Curbside consultation: Challenging Lupus Nephritis Cases

Meghan Sise, MD, MS

Director of Onconephrology

MGH Renal Division

27yoF w hematuria/proteinuria

- Previously healthy African American woman
- Recently sent to rheumatology for arthritis, leukopenia, low grade fevers

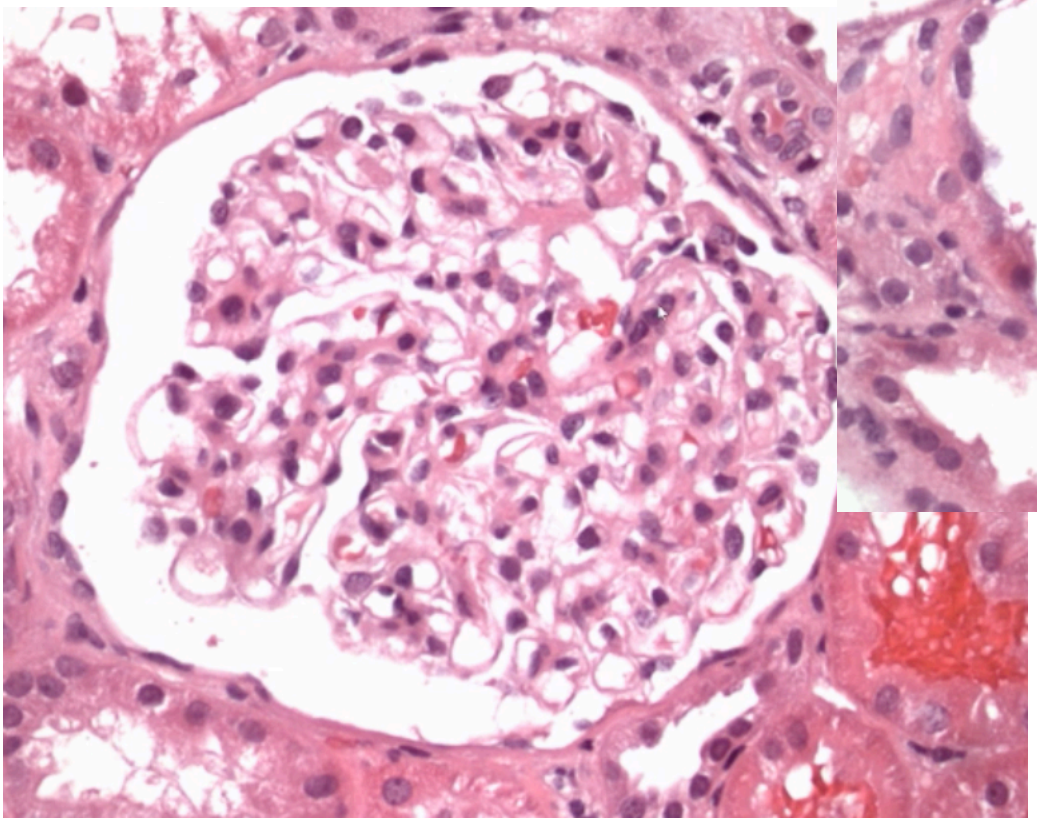
- AKI with creatinine 1.7mg/dL
- Urinalysis: sediment 85 RBC, WBC, few RBC casts
- 24 hour urine protein 1.2G/day
- Serum albumin 3.5
- ESR 120
- Low C3 C4
- ANA 1:160, Anti-DNA – 450 (<25)
- ANCA and anti-GBM negative

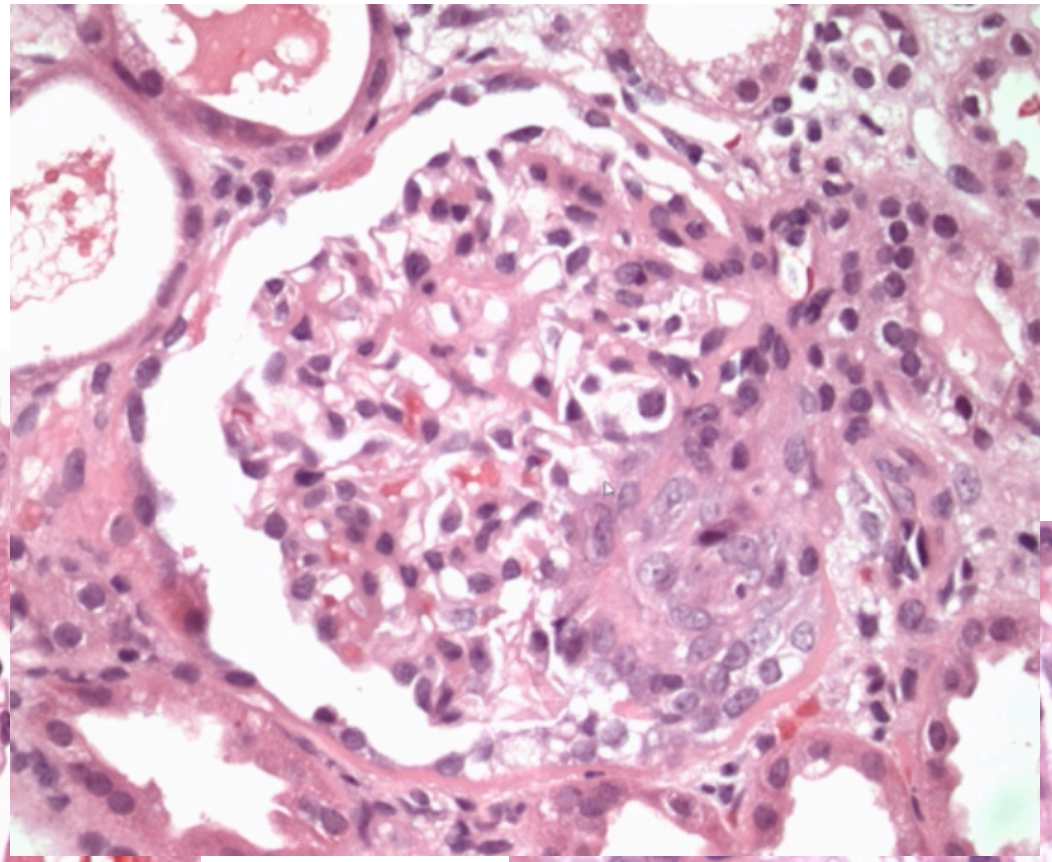
What do you expect to find on biopsy

- Could you treat without a biopsy

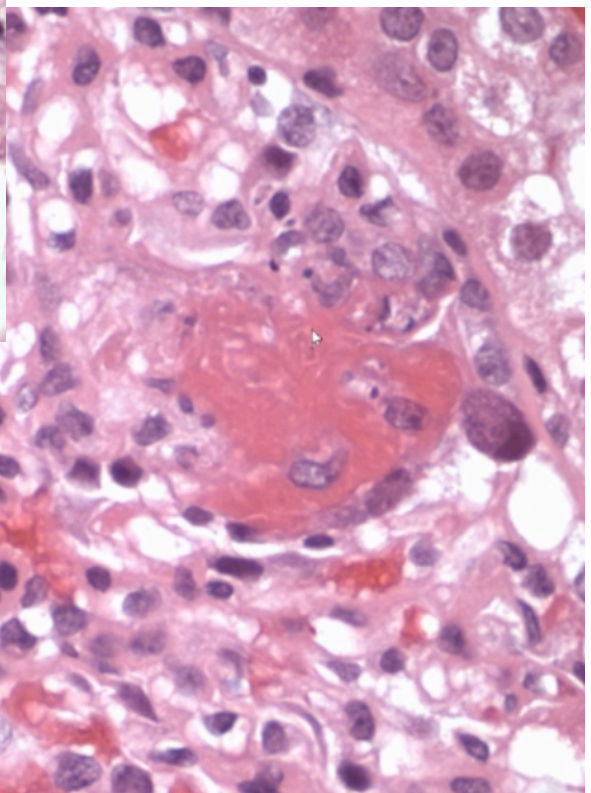
Why to do a biopsy

- Ensure no TMA / APLS
- Determine amount of crescents, especially with creatinine 1.7



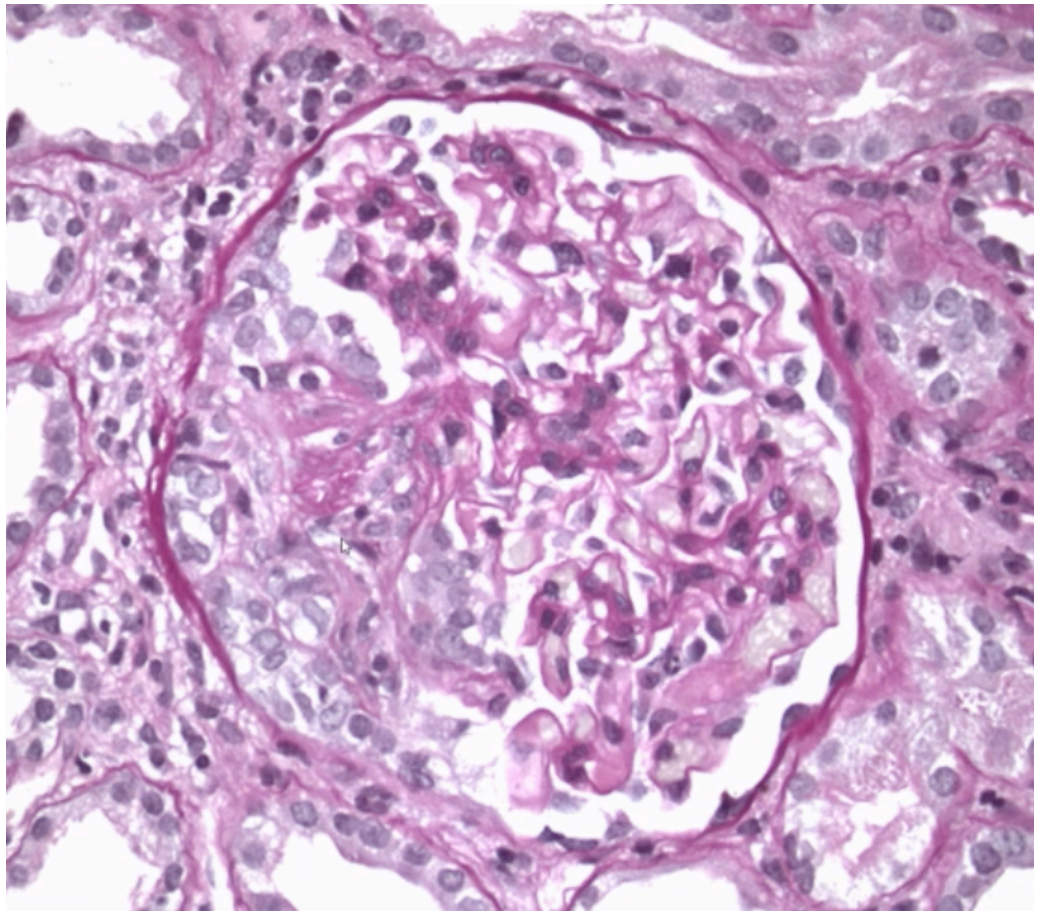


Segmental crescent

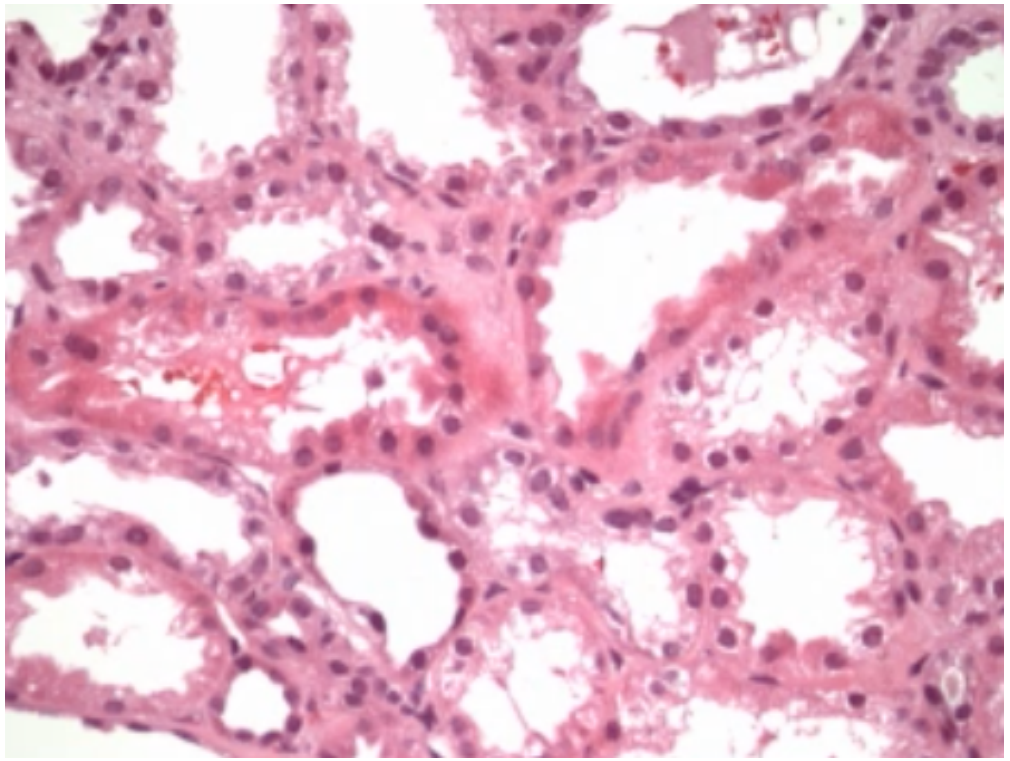


Fibrinoid necrosis

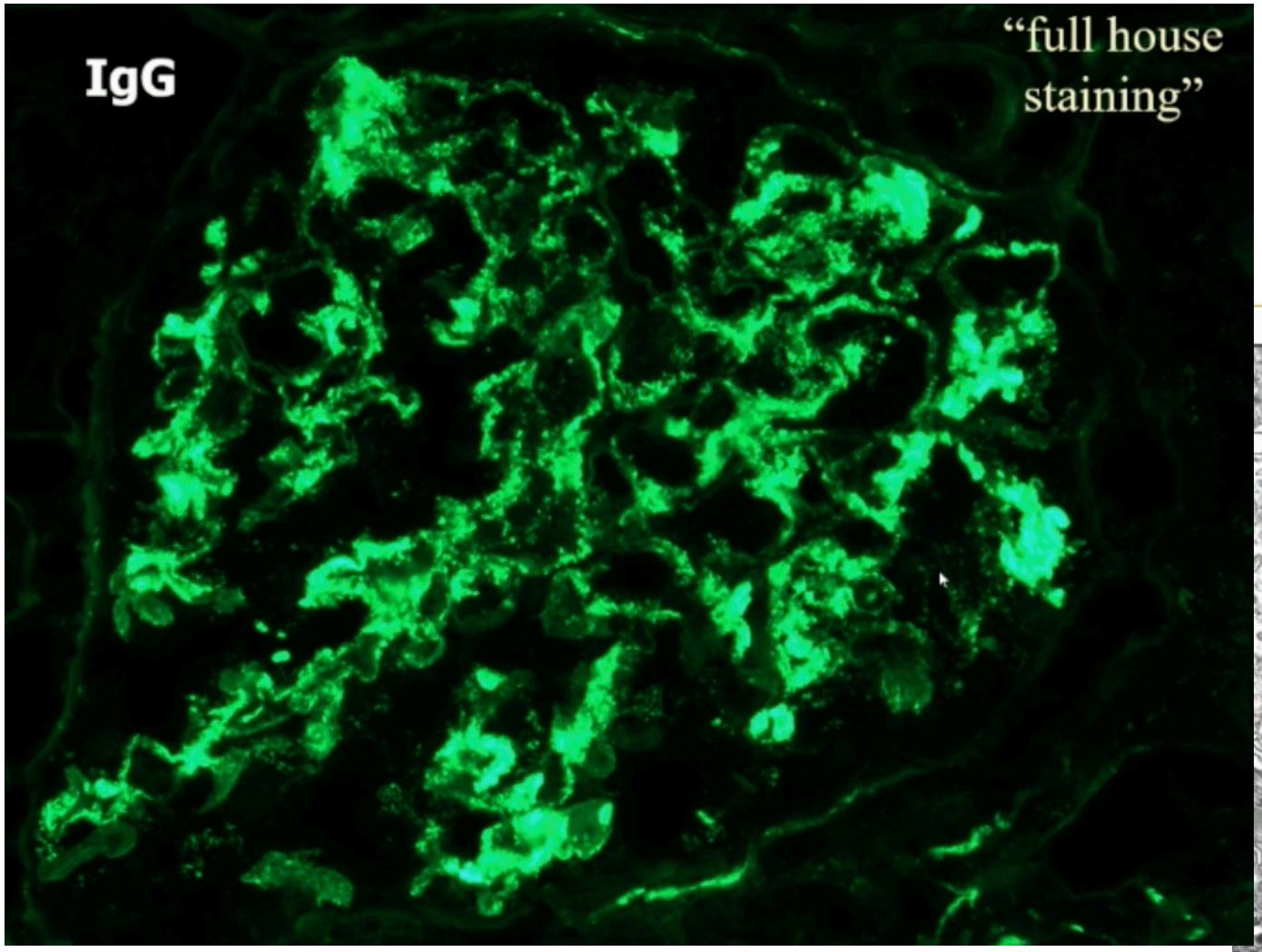
Courtesy of Glen Markowitz

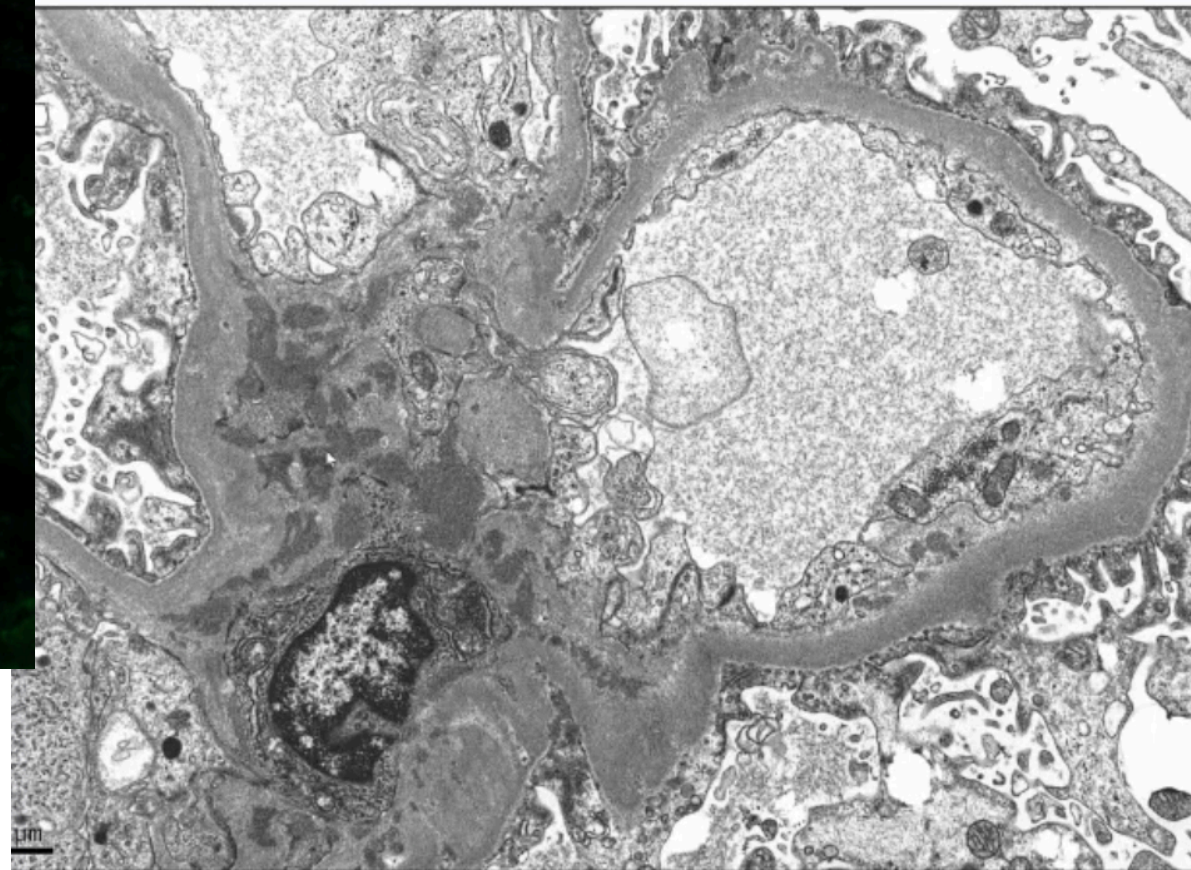


crescent



Acute tubular injury


IgG
“full house staining”


1µm

Path diagnosis

- Diffuse mesangial and focal endocapillary proliferative GN with necrotizing features and cellular crescents
- Class III
- NIH activity index 8/24
- NIH chronicity index 0/12

NIH activity and chronicity indices	
Activity indices	**Score**
Endocapillary hypercellularity	0-3
Neutrophils / karyorrhexis	0-3
Hyaline deposits / wire loops	0-3
Fibrinoid necrosis	(0-3) x 2
Cellular or fibrocellular crescents	(0-3) x 2
Interstitial inflammation	0-3
Total score	__/12
Chronicity indices	
Global glomerulosclerosis	0-3
Fibrous crescents	0-3
Tubular atrophy	0-3
Interstitial fibrosis	0-3
Total score	__/12

Bajema, I.M., et al., Revision of the ISN/RPS classification for LN. KI, 2018.

Risk factors for poor outcome

Table 4| | Lupus nephritis patients at high risk for poor renal outcome (risk increases with the number of risk factors present)

Patient characteristics	Serologic characteristics	Histologic characteristics
• African or Hispanic ancestry	• Antiphospholipid antibodies or antiphospholipid syndrome	• Crescentic glomerulonephritis
• Male	• Persistent hypocomplementemia	• Thrombotic microangiopathy
• Pediatric onset	• High titer dsDNA antibodies	• Extensive tubulointerstitial damage
• Frequent relapses	• High titer C1q antibodies	
• Incomplete remission		
• Neuropsychiatric lupus		
• Proteinuria >4 g/d at diagnosis		

dsDNA, double-stranded DNA.

Rovin. KI. 2019

15-year risk of ESRD

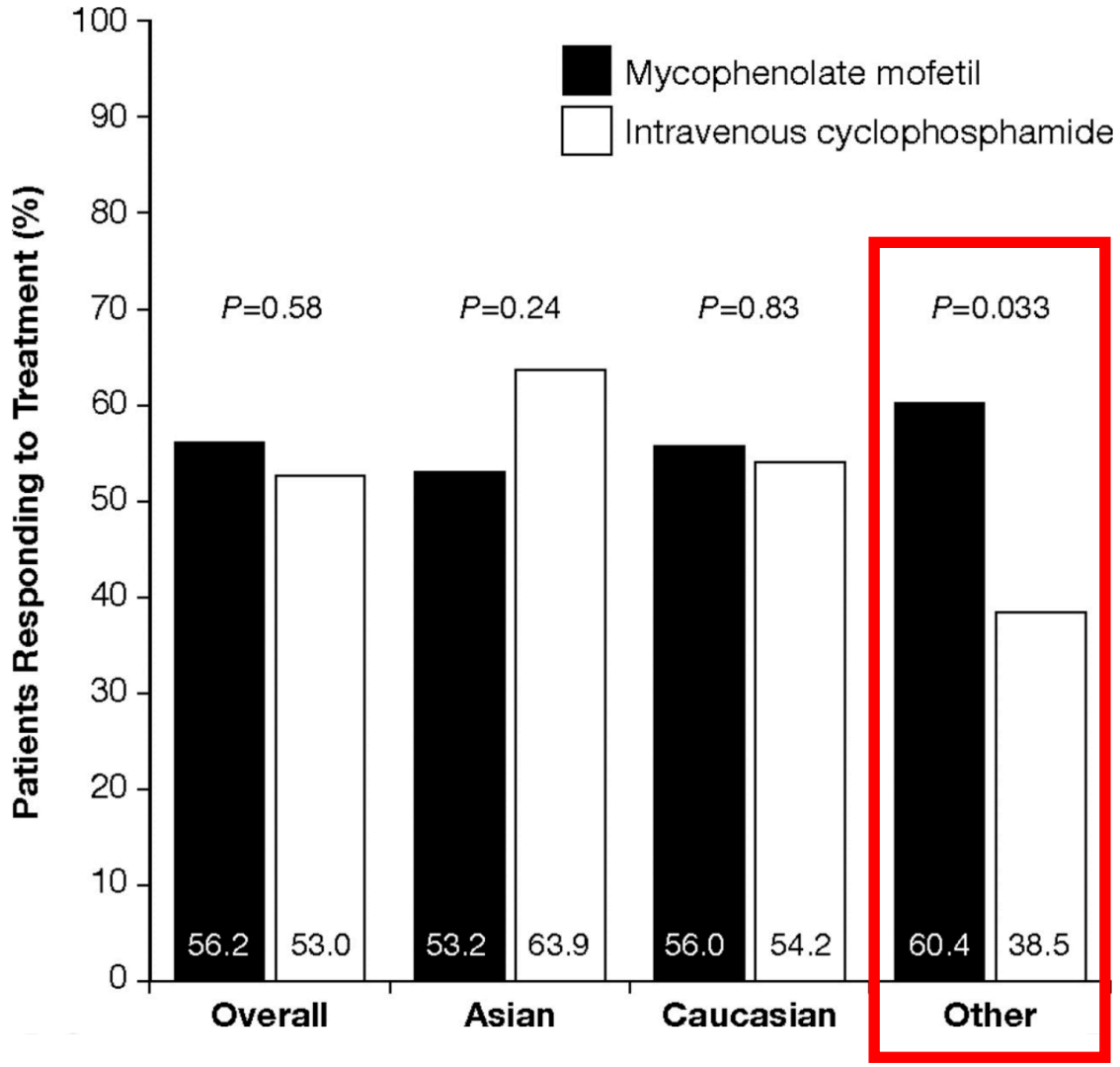
All Lupus nephritis

(11% at 5y, 17% at 10y)

Class IV Lupus

Tektonidou M.G. Risk of End-Stage Renal Disease in Patients With Lupus Nephritis, 1971-2015: A Systematic Review and Bayesian Meta-Analysis.*Arthritis Rheumatol.* 2016; **68**: 1432-1441

Subgroup based on race/ethnicity



Appel. JASN. 2009

A few thoughts about this case

- Why reviewing the biopsy is so important (hearing class 3 you may not think its so bad)
- Proteinuria is a poor surrogate for severity
  - Anything > 0.5 g/g is likely to be proliferative
- AA ancestry is a key demographic feature
  - MMF

How should the patient be treated

- Options:
  - Eurolupus (500mg q 2 weeks x 6 doses)
  - MMF 500mg BID → 1000mg BID → 1500mg BID
- Some may look at crescents and go for cyclophosphamide, but you really cant find a difference anywhere in the literature even for RPGN or crescentic GN
- Give a solumedrol pulse 500mg daily x 3 bc of crescents
- Try to taper pred to 5mg by 3mo

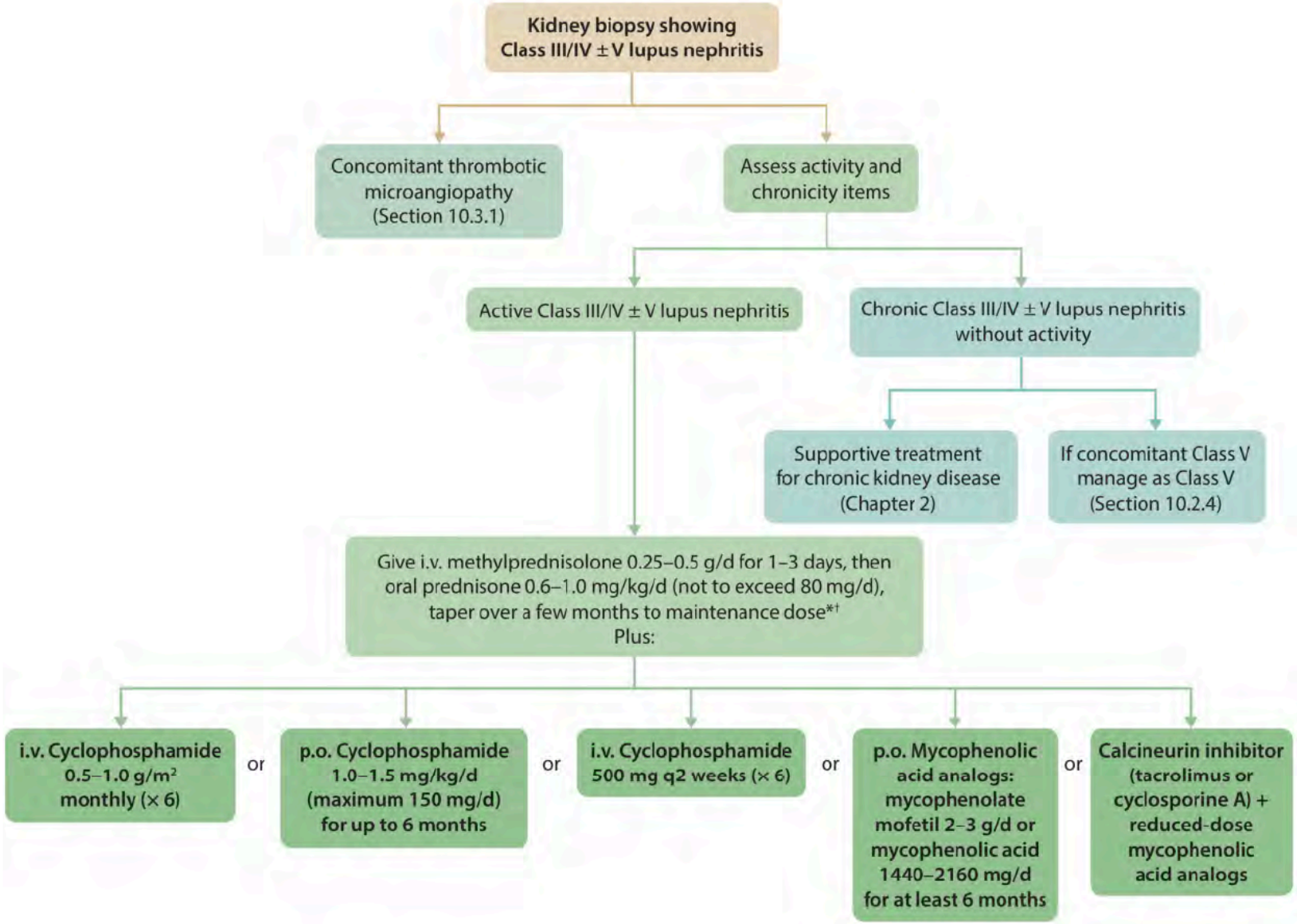
Choosing a steroid regimen

Table LN3. Example of corticosteroid regimens for LN

	Standard-dose scheme	Reduced-dose scheme
Methylprednisolone pulses	0.25–0.5 g/day × 3	0.25–0.5 g/day × 2–3
Oral prednisone equivalent		
Week 0–2	0.6–1.0 mg/kg (max 80 mg/day)	20–25 mg
Week 3–4	0.3–0.5 mg/kg	20 mg
Week 5–6	20 mg	15 mg
Week 7–8	15 mg	10 mg
Week 9–10	12.5 mg	7.5 mg
Week 11–12	10 mg	5 mg
Week > 12	5.0–7.5 mg	2.5 mg

Induction therapy for lupus

Figure LN3. Recommended approach for initial therapy of active Class III/IV LN



i.v., intravenous; p.o., oral

*Refer to Table LN3 for examples of corticosteroid treatment regimen

†Refer to Table LN4 for comments on cyclophosphamide regimens.

Cyclophosphamide vs. MMF – initial regimen

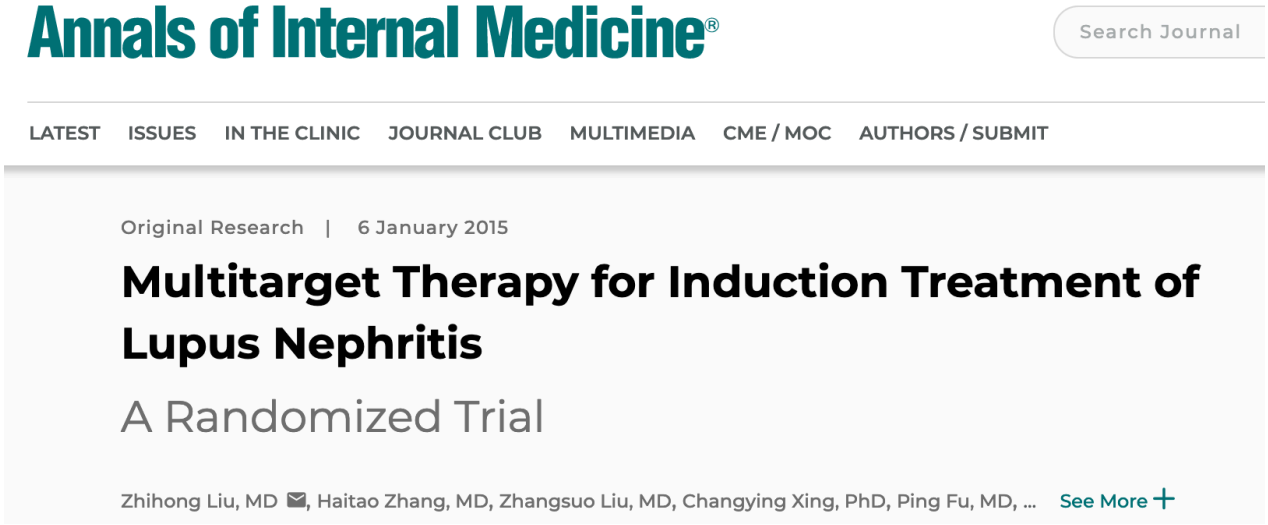
Favors IV Cytoxan

- Compliance issues

Favors MMF

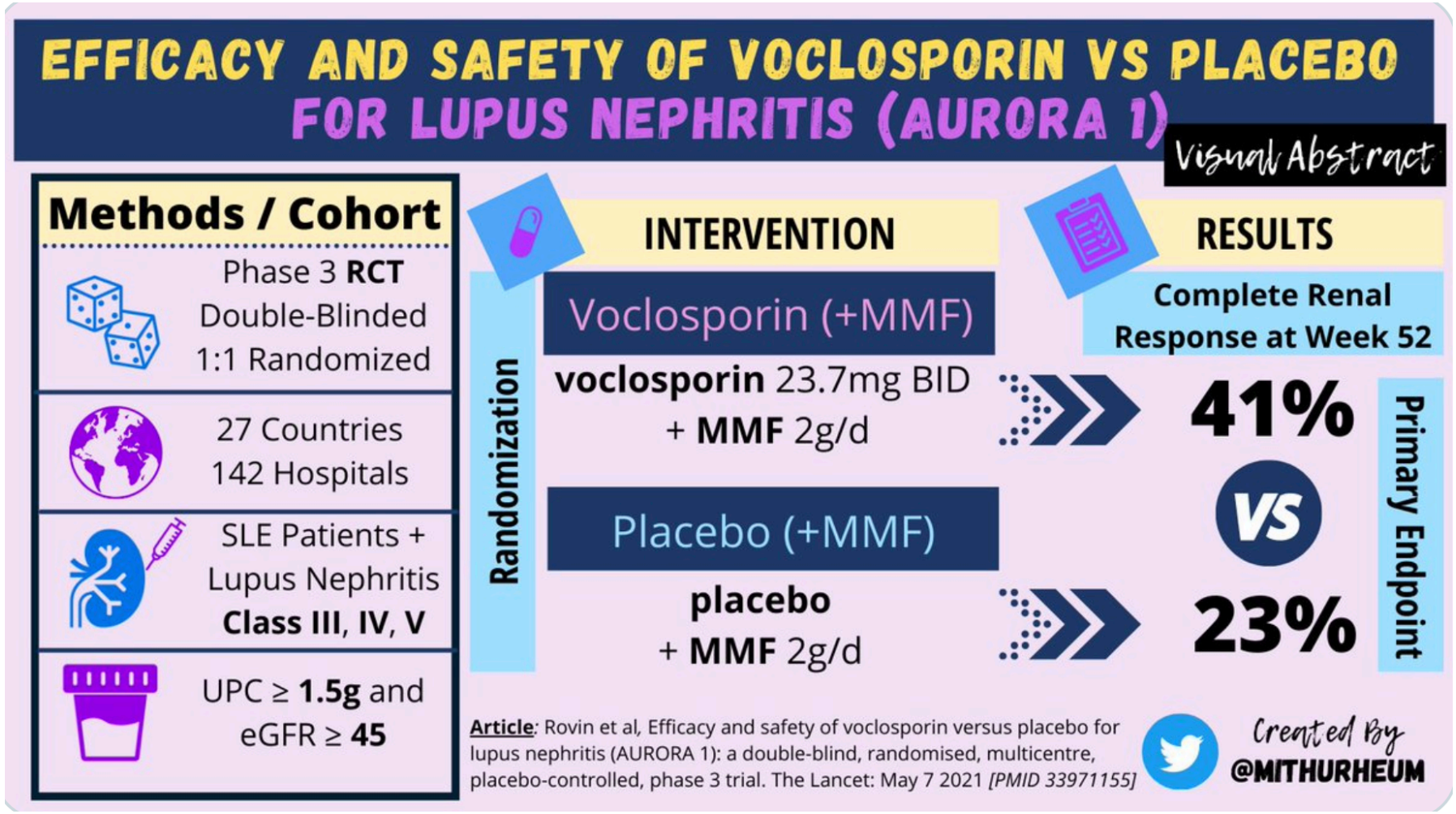
- non-white Race
- At risk for infertility
- Prior Cytoxan exposure

Multi-target therapy



- Tacrolimus, 4 mg/d, and mycophenolate mofetil, 1.0 g/d, versus intravenous cyclophosphamide with a starting dose of 0.75 (adjusted to 0.5 to 1.0) g/m^2 of body surface area every 4 weeks for 6 months.
- Both groups received 3 days of pulse methylprednisolone followed by a tapering course of oral prednisone therapy.
- complete response achieved by 45.9% subjects in the multitarget group compared with 25.6% ($p<0.001$)

Aurora-1 trial: Voclosporin – calcineurin inhibitor, reduces T cell immunity… may also stabilize podocytes



MMF dose 2g/d

25 mg/day to
5 mg/day by week
8 and 2.5 mg/day
by week 16

MMF superior to Aza for maintenance

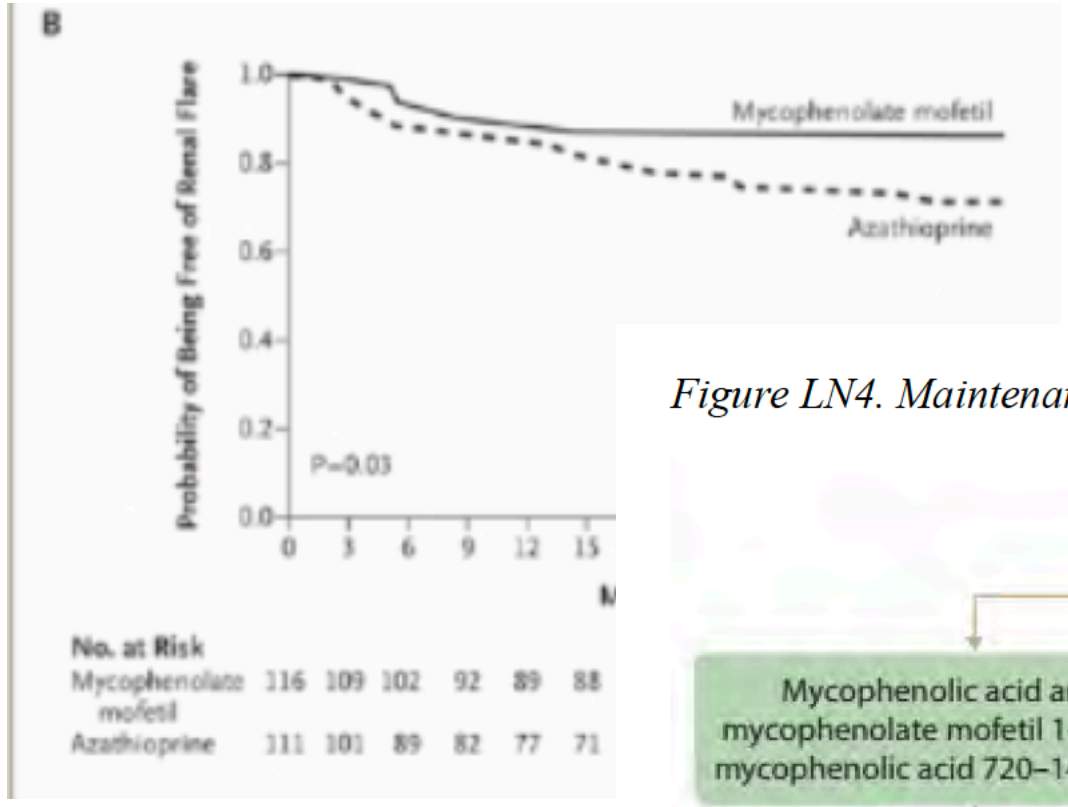
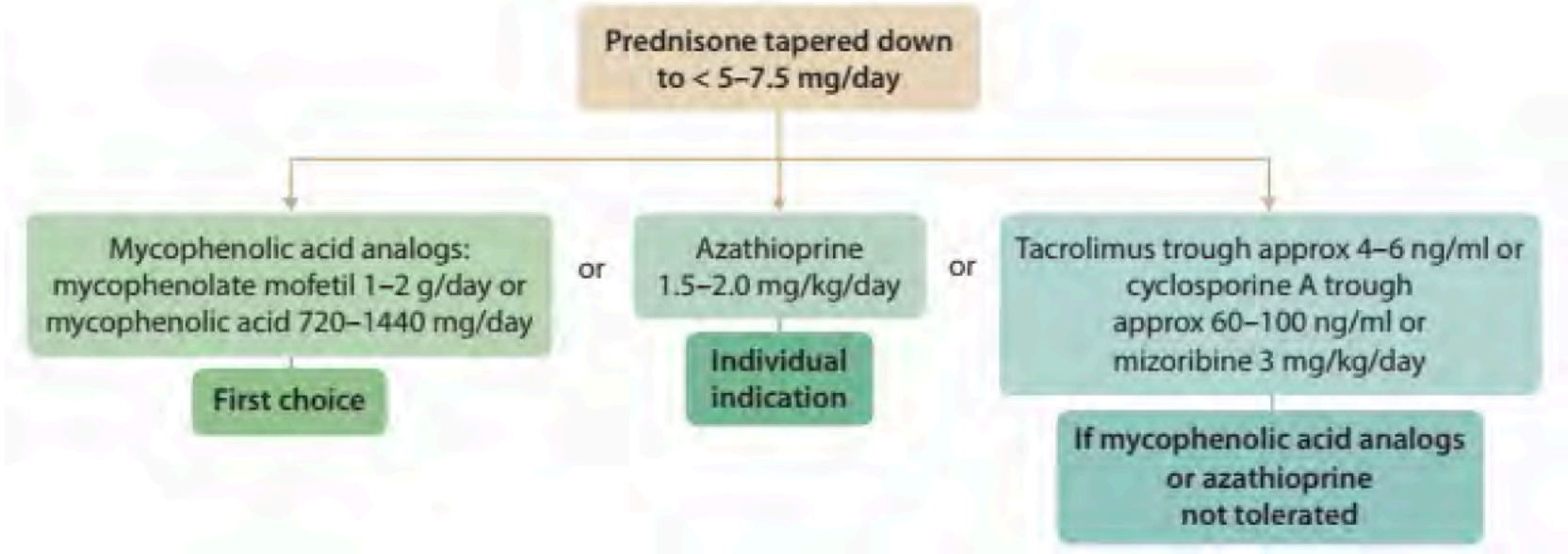


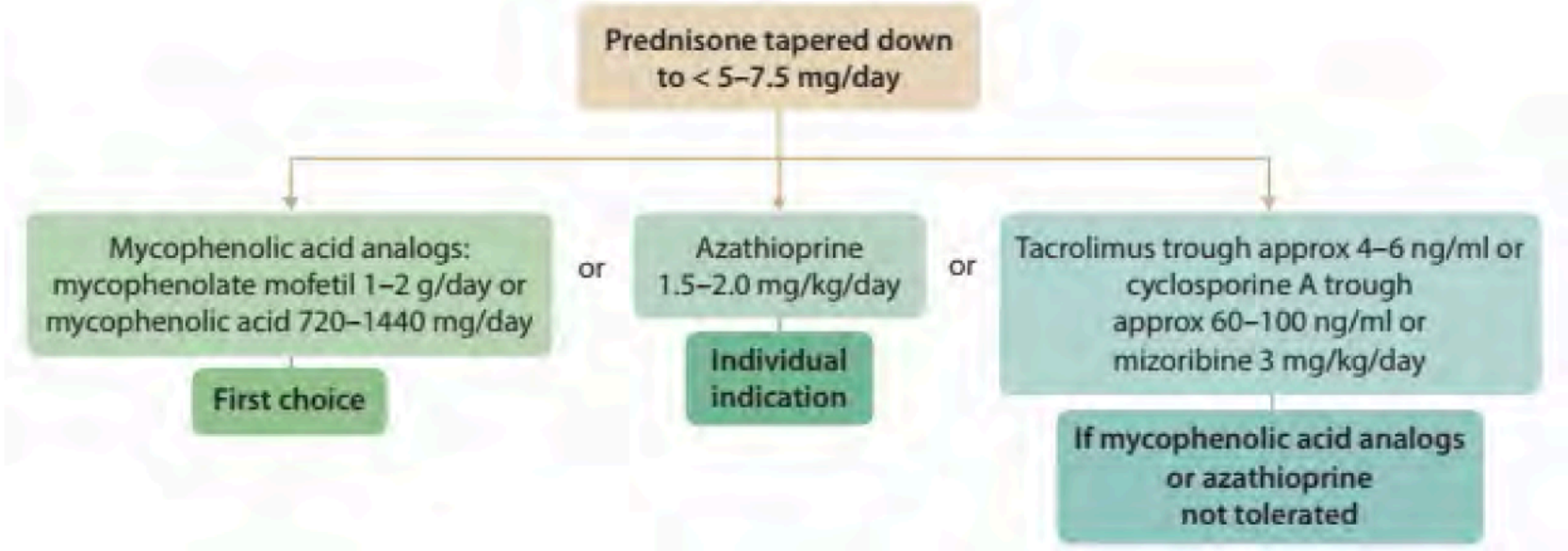
Figure LN4. Maintenance therapy for Class III and Class IV LN



Excepting for a planned pregna

MMF superior to Aza for maintenance

Figure LN4. Maintenance therapy for Class III and Class IV LN



Excepting for a planned pregnancy, MMF should be agent for maintenance

This patients case

- Given prednisone 60mg daily and MMF 1.5G BID
- PCP prophylaxis?

PCP prophylaxis in lupus

- Bactrim >> Atovaquone for actually preventing PCP
- But Bactrim in lupus is controversial:
  - 31% reported allergy (mostly rash) to sulfonamide and 20% also reporting worsening of SLE with the drug intolerance (N=221, US)
  - Allergy/intolerance in 9.4% of SLE patients given prophylaxis (N=132, Thailand)
  - Allergy/intolerance in 41% compared to 10% w gradual exposure (N=59, Japan)

Petri M J Rheumatol 1992; 19: 265-269. Vananuvat P, Semin Arthritis Rheum 2011; 41: 497-502. Suyama Y, Mod Rheumatol 2016; 26: 557-561.

This patients case

- Given prednisone 60mg daily and MMF 1.5G BID
- Atovaquone for first 2 months*
- At 6 months
  - Creatinine 0.8
  - UPC 0.16
  - Bland UA
  - Normalization of complements
- Stable at 12mo on MMF 1500mg BID
  - Creatine 0.9
  - UPC 0.18

What happened

- MMF lowered to 1000mg BID x 6mo, 750mg BID x 6mo, then 500mg BID x 3 more years.
- My practice is to continue 1000mg BID x 3 years

Practice Point 10.2.3.2.3. The dose of MMF in the early maintenance phase is approximately 750 to 1000 mg twice daily, and for MPA, approximately 540 to 720 mg twice daily.

Practice Point 10.2.3.2.5. The total duration of initial immunosuppression plus combination maintenance immunosuppression for proliferative LN should not be less than 36 months.

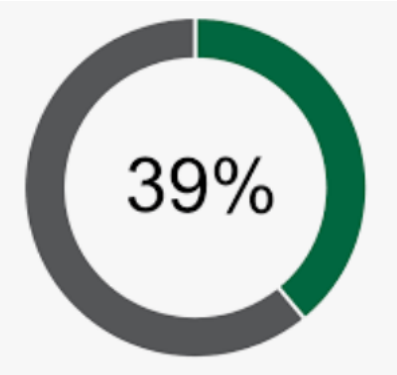
What happened…

- At the 4-year mark (on MMF 500mg BID), she came for routine followup, noting slight LE edema

  - UA: 3+ protein, some RBCs, no casts
  - Albumin 2.1
  - UPC 3G/g
  - Creatinine 0.9
  - DSDNA 180
  - Normal complements

She’s relapsing!

- Relapses occur in 39% of patients who have a complete response, median time is 36mo



  - (more relapses and sooner if you only get a partial response!)

- Illei GG, Austin HA, Crane M, et al. Combination therapy with pulse cyclophosphamide plus pulse methylprednisolone improves long-term renal outcome without adding toxicity in patients with lupus nephritis. Ann Intern Med 2001; 135: 248-257.

What if you HAD to treat empirically?

- Ie. if she refused a biopsy?

What if you HAD to treat empirically?

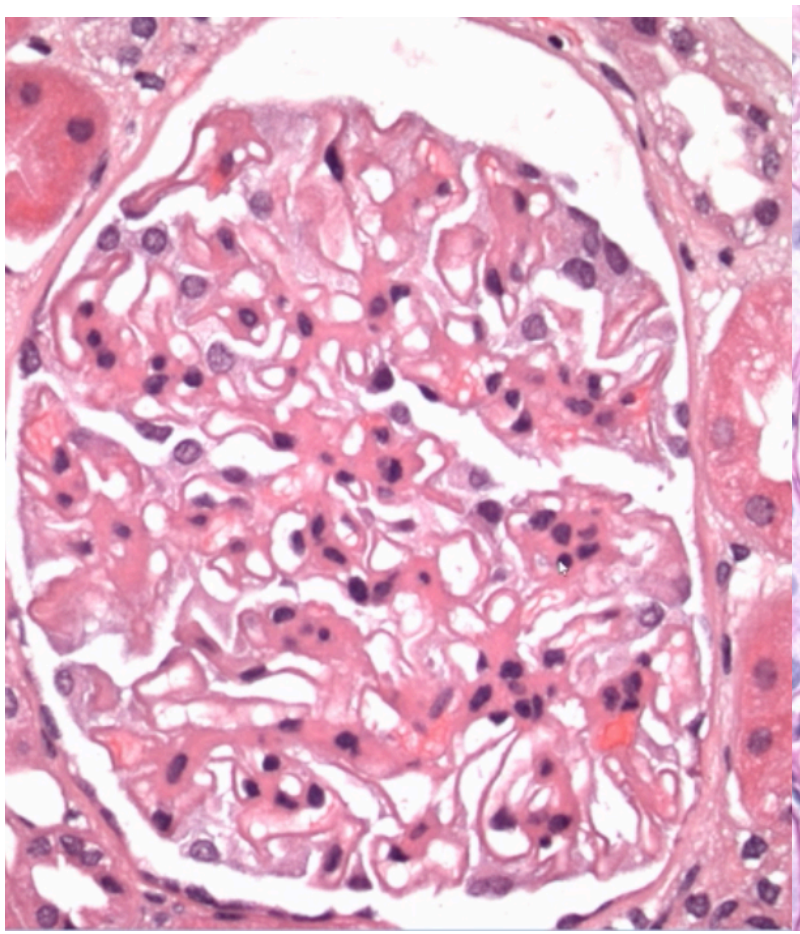
- Ie. if she refused a biopsy?

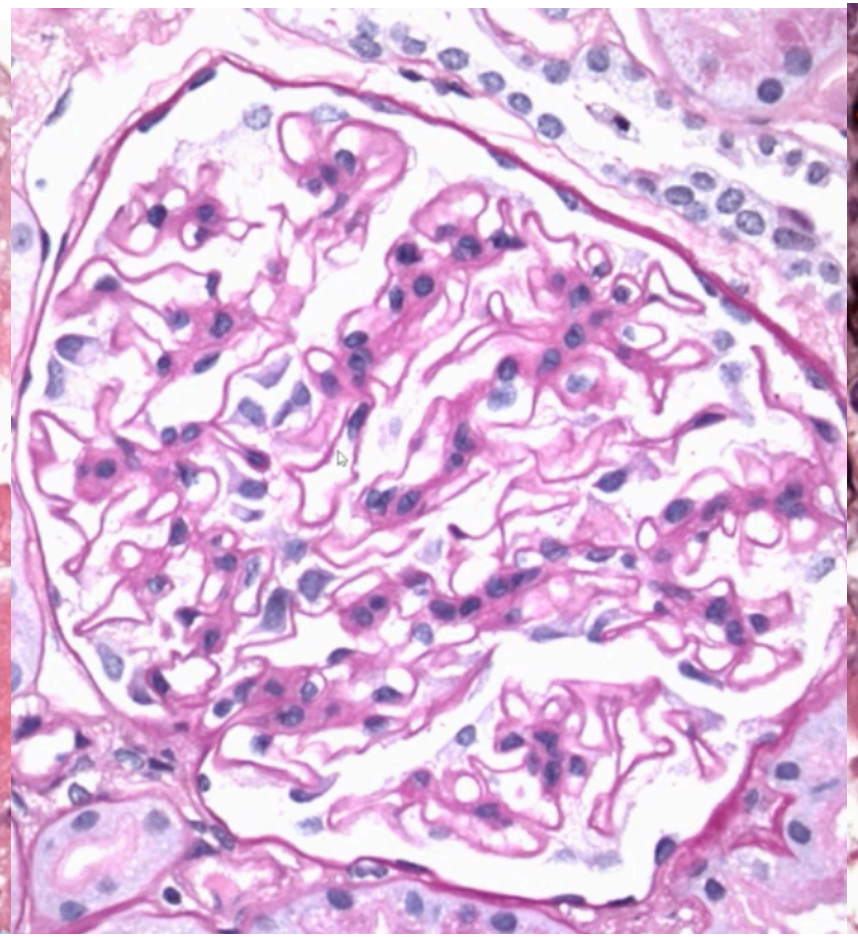
- Options
  - MMF back to MMF 1.5mg BID
  - Reinduce with Cytoxan
  - MMF +/- second agent (CNI, Rituximab)

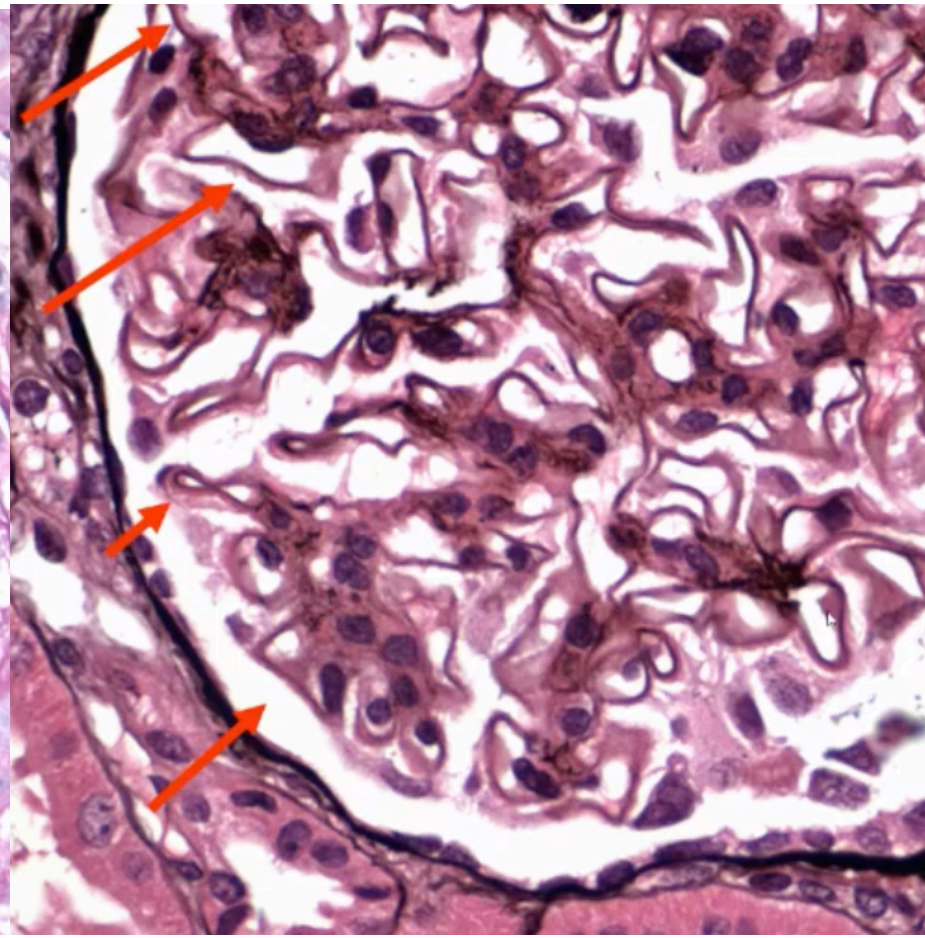
Initially she refused a biopsy

- 12 weeks later, labs unchanged on MMF 1.5G BID
  - (Generally relapses are treated with the same induction regimen)
- Patient agreed to biopsy
  - (This isn’t long enough to see a response, but we had wanted the biopsy in the first place so we went for it!!)

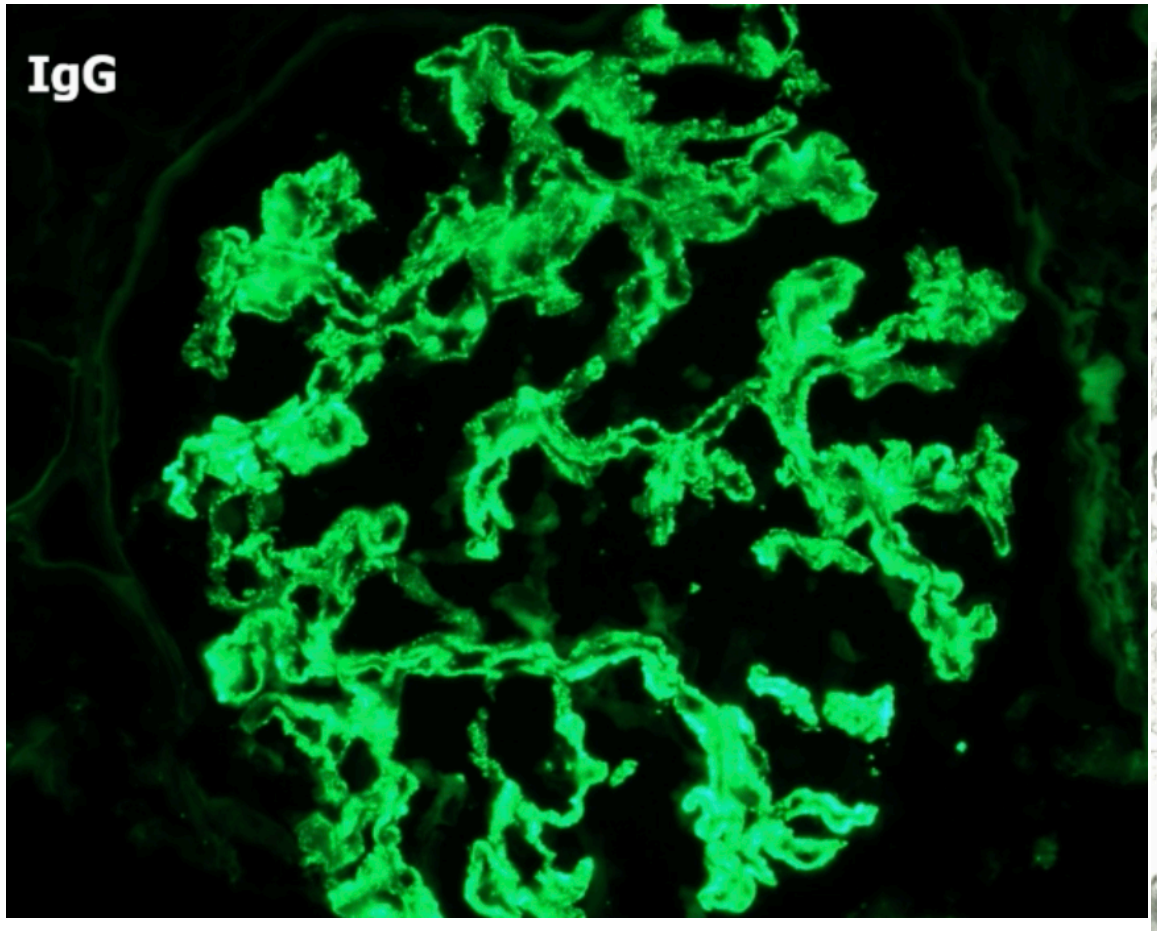
Repeat biopsy findings

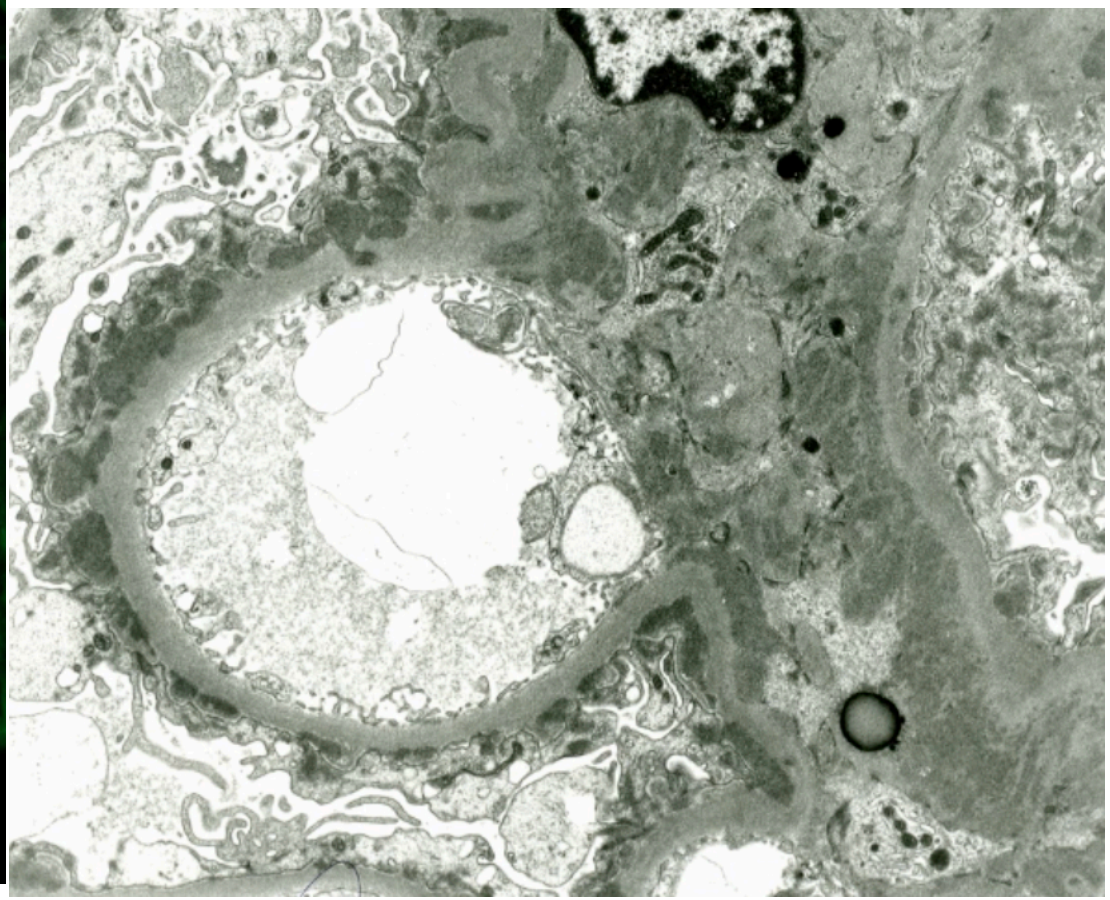






Granular peripheral capillary wall staining



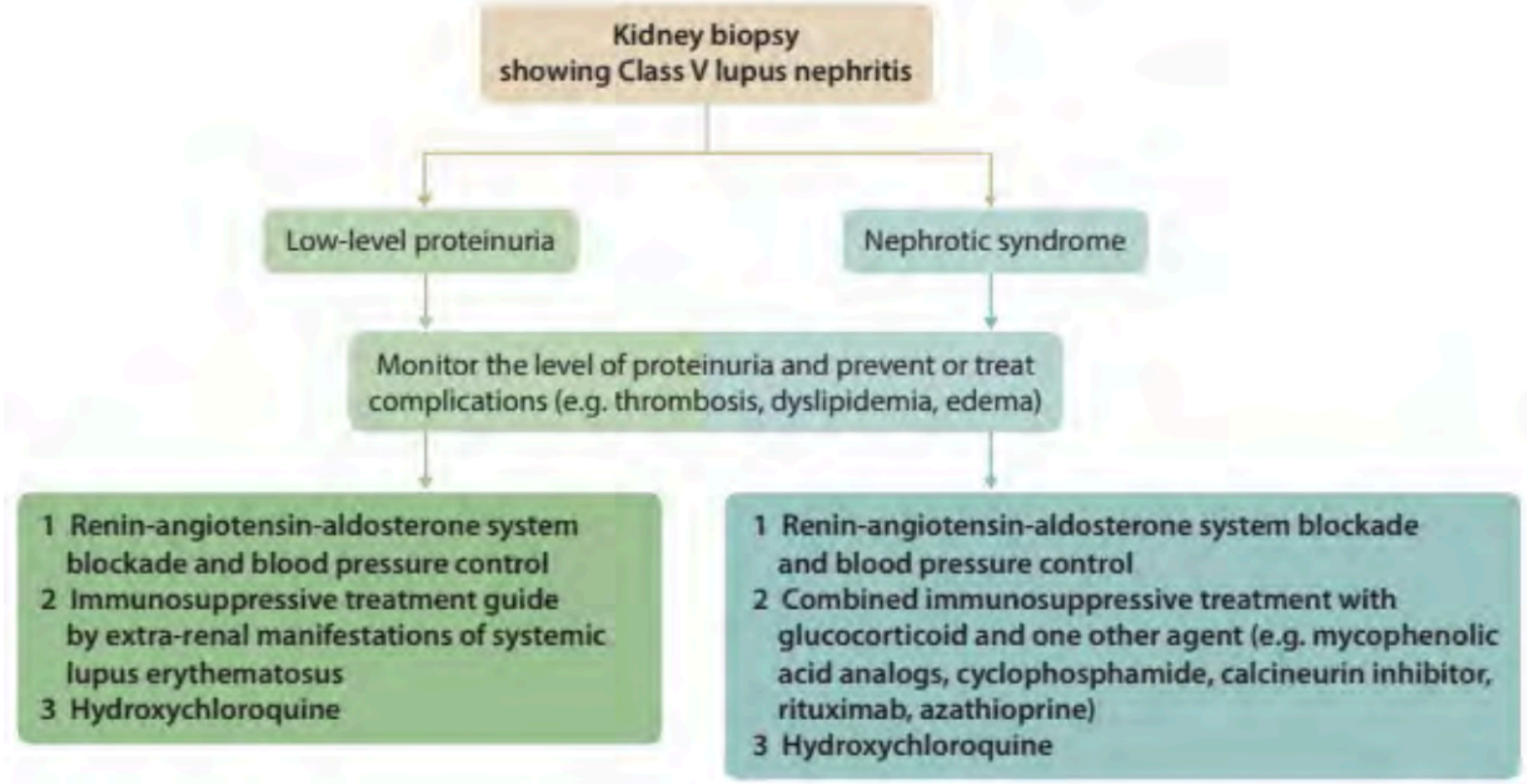


Final diagnosis

- Membranous lupus nephritis
- How do you treat a pure class V membranous lupus nephritis?

Class V lupus is an understudied disease, often gets lumped in to trials with proliferative disease

Figure LN5. Management of patients with pure Class V LN



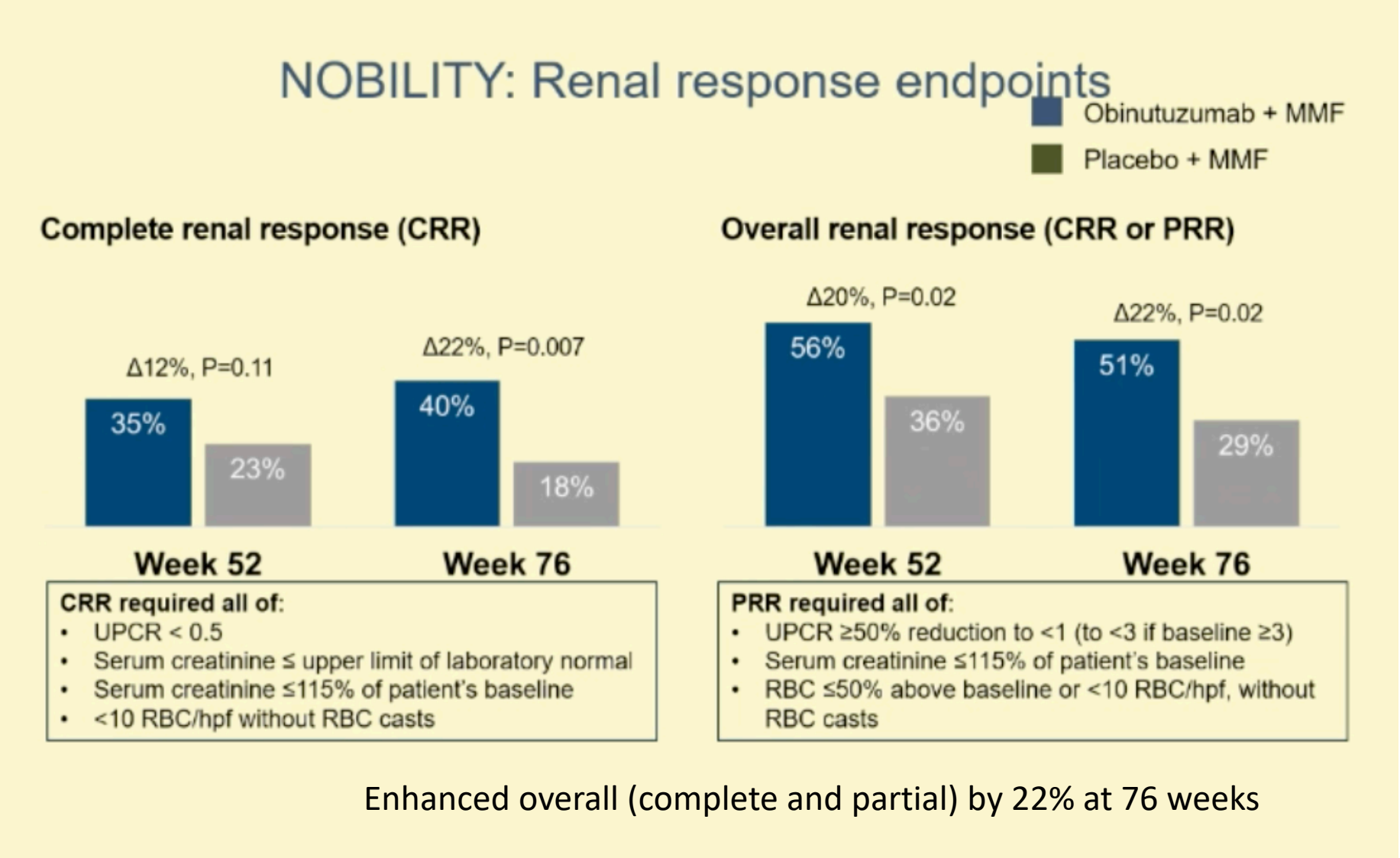
Options for this patient

- Stay the course (12 weeks isn't really enough to assess response)
  - Membranous can take a long time to resolve
- Add in a CNI (tacrolimus) – targeting level of 5-8
  - If adding CNI I would lower the MMF (500mg qDay or BID)
- No real data for Rituxan in class V
- Don't yet have data for belimumab in class V

New treatments for Lupus nephritis

- A good year for lupus nephritis trials

Obinutuzumab – anti CD20



Enhanced overall (complete and partial) by 22% at 76 weeks

Belimumab

2 year trial of belimumuab + standard of care of induction (>400 patients). (Belimumab selectively binds to soluble human B lymphocyte stimulator protein (BLyS))

Belimumab or placebo on days 1 (baseline), 15, and 29 and every 28 days thereafter to week 100, with final assessments at week 104.

Stratified by race and induction regimen (only 14% black patients enrolled)

PERR – UPC ≤0.7, GFR no worse than 20% below the value before the renal flare (pre-flare value) or ≥60, no use of rescue therapy

CRR(UPC <0.5, eGFR within 10% pre-flare value or ≥90, no use of rescue therapy)

Additive value in subgroup appeared restricted to MMF

Concerns about the much lower response rates compared to historical data

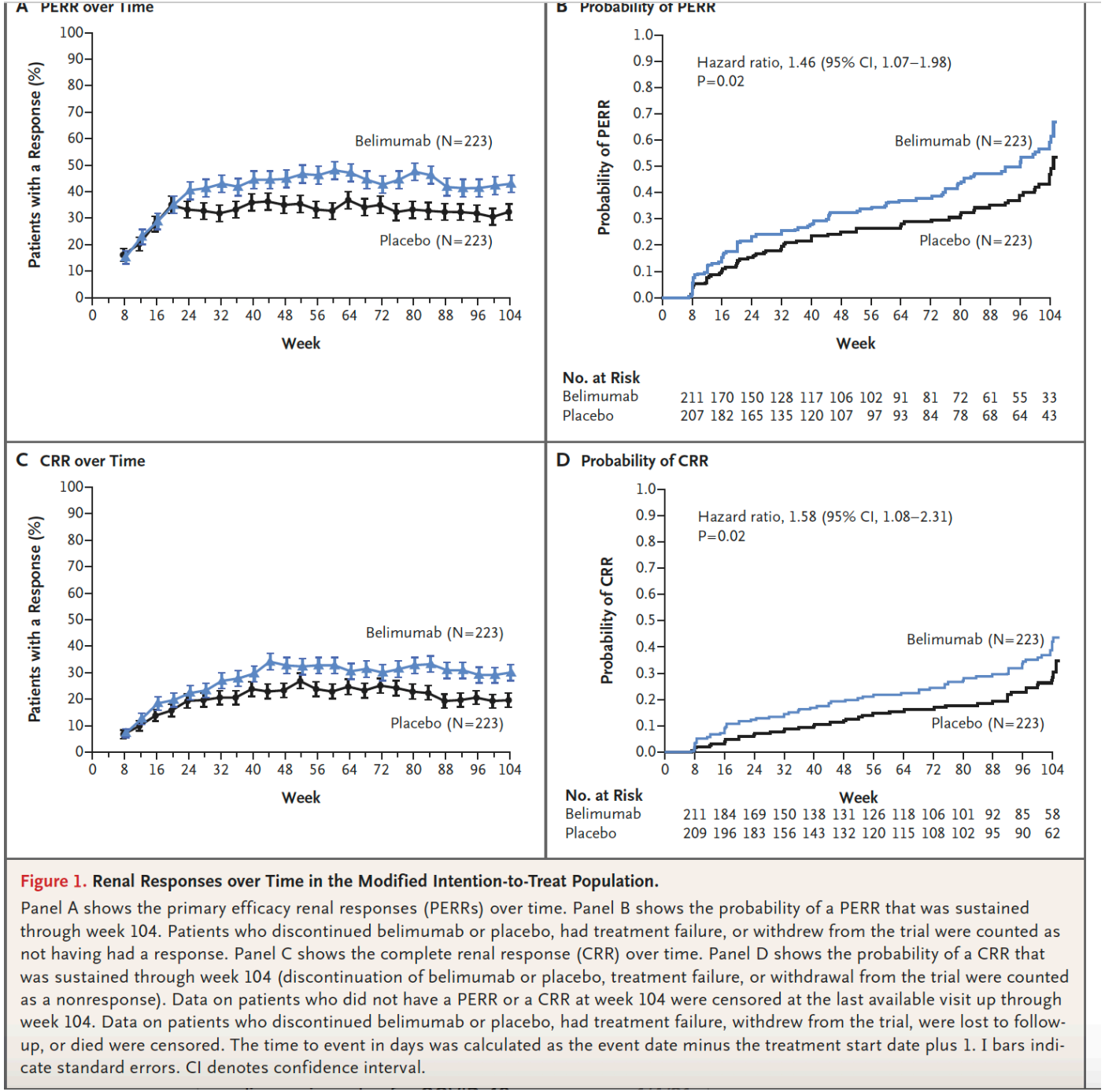


Figure 1. Renal Responses over Time in the Modified Intention-to-Treat Population.

Panel A shows the primary efficacy renal responses (PERRs) over time. Panel B shows the probability of a PERR that was sustained through week 104. Patients who discontinued belimumab or placebo, had treatment failure, or withdrew from the trial were counted as not having had a response. Panel C shows the complete renal response (CRR) over time. Panel D shows the probability of a CRR that was sustained through week 104 (discontinuation of belimumab or placebo, treatment failure, or withdrawal from the trial were counted as a nonresponse). Data on patients who did not have a PERR or a CRR at week 104 were censored at the last available visit up through week 104. Data on patients who discontinued belimumab or placebo, had treatment failure, withdrew from the trial, were lost to follow-up, or died were censored. The time to event in days was calculated as the event date minus the treatment start date plus 1. I bars indicate standard errors. CI denotes confidence interval.

Belimumab opinions?

- Should it be used exactly as listed in study?

- Should it be used for refractory cases?
  - **Atisha-fregoso Y.** CALIBRATE *Arthritis Rheumatol.* 2020, n=43 negative in refractory or recurrent LN

- Awaiting results of EMBRACE study – will study belimumab in black patients, >500 enrolled (NCT01632241)

Too old to be lupus?

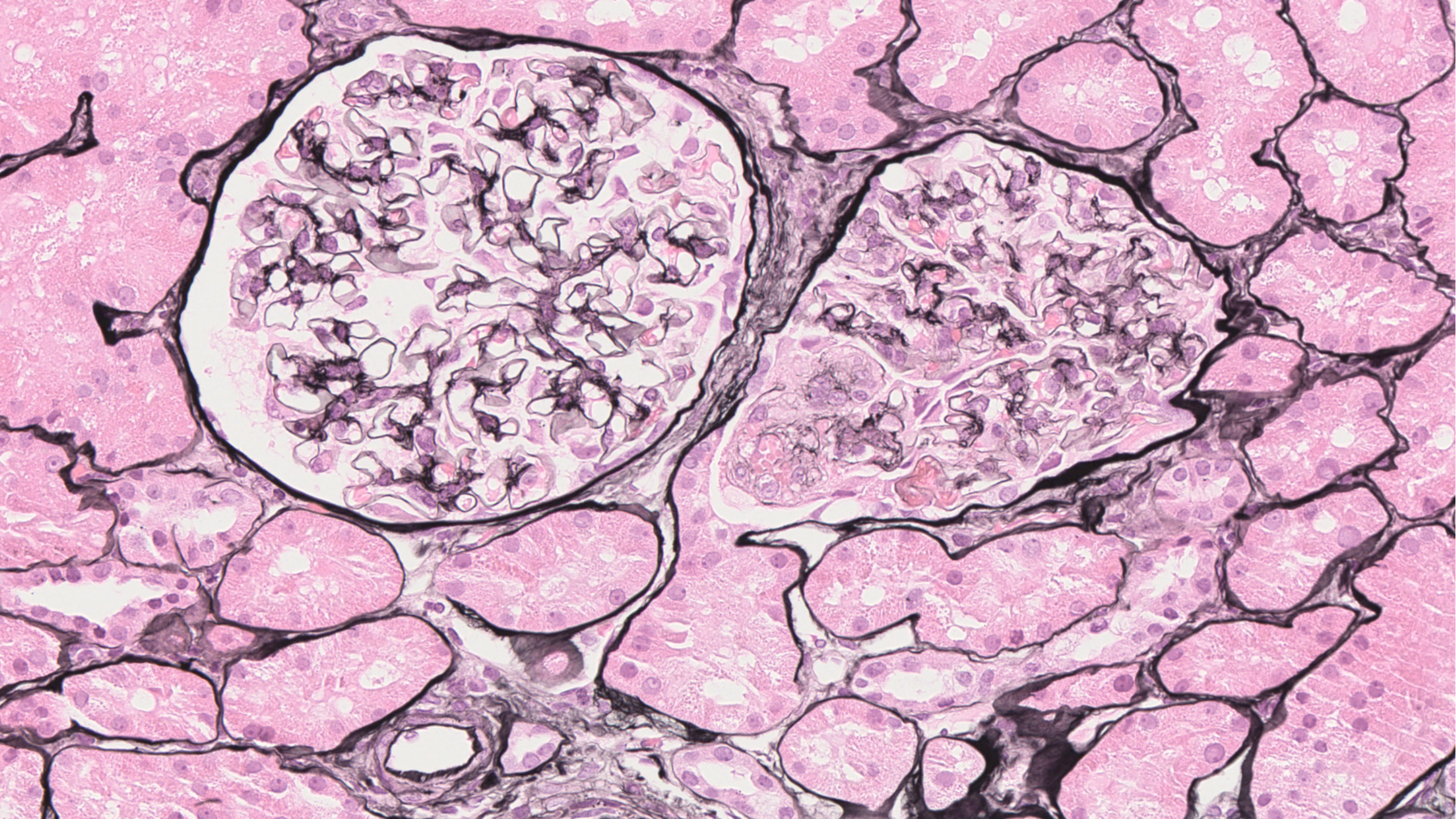
- 75 yo F with two years of arthralgias (wrists, fingers, knees), 4 months of worsening morning stiffness and fatigue and 10lb weight loss.

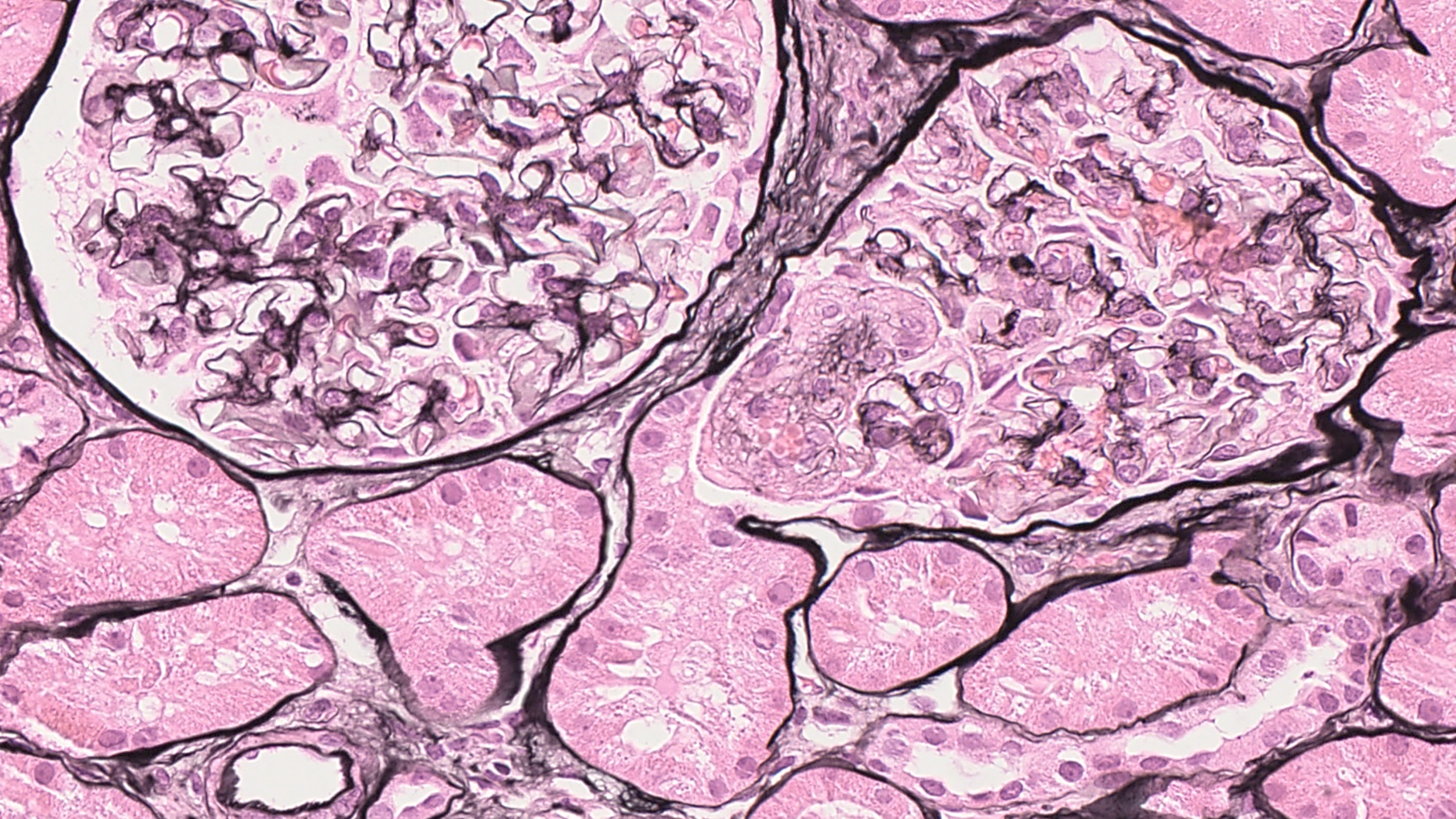
- Recent diagnosis of of infectious colitis, treated with cipro and flagyl with resolution and a follow-up colonoscopy showing resolutioin fo colitis, notable diverticulosis, and one small polyp that was resected

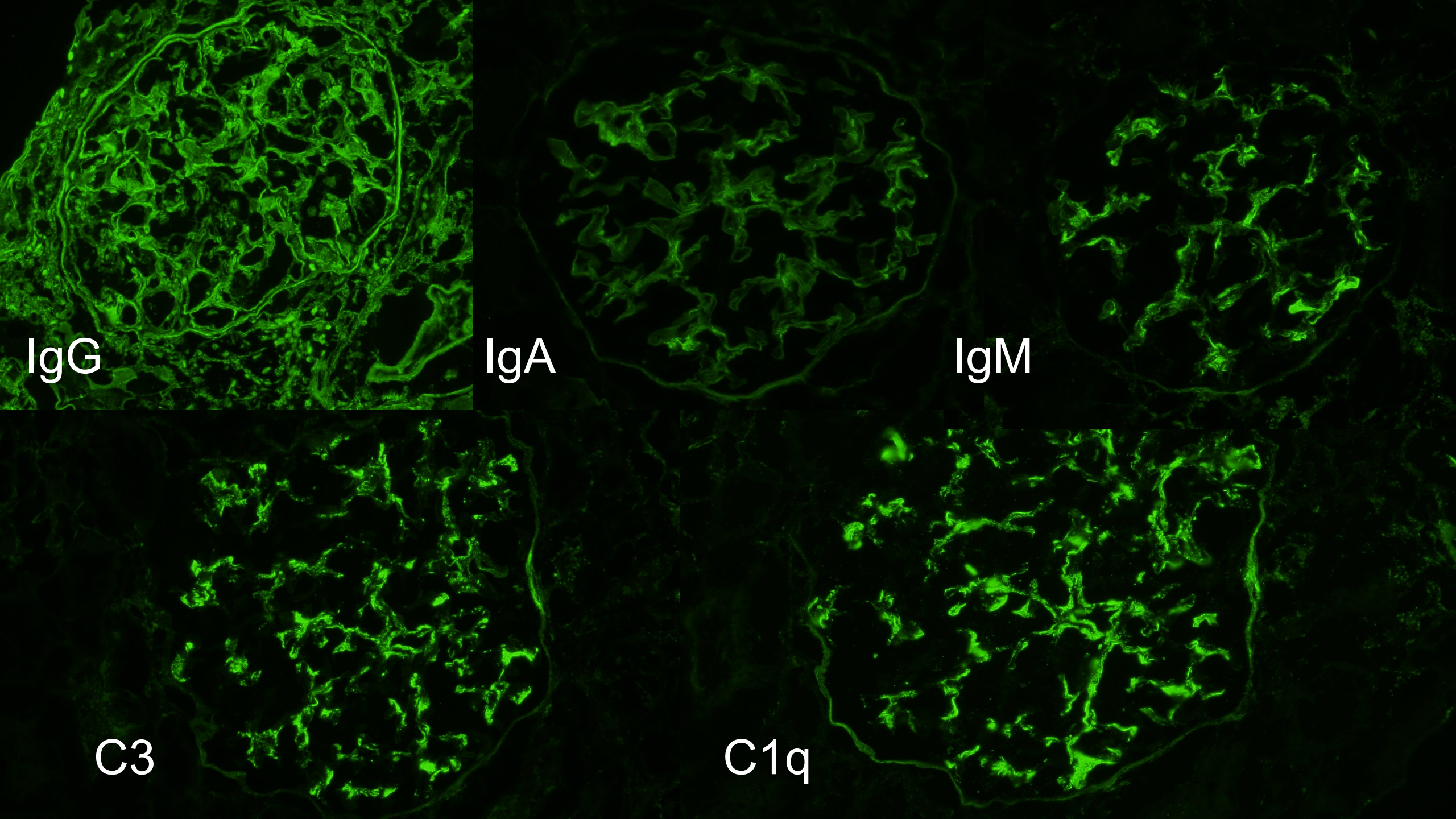
- Physical exam: BP 156/90, well appearing, normal CV exam, no rash or edema edema.

Too old to be lupus?

- Laboratory workup notable for:
  - Creatinine 0.6
  - ANA 1:5120, DSDNA 1:320
  - Positive: Anti-Sm, Anti-RNP, Anti-histone, Rheumatoid factor
  - Negative/Noral ANCA, SPEP, CCP
  - Low C3/C4
  - UA: 1+ proteinuria, negative for RBC or WBC
  - UPC (repeated) showed 0.85g/g spot protein/creatinine






IgG
IgA
IgM
C3
C1q

Diagnosis

Lupus nephritis, Class III (Focal lupus nephritis)

Activity: 1/24
Chronicity: 1/12

6% global glomerulosclerosis (2/35)
5% interstitial fibrosis and tubular atrophy

Aura trial: placebo group

AURA PLACEBO	ALMS	BELONG PLACEBO
MMF 2G/D Pred 25mg/d	MMF 3G/D Pred 60mg/d	MMF 3G/D Pred 0.5-0.75mg/kg/d
23.9% CR <500mg/d	23.8% CR <500mg/d	40% CR <500mg/d

Interesting analyses on induction

- The propensity analysis identified 63 matched pairs of patients derived from 370 in ALMS study and 88 patients enrolled in the

Table 5 Response to treatment in the 63 matched pairs of patients in ALMS and AURA

	ALMS			*AURA*			*AURA* vs. *ALMS*		
	n	N	%	n	N	%	*Odds ratio*	*(95% CI)*	p-*value*
Week 24 response[a]	34	63	54.0	28	63	44.4	0.68	(0.34, 1.38)	0.2857
Week 24 remission[b]	10	63	15.9	9	63	14.3	0.88	(0.33, 2.35)	0.8035
Week 24 partial remission[c]	34	63	54.0	31	63	49.2	0.83	(0.41, 1.66)	0.5932
C3 normalization, week 12[d]	15	55	27.3	13	56	23.2	0.81	(0.34, 1.90)	0.6628
C4 normalization, week 12[e]	25	55	45.5	18	56	32.1	0.57	(0.26, 1.23)	0.1516
C3 and C4 normalization, week 12	9	55	16.4	9	56	16.1	0.98	(0.36, 2.69)	0.9667
C3 or C4 normalization, week 12	31	55	56.4	22	56	39.3	0.50	(0.24, 1.07)	0.0731
C4 normalization, week 24[f]	19	47	40.4	5	42	11.9	0.20	(0.07, 0.60)	0.0041
Anti-dsDNA pos, ≥30 IU/ml, week 24	26	48	52.4	25	51	49.0	0.81	(0.37, 1.79)	0.6087
>25% decrease proteinuria, week 24	28	52	53.8	33	60	55.0	1.05	(0.50, 2.21)	0.9027
UPCR ≤ 1 at week 24	32	48	66.7	24	53	45.3	0.41	(0.18, 0.93)	0.0323

Choosing a steroid regimen

Table LN3. Example of corticosteroid regimens for LN

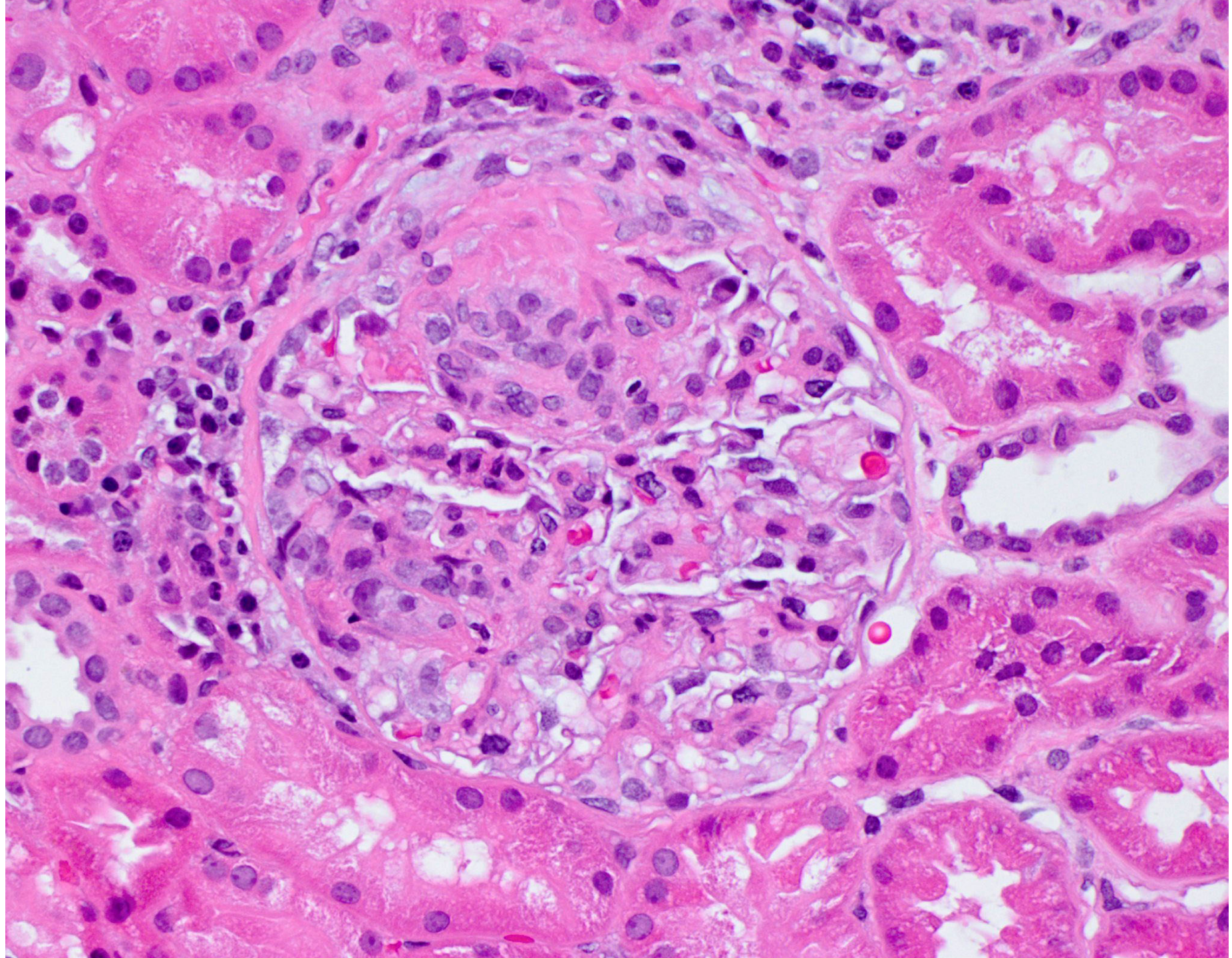
	Standard-dose scheme	Reduced-dose scheme
Methylprednisolone pulses	0.25–0.5 g/day × 3	0.25–0.5 g/day × 2–3
Oral prednisone equivalent		
Week 0–2	0.6–1.0 mg/kg (max 80 mg/day)	20–25 mg
Week 3–4	0.3–0.5 mg/kg	20 mg
Week 5–6	20 mg	15 mg
Week 7–8	15 mg	10 mg
Week 9–10	12.5 mg	7.5 mg
Week 11–12	10 mg	5 mg
Week > 12	5.0–7.5 mg	2.5 mg

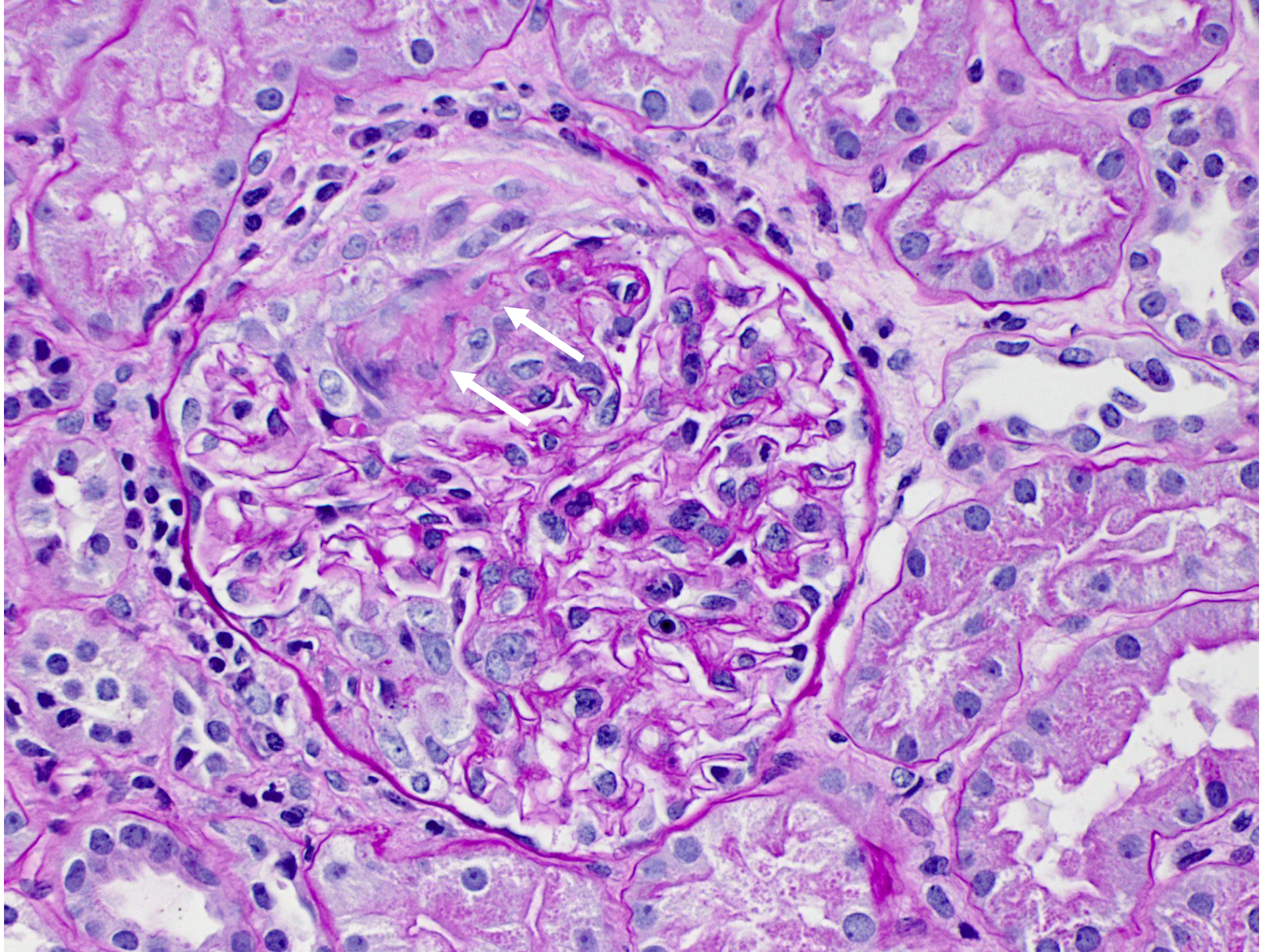
Plans for patient

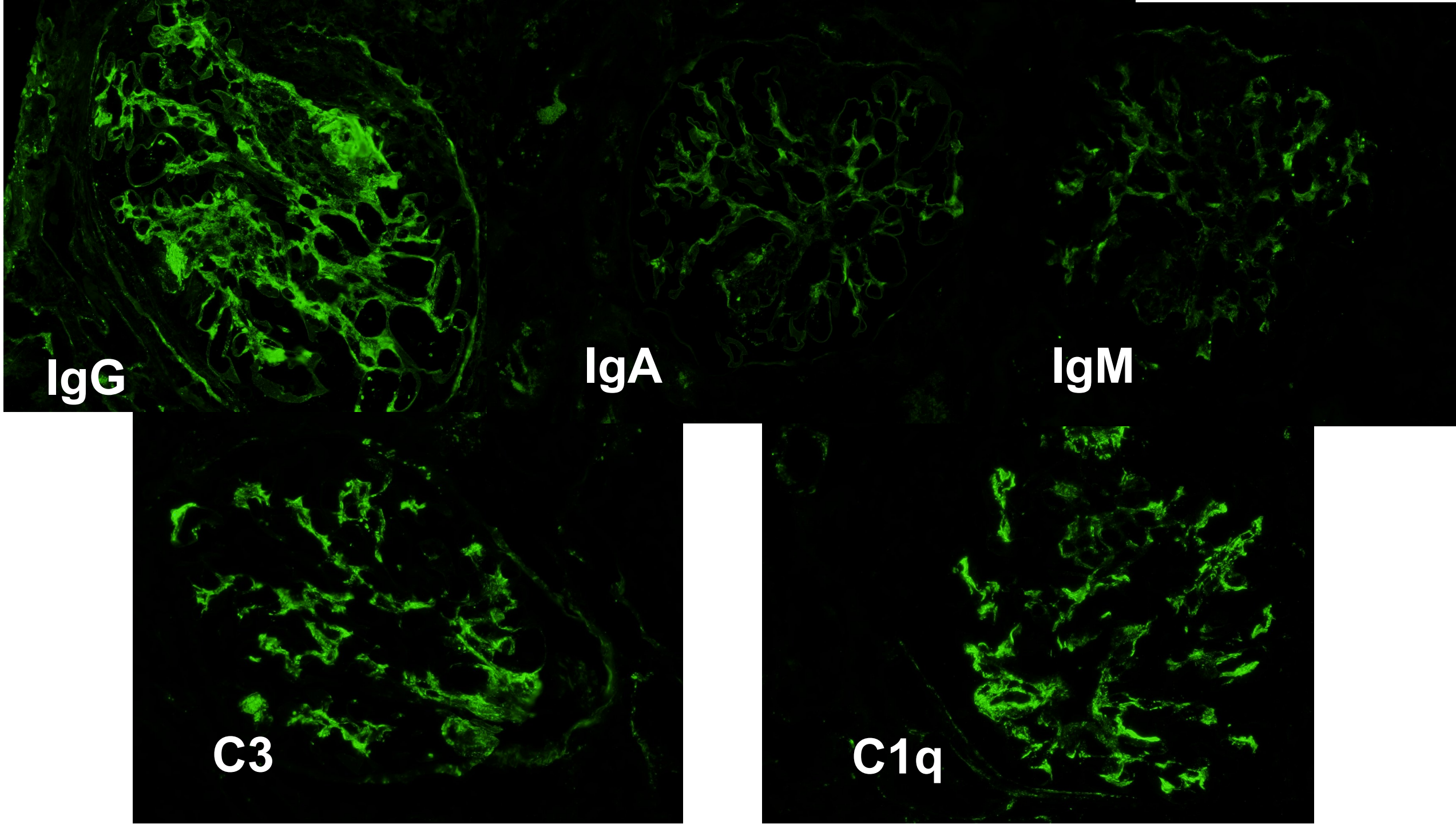
- Rapid steroid taper (starting at 25mg/day)
- Cellcept 500mg BID, goal to get to 2G daily

Case 3: 31yoF w hematuria/proteinuria post partum

- 31 yo F with lupus
  - diagnosed in 2015 (arthralgia, reynauds, photosensitivity, +serologies)
    - Short steroid taper and plaquenil
  - Delivered a healthy son in 2017, plaquenil thru pregnancy
  - Lupus flare 5 weeks after delivery (arthralgia and photosensitivity) tx prednisone
    - 7 months after delivery she presented due to 700-900mg proteinuria (creatinine 0.78mg/dL).
- Exam: Well appearing, + Small/Mod Ascites
- Urinalysis: sediment 85 RBC, WBC, few RBC casts
- 24 hour urine protein 1.2G/day
- Serum albumin 3.5
- Low C3 C4
- ANA 1:160, Anti-DNA –1:640
- ANCA and anti-GBM negative






IgG
IgA
IgM
C3
C1q

Class IV lupus

31yoF w hematuria/proteinuria post partum

- Cellcept 1500mg BID and prednisone taper
- Maintained on this regimen for 6 months
- 24 hour urine showed 2.8g proteinuria

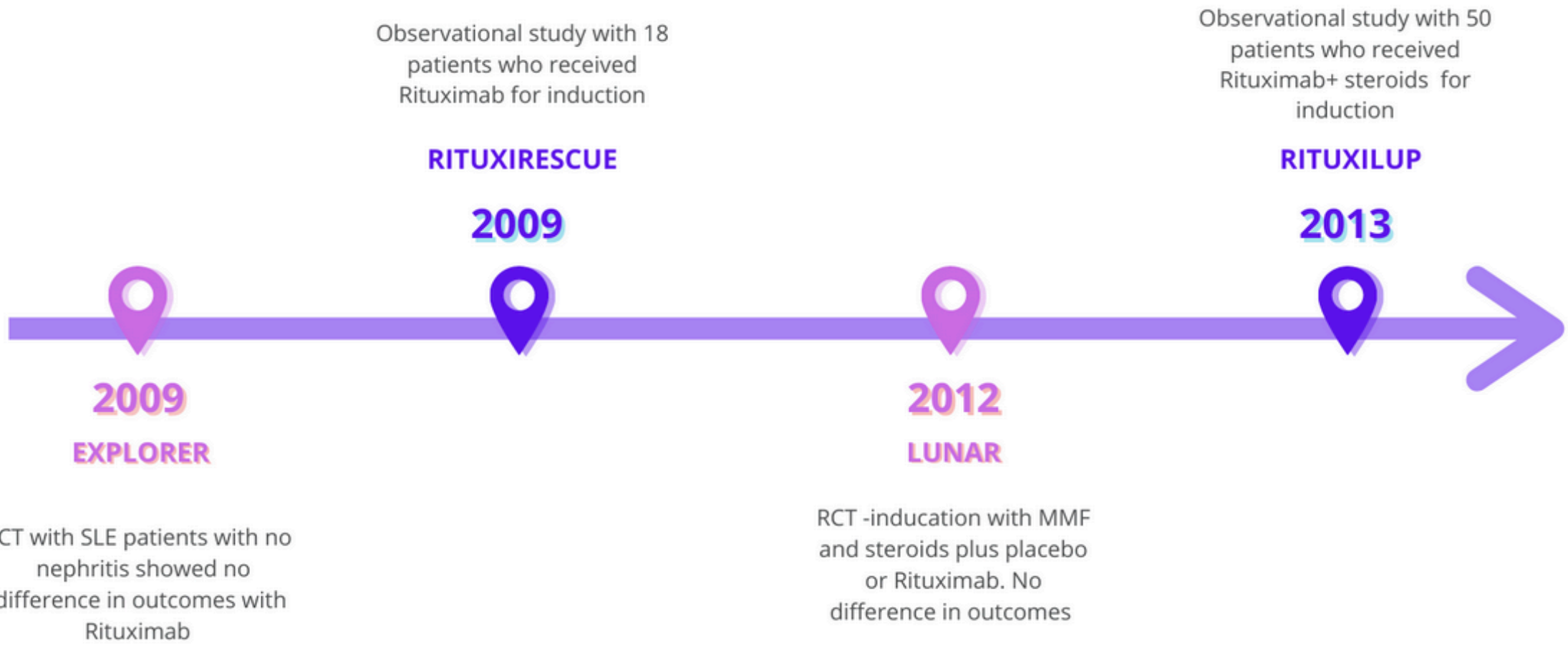
How do we define a response?

Criteria	Definition
Complete response	• Reduction in proteinuria to <0.5 g/g measured as the PCR from a 24-hour urine collection • Stabilization or improvement in kidney function (±10–15% of baseline) • Within 6–12 months of starting therapy, but could take more than 12 months
Partial response	• Reduction in proteinuria by at least 50% and to <3 g/g measured as the PCR from a 24-hour urine collection • Stabilization or improvement in kidney function (±10–15% of baseline) • Within 6–12 months of starting therapy
No kidney response	• Failure to achieve a partial or complete response within 6–12 months of starting therapy

Managing Partial/No responses

- Step 1: Discuss and confirm adherence (MMF level)
- Step 2: Consider re-biopsy: to exclude TMA, or persistent proteinuria from chronic changes
- Step 3: Recommendation: Switch to cyclophosphamide induction (oral or IV)
    - Alternative: Addition of rituximab, trial of MMF+CNI

Rituximab for Lupus Nephritis



Adding rituximab

- Meta-analysis 2005-2016, 31 studies, > 1000 patients
- The pooled proportion for complete response was 51% (95% CI, 34% to 68%) in LN patients

Alshaiki et al. Rituximab for refractory lupus Eur J Rheumatol 2018; 5: 118-26

Back to case

- Given rituximab (1 gram q 14 days) x 2 doses, then quarterly

- Urine protein/creatinine: 0.39 within 4 months

Until

Until

- Noted to have neutropenia on routine labs
- Received filgrastim at a local ED
- 4 weeks later developed fever, referred to ED, was neutropenic
  - Treated for febrile neutropenia with vancomycin and cefepime
  - Another dose of filgrastim

Late–onset Neutropenia from Rituximab

- The cumulative incidence at 1 year of B cell depletion therapy was 6.6% (95% CI 5.0-8.7)
- The majority of episodes (59.4%) were asymptomatic
- Fever and sepsis complicated 31.3% and 8.5% of episodes, respectively. Most patients (69%) were treated with filgrastim.
- Rituximab rechallenge occurred in 87% of patients, of whom 21% developed recurrent neutropenia

Zonozi R, et al. Arthritis Rheumatol 2021 Feb;73(2):347-354.

Outcome

- Remains in full remission on azathioprine
- Not rechallenged with Rituximab (had already received 3G at the time of developing neutropenia)
- No further recurrence of neutropenia
- Delivered another healthy baby two months ago with no complications and no proteinuria developing during pregnancy (most recent UPC 0.15)

Thank you for joining!

- msise@partners.org