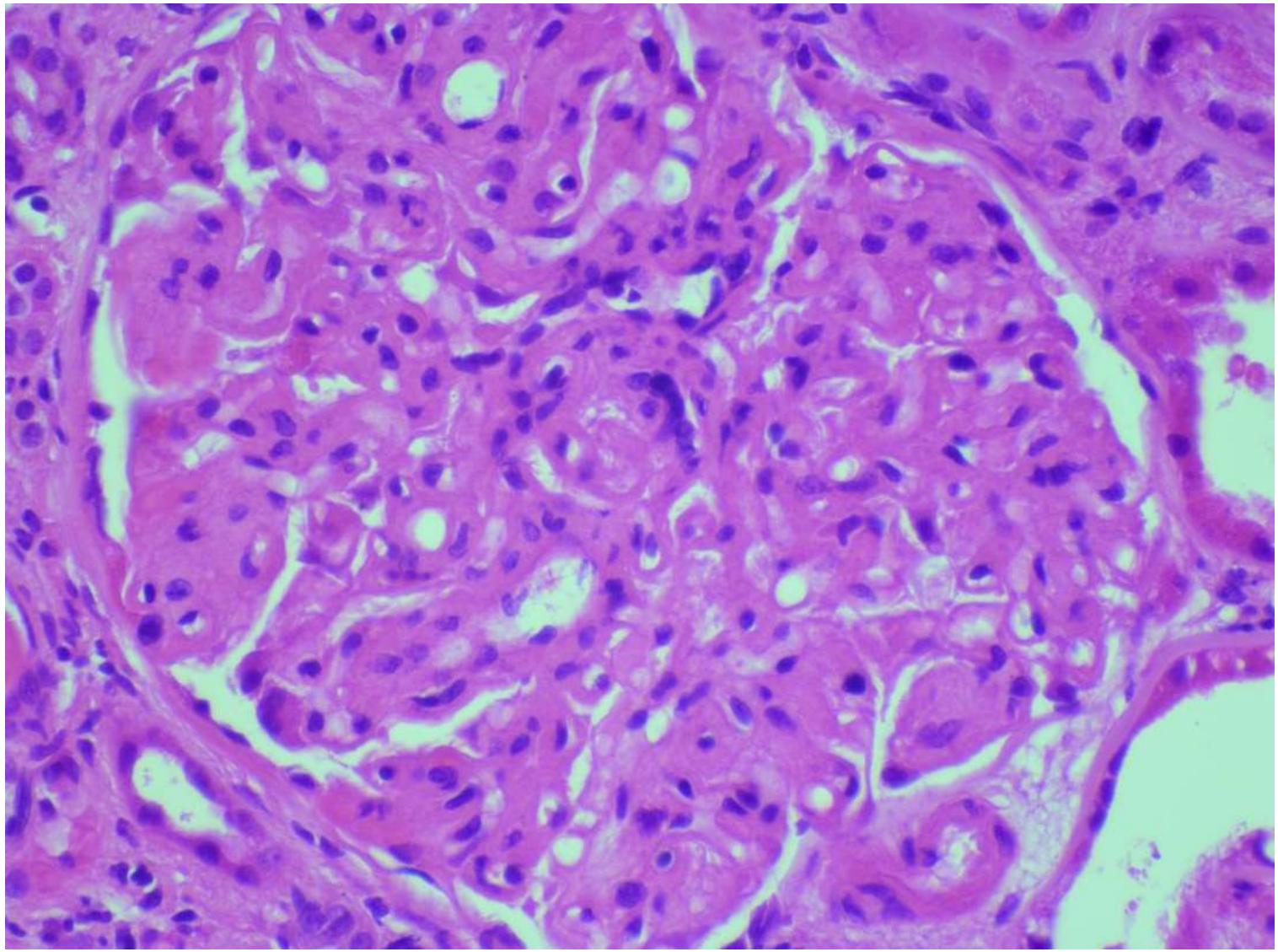
ACE inhibitor + loop diuretic for 6 months

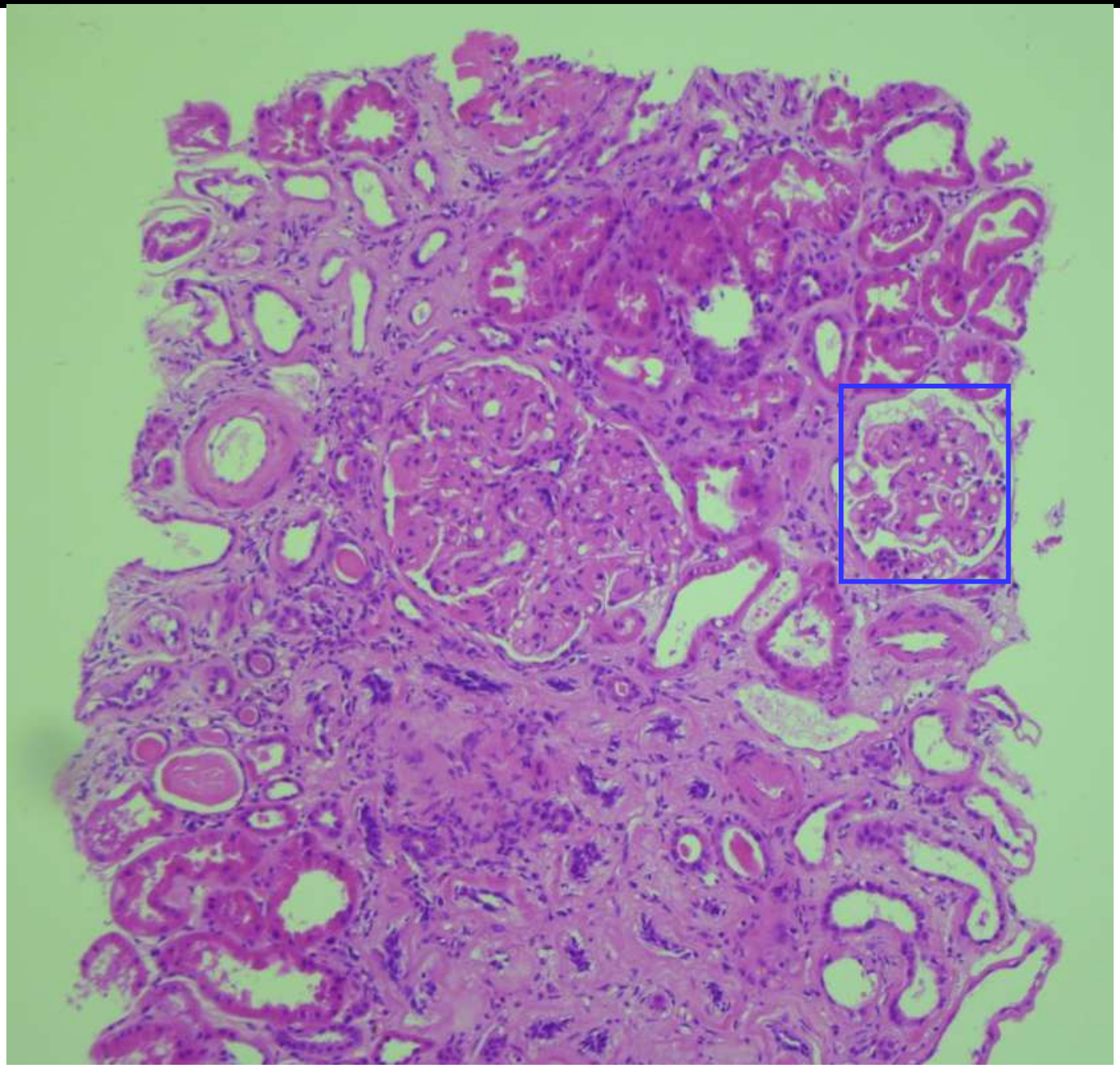
Ciclosporin 5mg/kg/d + prednisolone 30 mg

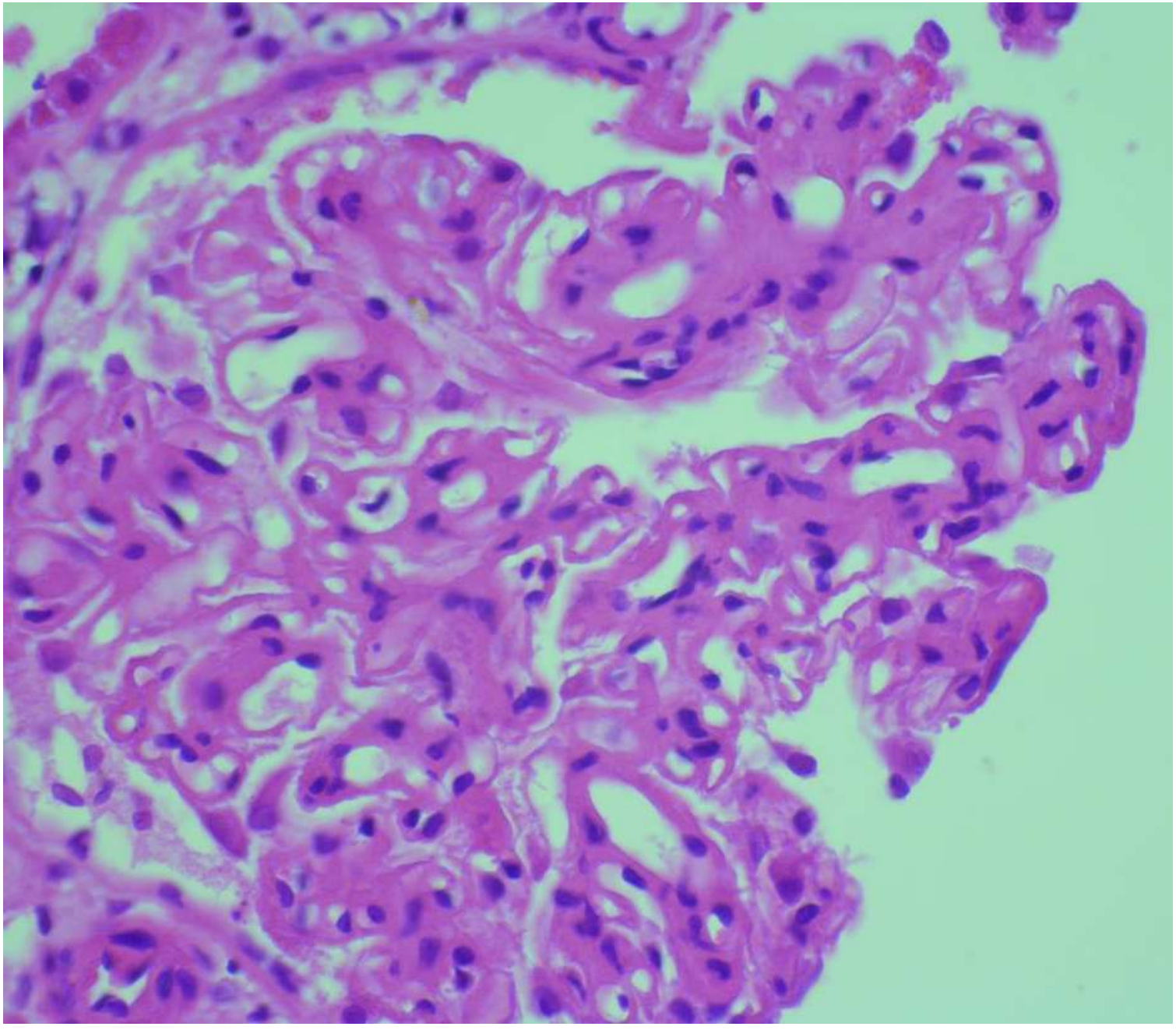
Cyclophosphamide/iv methylprednisolone + oral prednisolone

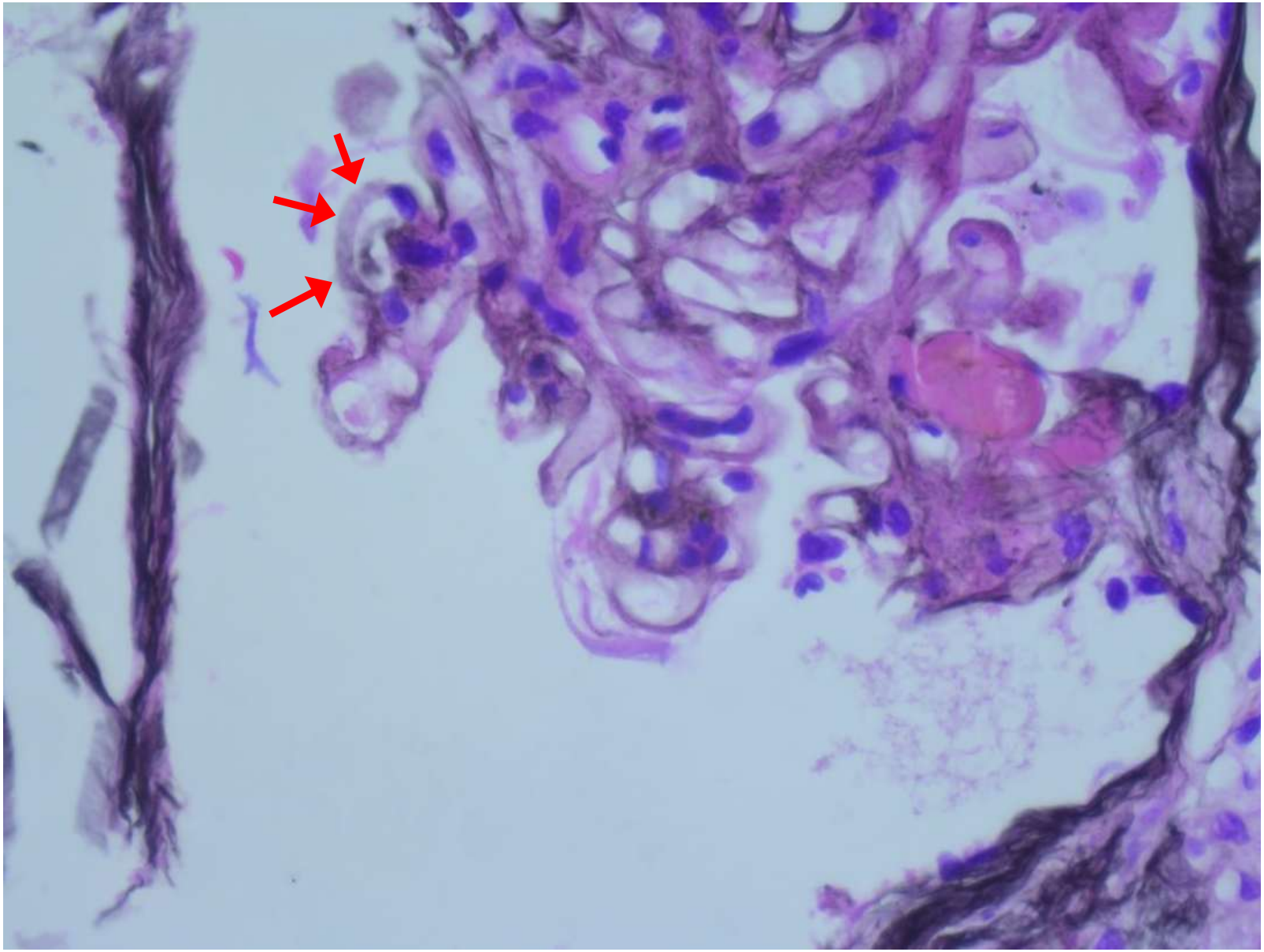
Rituximab 1 g x2











Silver stain:

No spikes!

Conclusions

- We can now specifically test for primary MN
  - But clinical history and biopsy are still important
- Drug treatment options haven't changed much
  - But one of them should work in most patients

Thank you

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