

The Clone WARS

CASE DEBATE

Raad B. Chowdhury, MD, FASN

Medical Director of Onconeurology

Associate Program Director (APD), Mass General Brigham Renal Fellowship

Vice President, American Society of Onconeurology (ASON)

Instructor, Harvard Medical School



Disclosures

Chowdhury: None

Jhaveri: None

Leung:

- Consultant: Omeros, Lilly
- Grant/Research Support: Omeros
- Stock Shareholder: AbbVie

★ THE ★
WAR
★ AGAINST ★
LIGHT CHAINS
A CASE DEBATE

PLEX OR **NO PLEX**

NELSON LEUNG, M.D.

★ TEAM PLEX ★

VS

KENAR JHAVERI, M.D.

★ TEAM NO PLEX ★

CASE PRESENTED BY



RAAD CHOWDHURY, M.D.



SUJAL SHAH, M.D.

THE CLONE WARS

DEBATE STRUCTURE

TOTAL ALLOCATED TIME

40 MINUTES

**05
MIN**

Introduction & Case Presentation

Presented by Raad Chowdhury & Sujal Shah.

TEAM NO PLEX **15 MIN**

Dr. Kenar Jhaveri, M.D.

15-minute presentation arguing against Plasma Exchange (PLEX) utilizing PowerPoint.

TEAM PLEX **15 MIN**

Dr. Nelson Leung, M.D.

15-minute presentation advocating for Plasma Exchange (PLEX) utilizing PowerPoint.

**05
MIN**

Moderated Discussion & Closing

Led by Raad Chowdhury. Audience interactive Q&A session followed by formal closing remarks.

Strict Adherence to Speaker Time Limits

THE CLONE WARS

PATIENT PRESENTATION

CLINICAL PROFILE

Patient: 75-year-old male with IgA MGUS presenting with back pain hypotension, Acute Kidney Injury.

Symptoms: Profound fatigue, back pain, and myalgias.

Medications: Hydrochlorothiazide, alendronate, losartan

DIAGNOSTIC DEBATE TRIGGERS

The Conflict: Presumed light chain cast nephropathy (LCCN) versus ATN

Pending: Bone Marrow with FISH PET/CT

LABORATORY & DIAGNOSTIC WORKUP

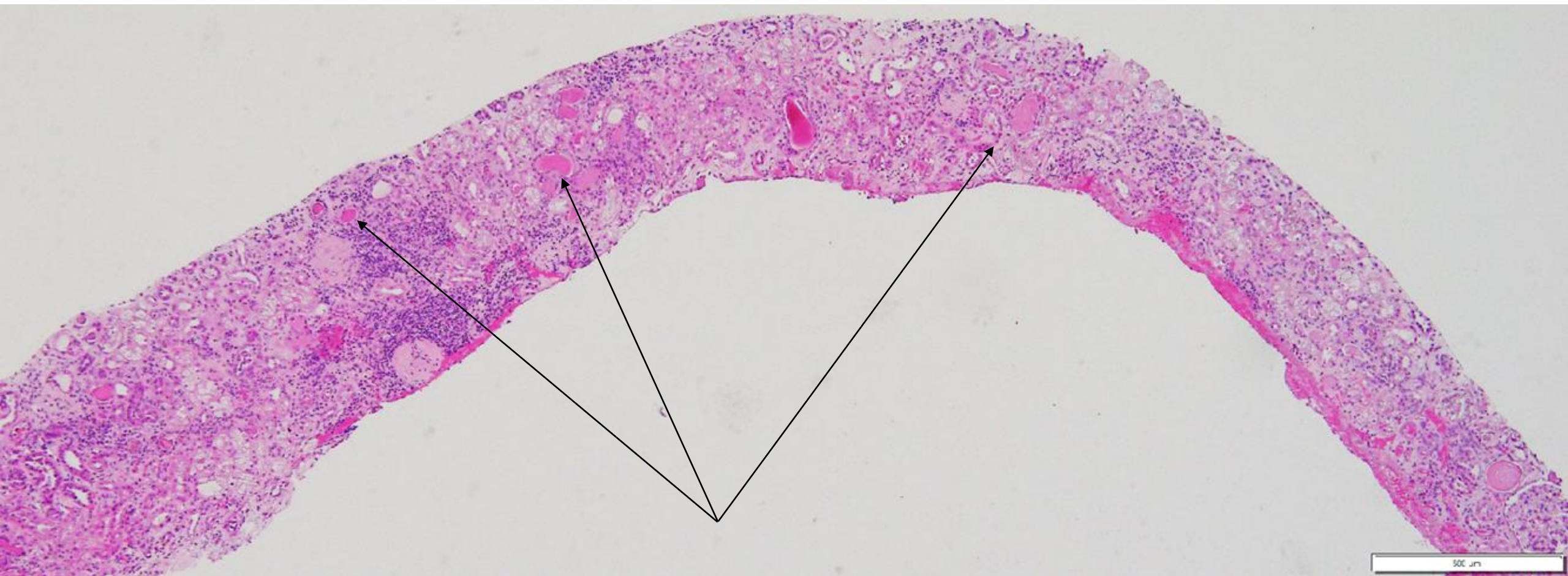
CREATININE	LAMBDA FLC	SERUM IgA
5.75 mg/dL	4,500 mg/L	2,031 mg/dL
BONE MARROW	HEMOGLOBIN	CALCIUM
PENDING	6.5 g/dL	14 mg/dL
ECHO (NEW EF)	NT-proBNP	TROPONIN
45% EF	5,000 pg/mL	55 (H)

Protein/Cr: 8g/day, Microalbumin/Cr 6.5g/day

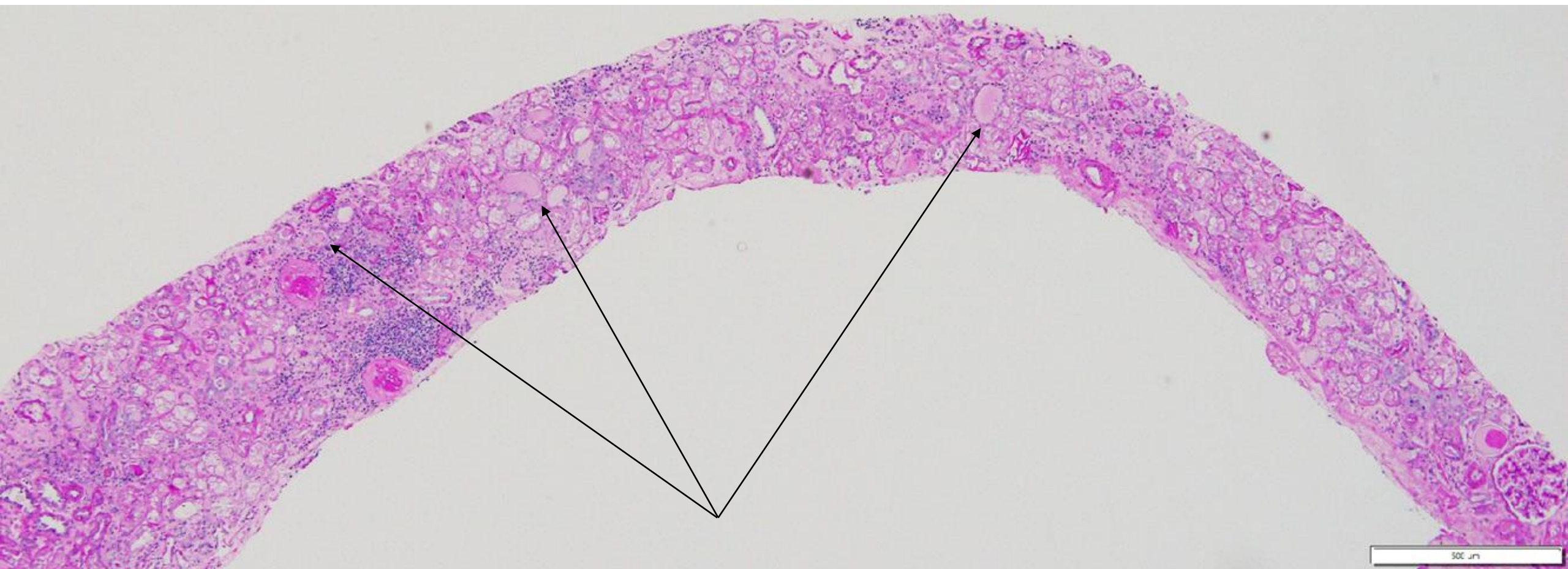
Treatment:

Clone Directed therapy pending bone marrow biopsy and cytogenetics

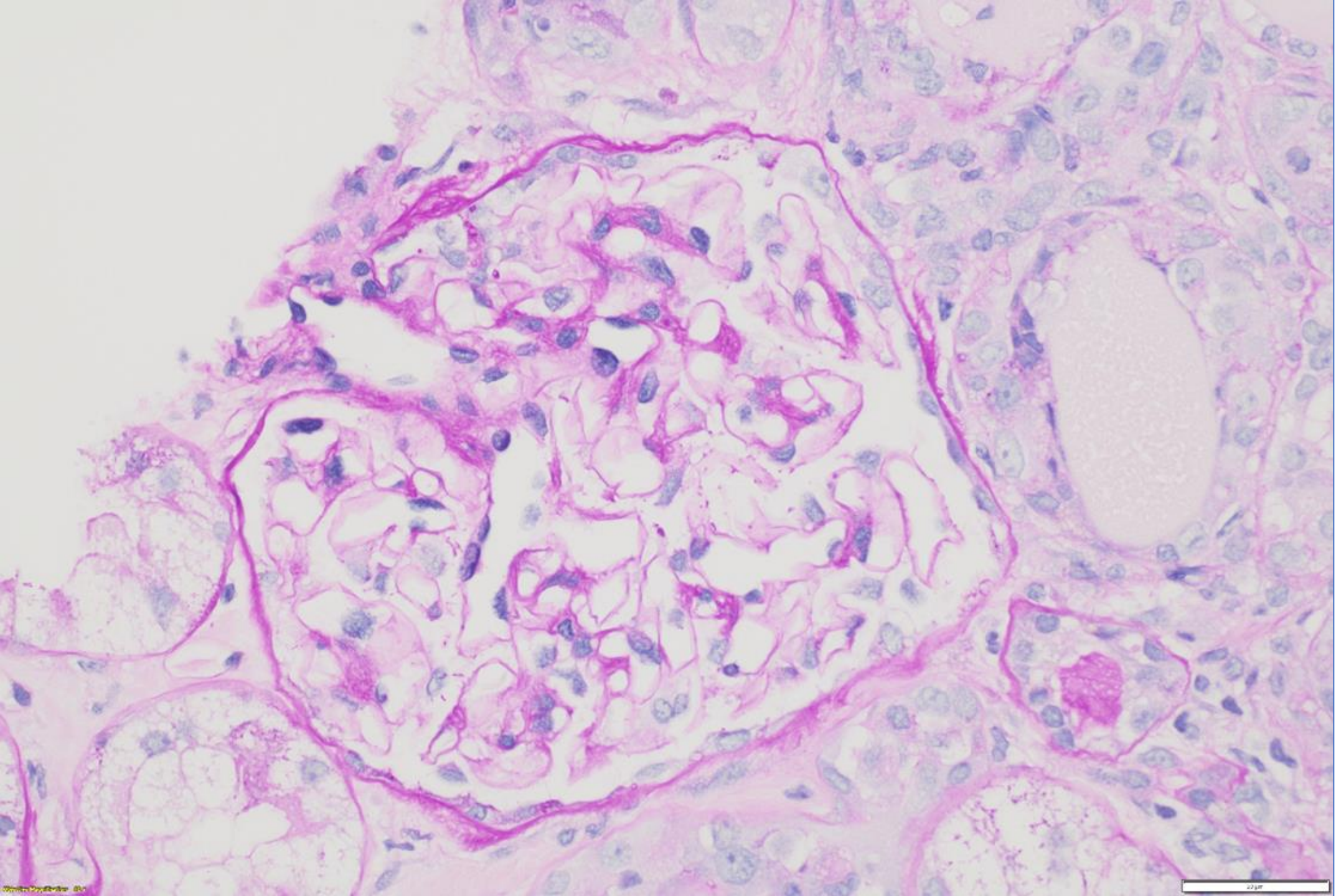
To Biopsy or Not to Biopsy?

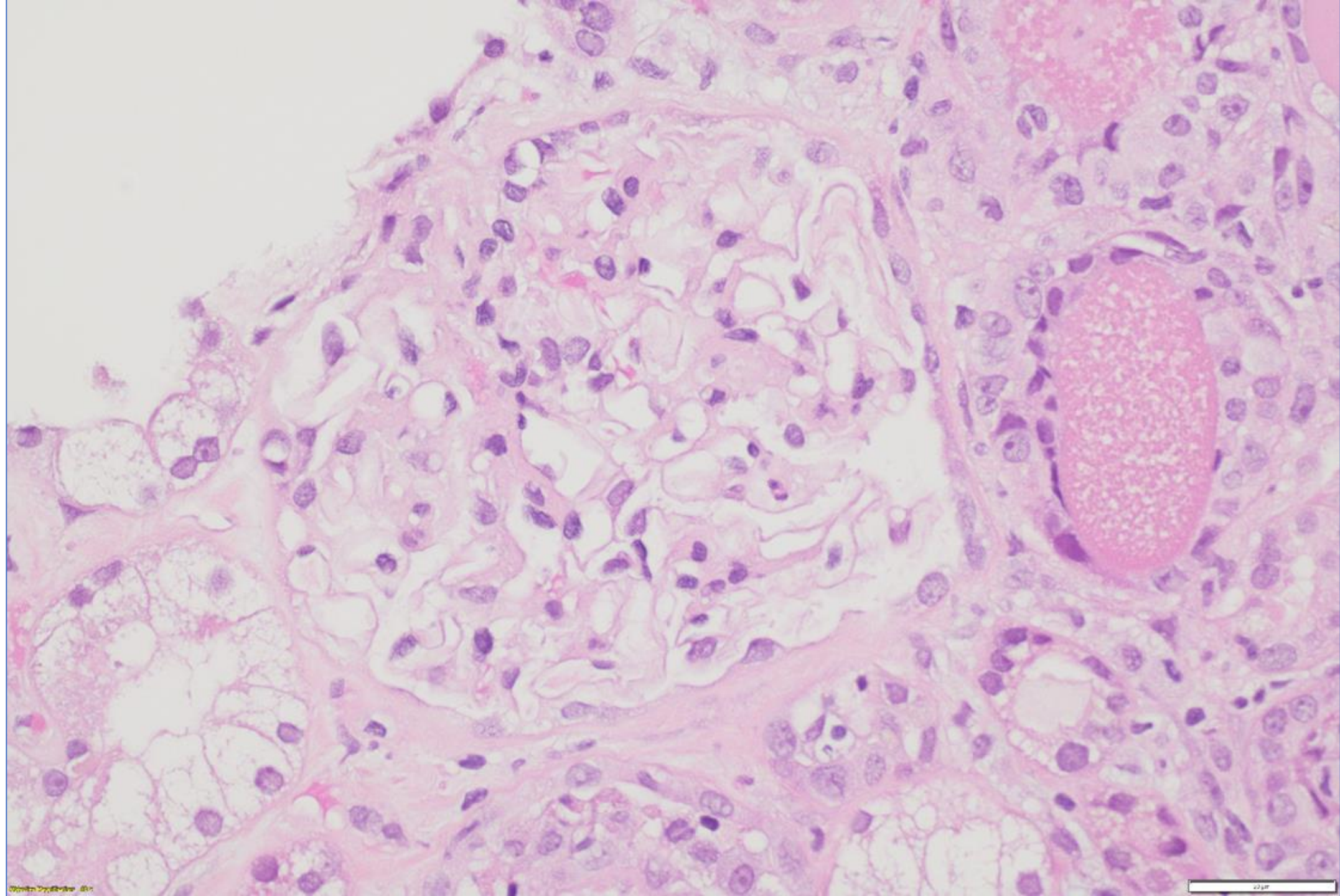


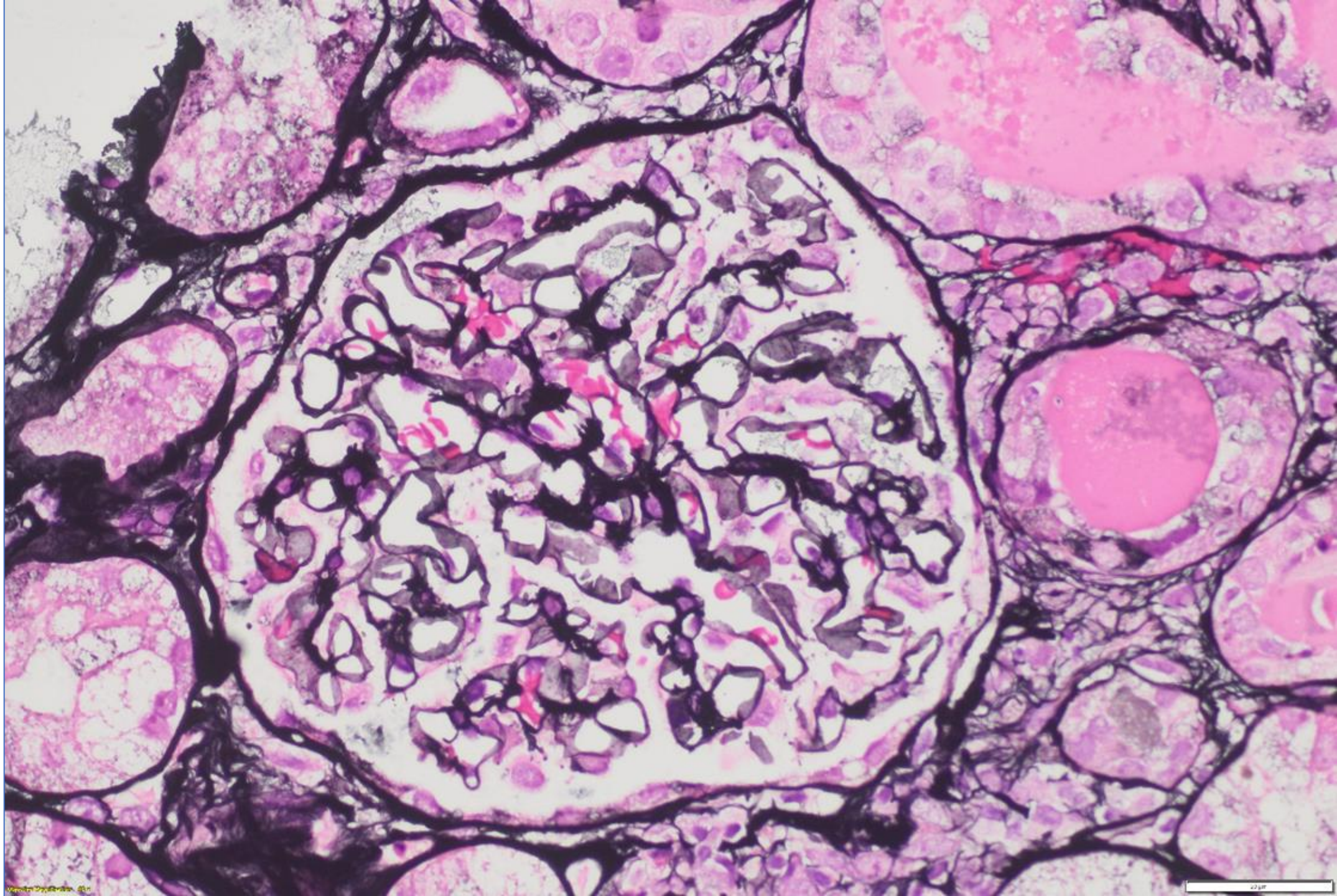
H&E
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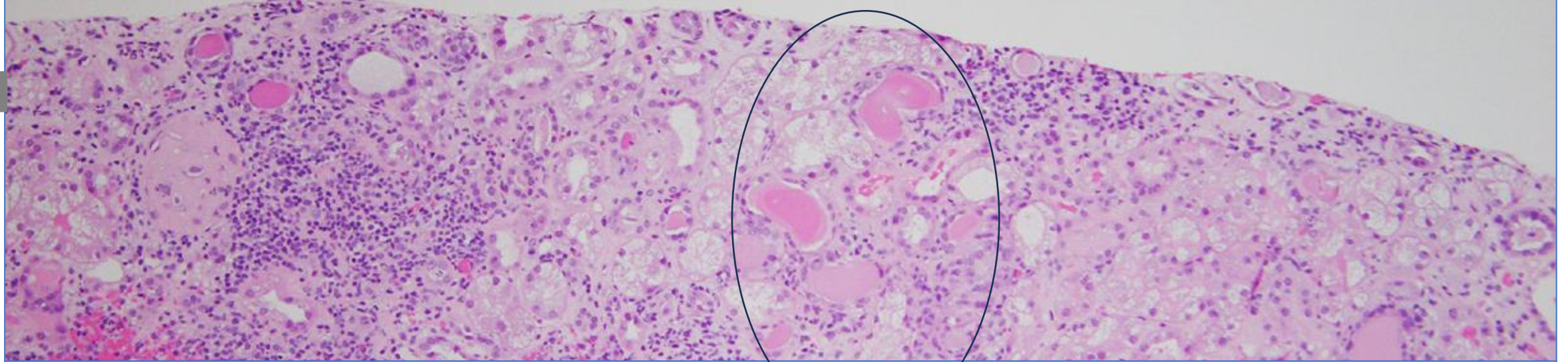
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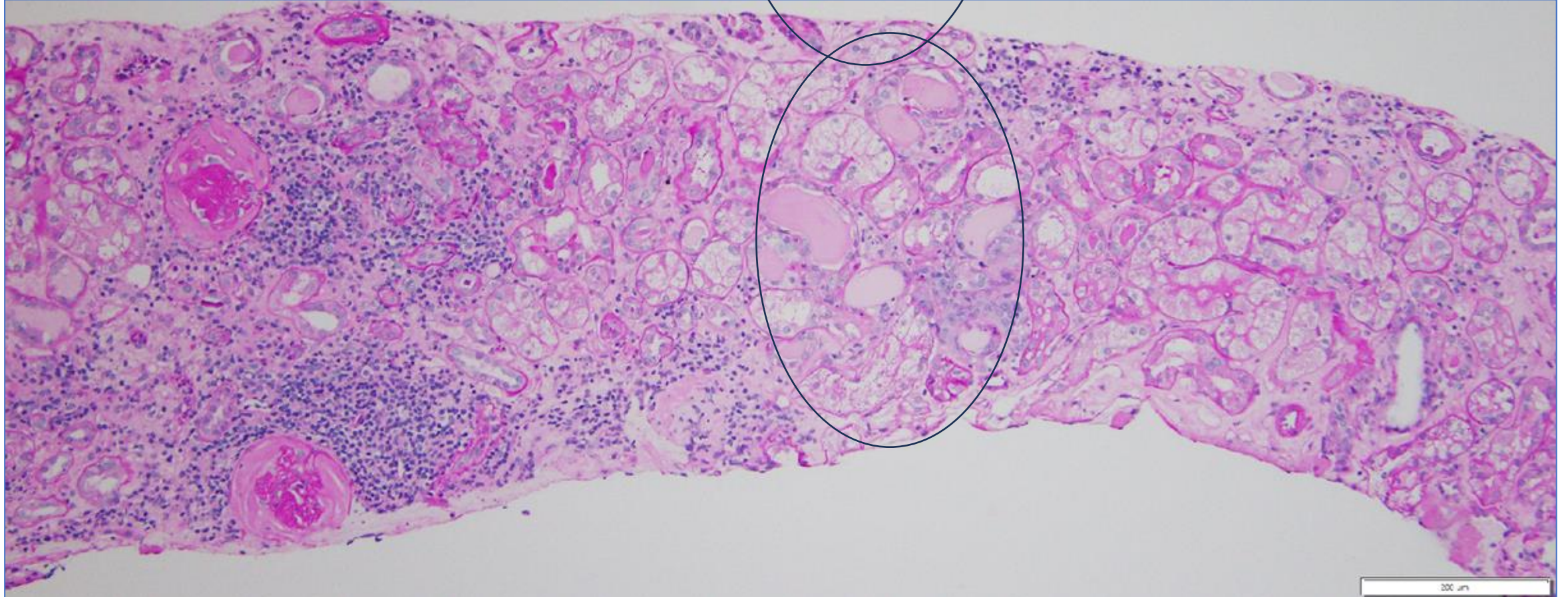


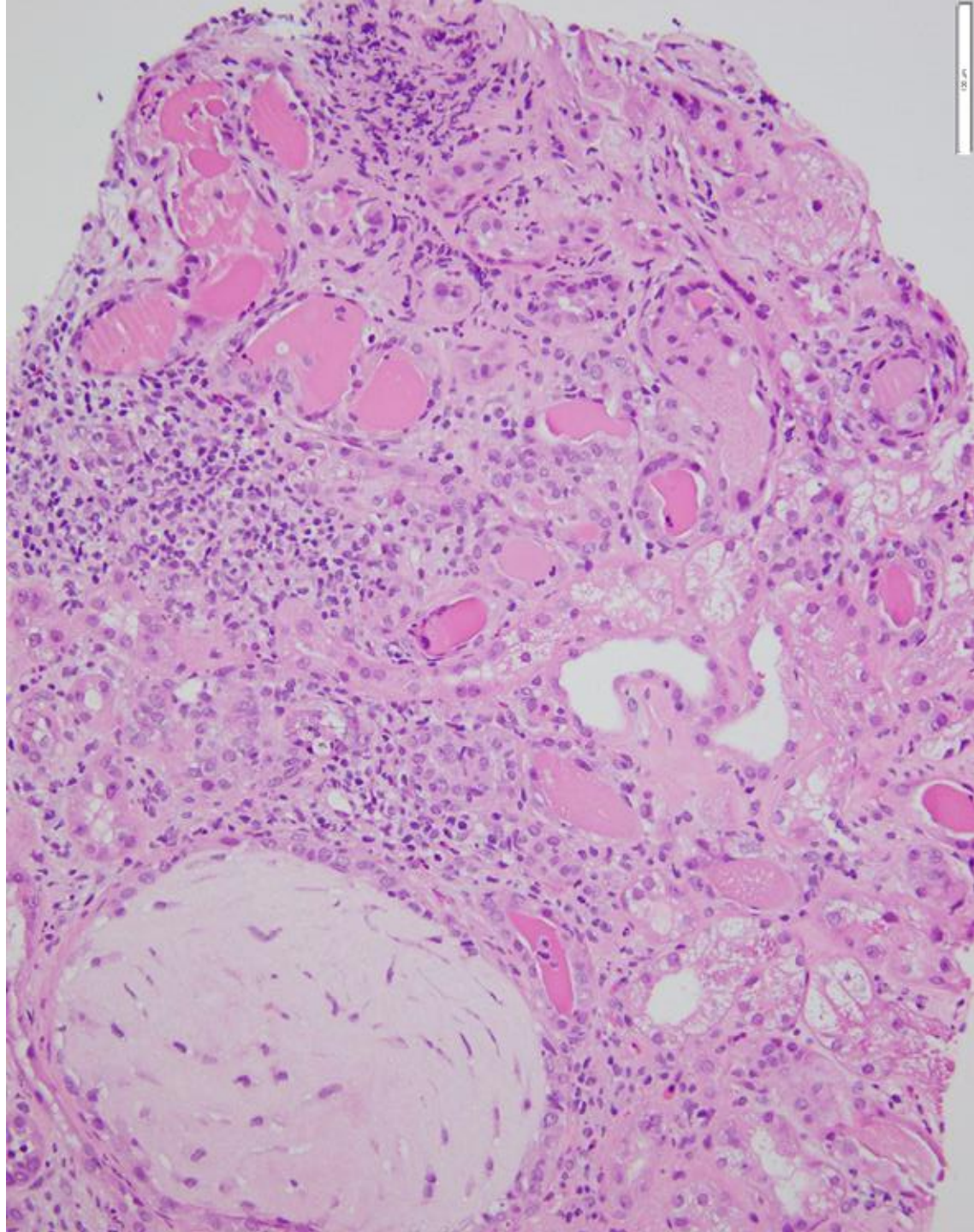


H&E
10x

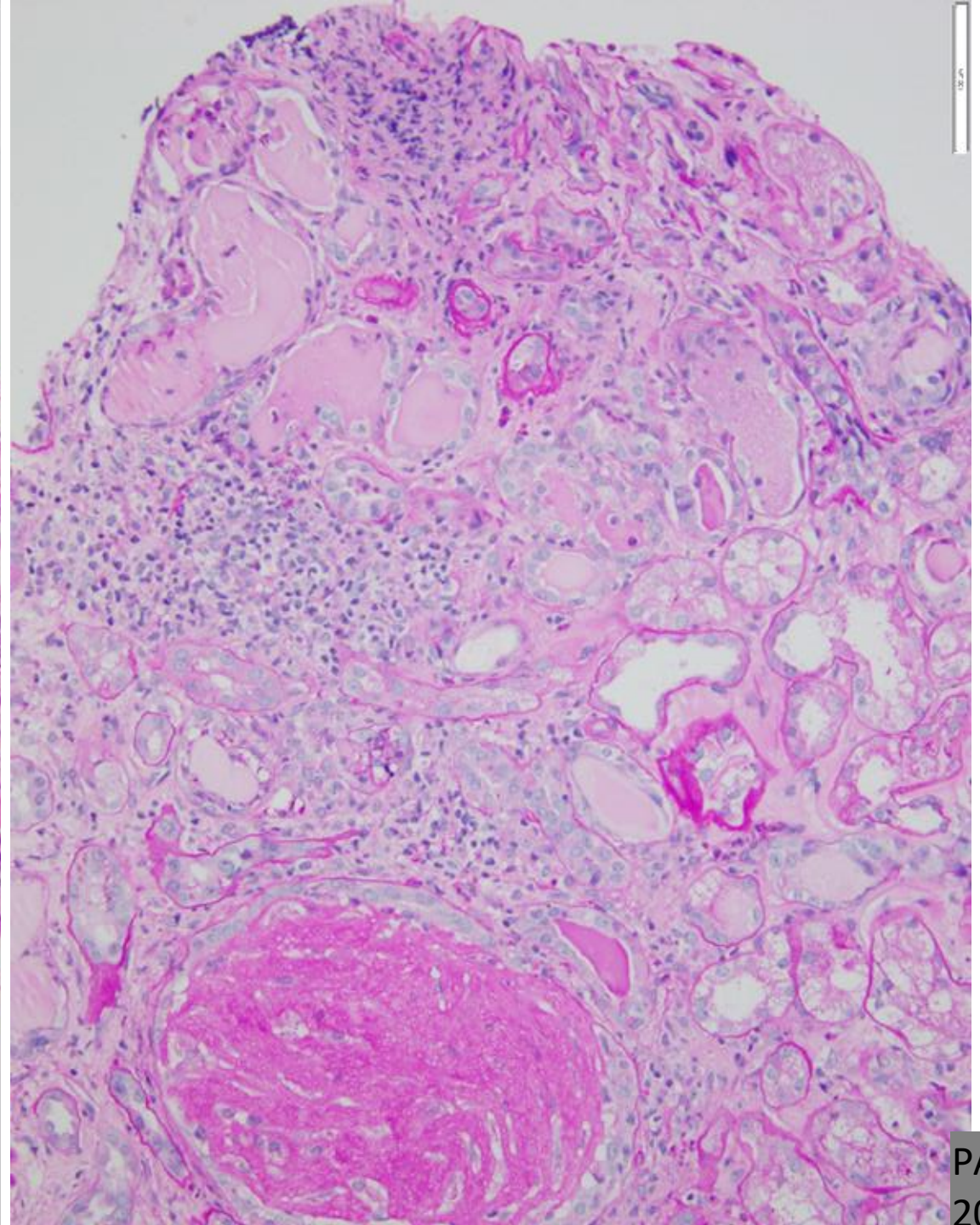


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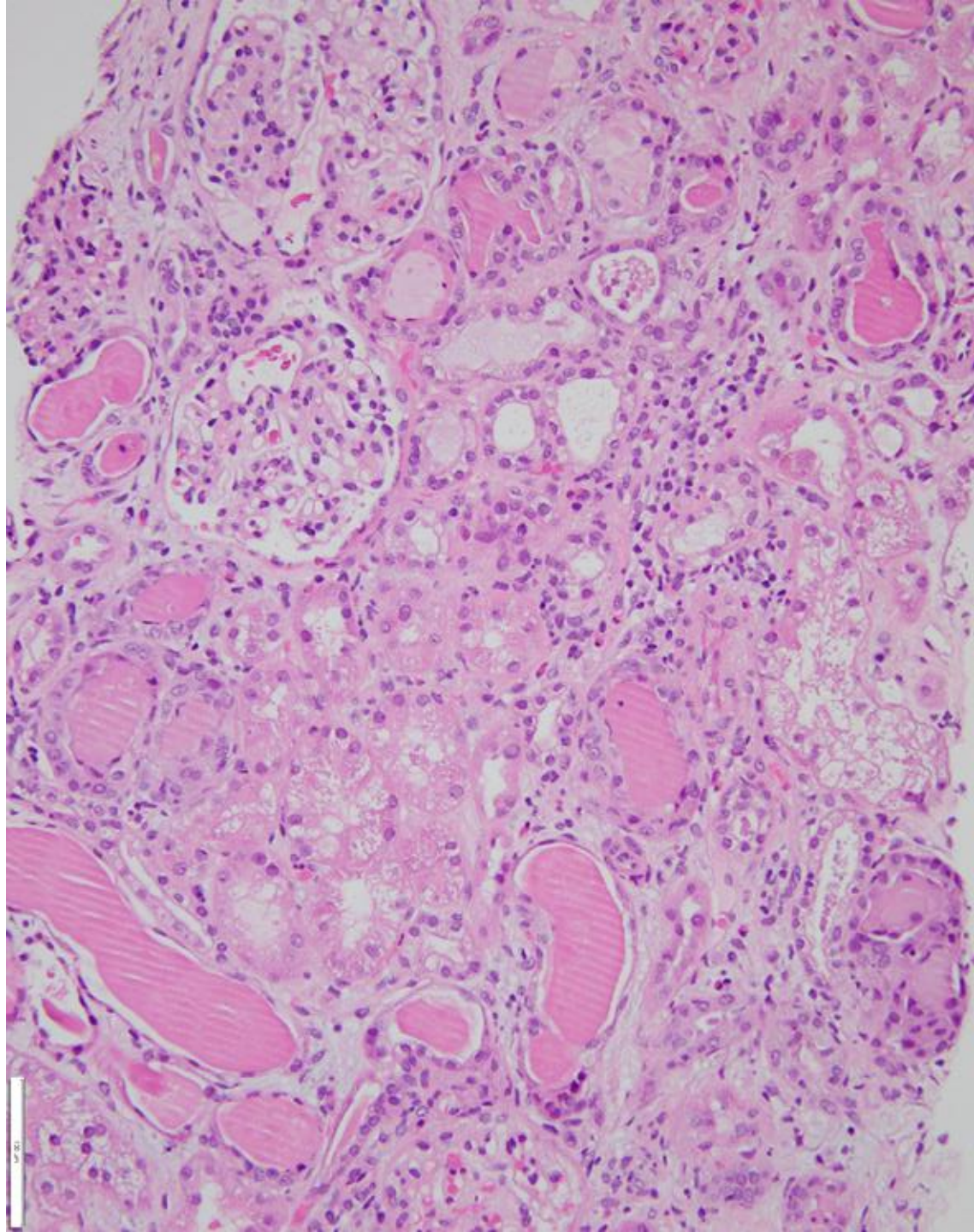




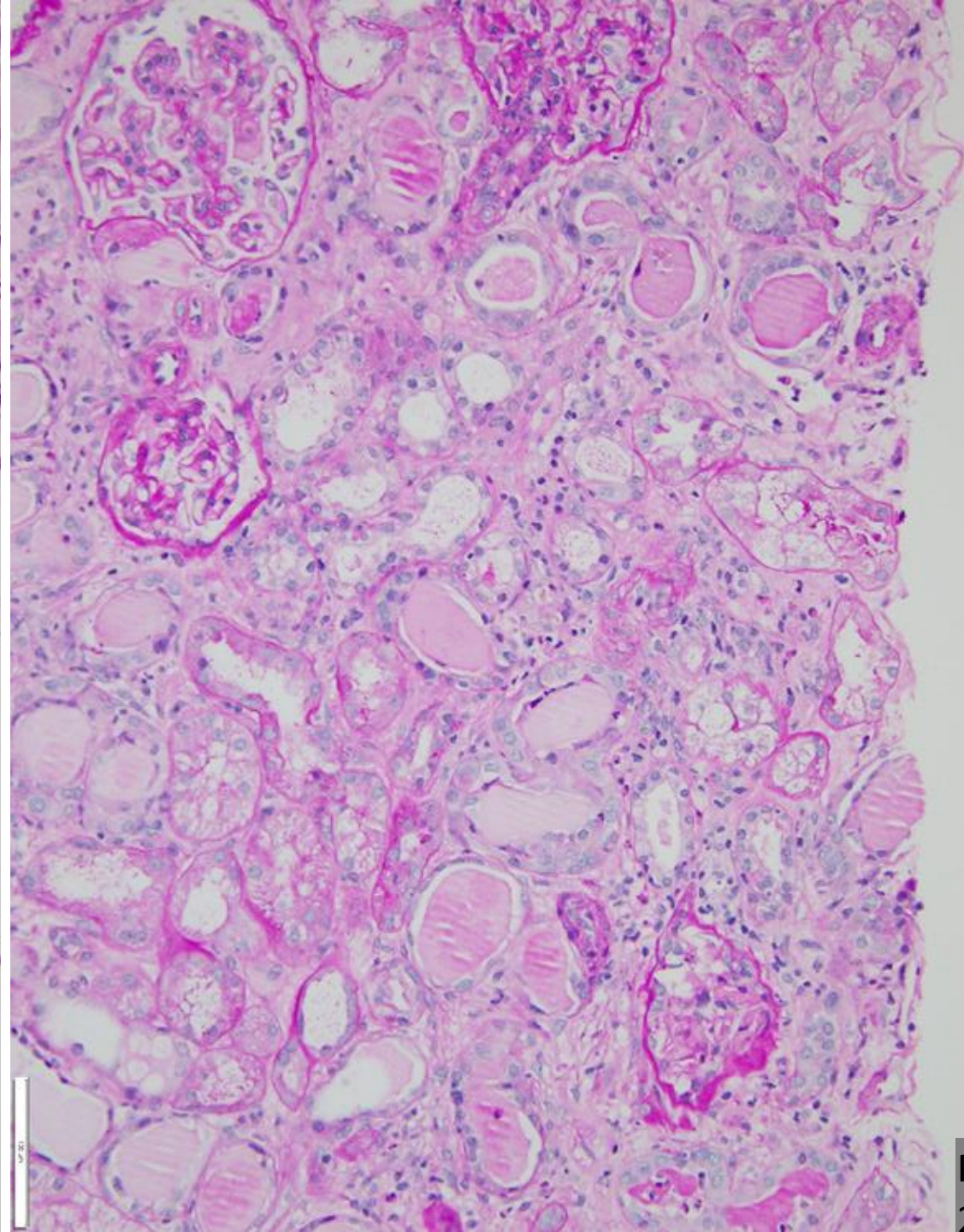
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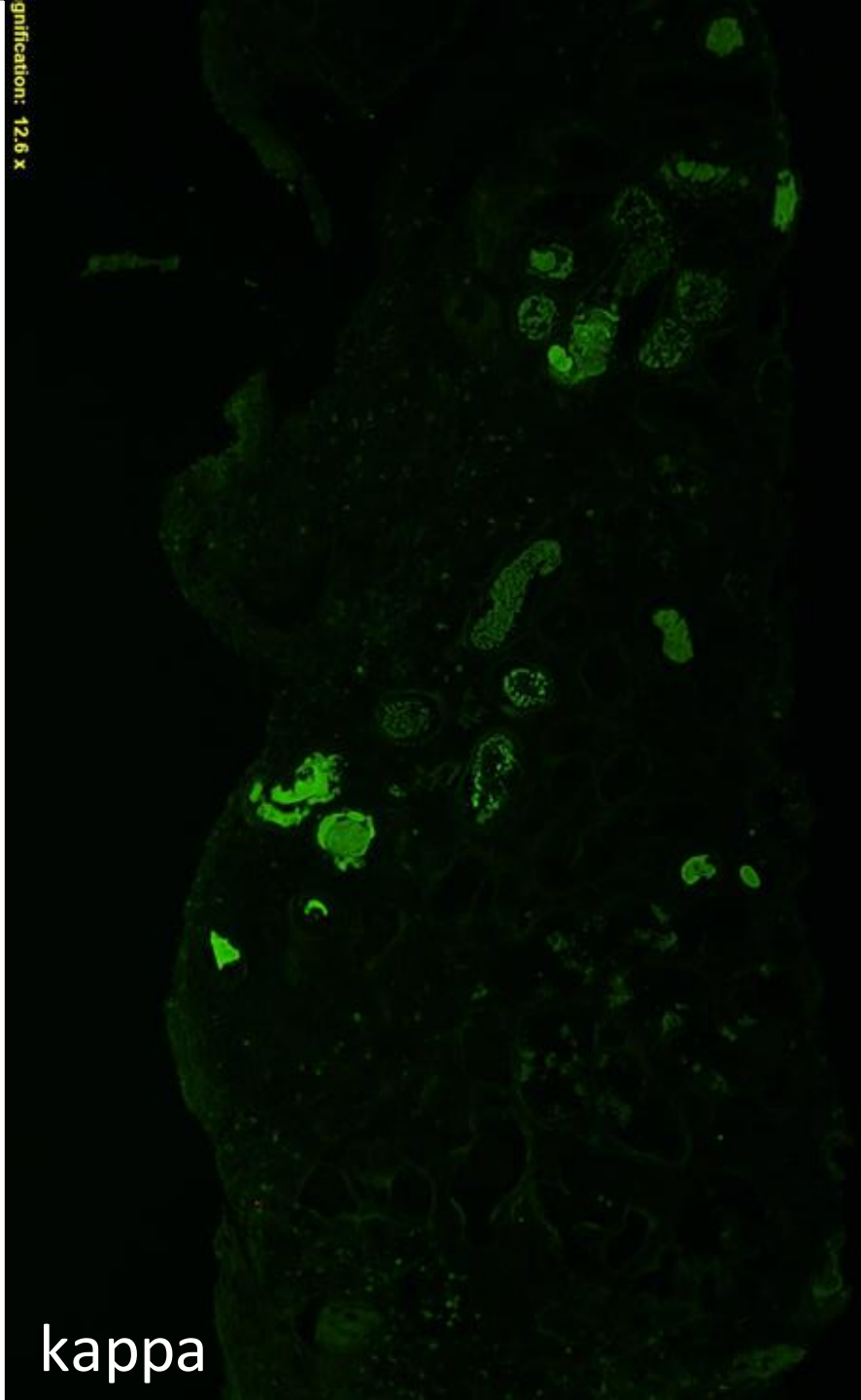
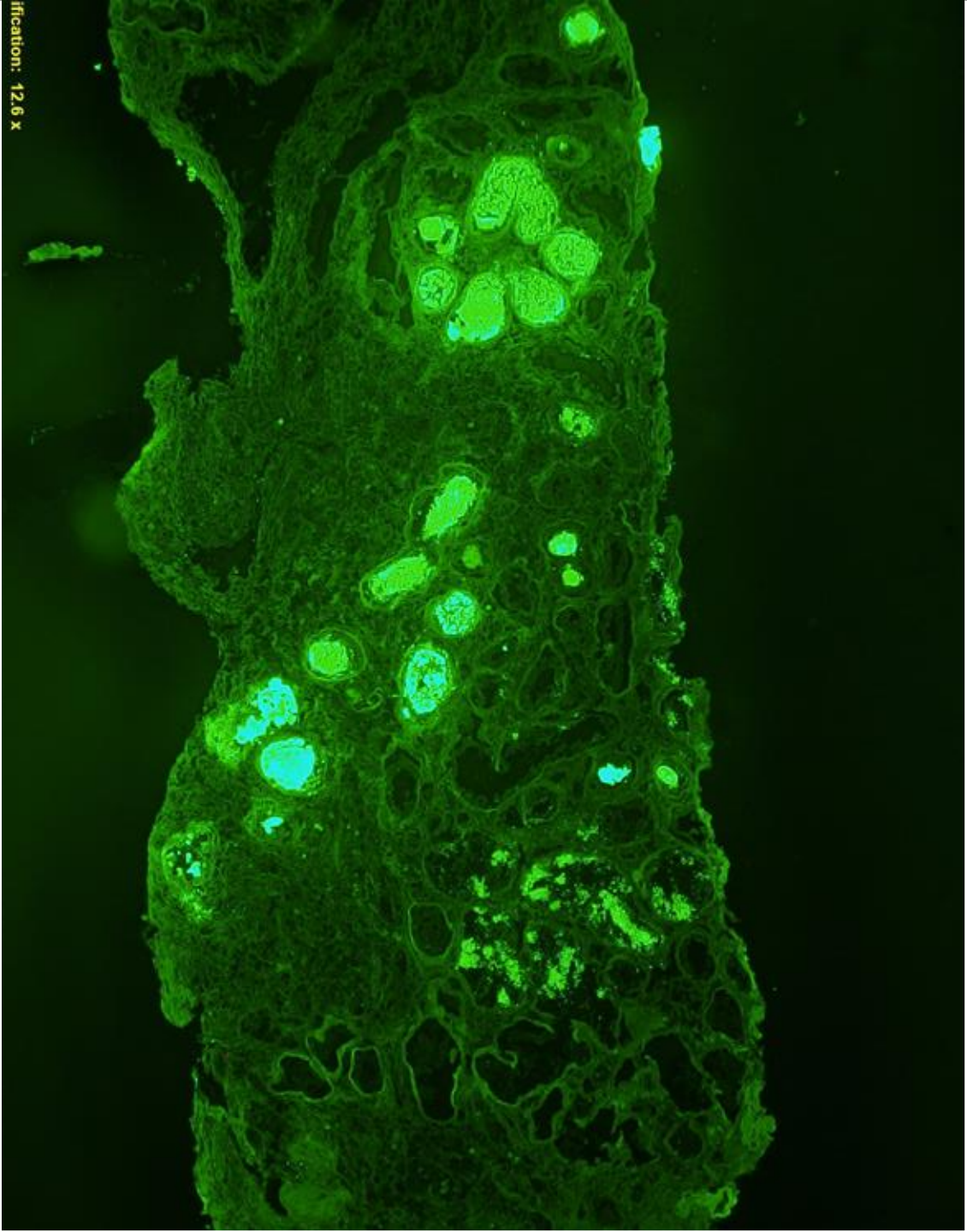
PAS
20x



H&E
20x



PAS
20x



kappa

Pathology Diagnosis

Light Chain Cast Nephropathy

with lambda light chain restriction of the casts



Plasma-exchange for Cast Nephropathy— Why bother?

Kenar D. Jhaveri, MD

Professor of Medicine

Northwell Health, NY

ASON Annual Meeting Debate 2026, Boston, MA

Disclosures

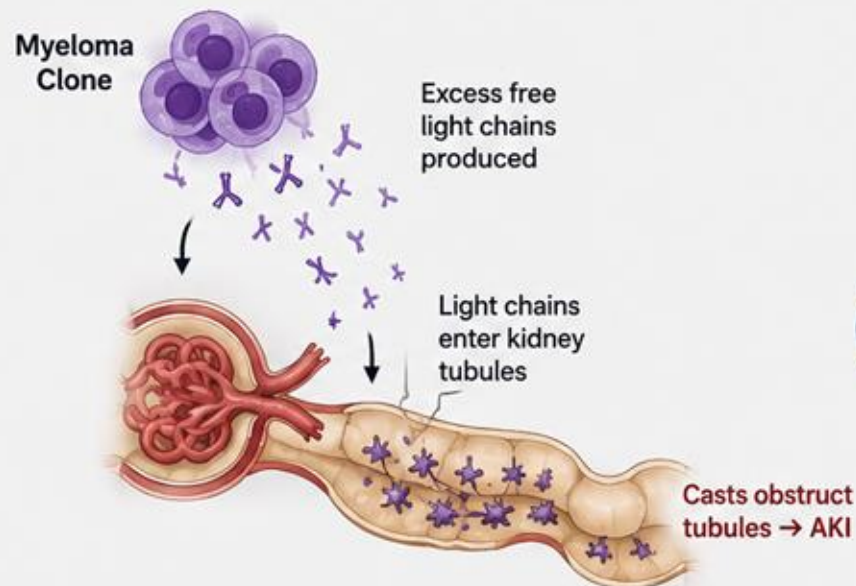
Stopped using Pheresis for Cast Nephropathy in 2015

Author and contributor of the recent study “Plasma Exchange and Daratumumab for Myeloma Cast Nephropathy” – also should be really called “**STOP**” Pheresis for Cast Nephropathy study.

CAST NEPHROPATHY: **TREAT THE SOURCE, NOT JUST THE SPILL**

Plasmapheresis cleans the spill, but chemotherapy stops the leak

THE PROBLEM CAST NEPHROPATHY



KEY POINT

Continuous production of light chains drives ongoing kidney injury

PHERESIS (PLASMAPHERESIS)

- Can rapidly reduce circulating light chains
- May provide temporary benefit
- Does NOT stop ongoing production
- Spill returns if the source continues



THE GOAL

Combine strategies:
Clean the spill AND
stop the source

THE ANALOGY OIL SPILL IN THE OCEAN

THE SOURCE: OIL LEAK

If the leak continues, the spill keeps spreading

PHERESIS = CLEANING THE OIL (THE SPILL)

Removes oil from the water, but doesn't stop the leak

CHEMOTHERAPY = STOPPING THE LEAK (THE SOURCE)

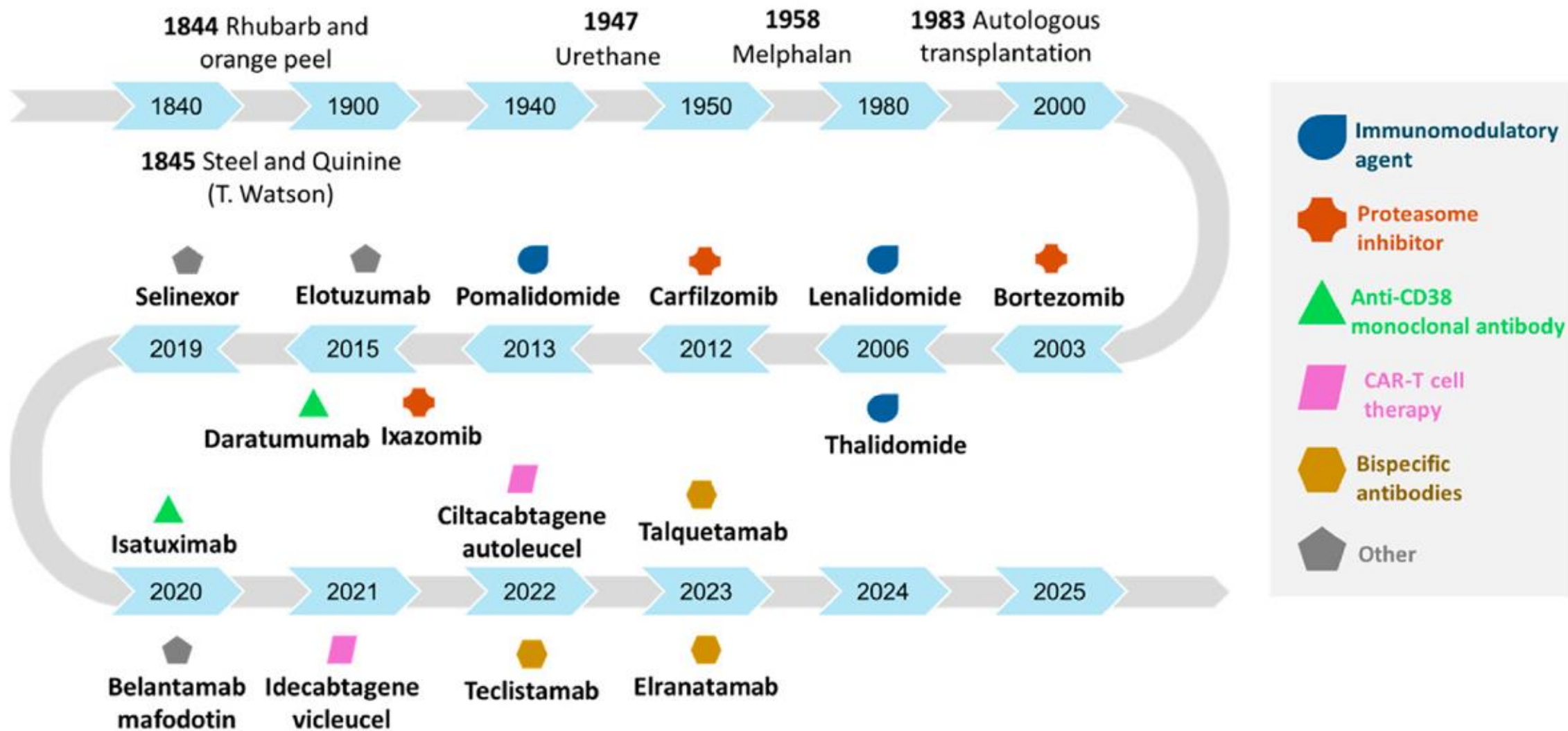
Stops production of light chains, allowing kidney to heal



TAKE HOME MESSAGE: Plasmapheresis cleans the oil. Chemotherapy stops the leak.

Clonal and chemo therapy for myeloma is the ultimate treatment for mortality and renal benefit.

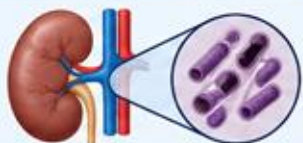
Modern ERA of
therapy— does
PLEX matter



Modern ERA agents – single center study

Modern-Era Outcomes in Myeloma Cast Nephropathy (MCN)

Excellent Renal Recovery and No Early Mortality with Contemporary Anti-Myeloma Therapy



MCN is a driver of renal failure in newly diagnosed multiple myeloma (NDMM) and has been historically associated with increased early mortality. Since patients with moderate to severe renal insufficiency are typically excluded from trials, we performed a retrospective study to characterize modern-era outcomes in MCN.

STUDY DESIGN



Retrospective review
at an academic center



Jan 2017 – Dec 2023



274 consecutive NDMM
patients reviewed

MCN COHORT



**46 patients (16.8%)
with MCN**



**96% received bortezomib
in frontline therapy**



**67% received anti-CD38+
monoclonal antibody**

6-MONTH OUTCOMES

RENAL RESPONSE (IMWG CRITERIA)



76.1%

Overall Renal
Response Rate
(35/46)



32.6%

Renal Complete
Response Rate
(15/46)

OVERALL SURVIVAL AT 6 MONTHS



MCN

100%

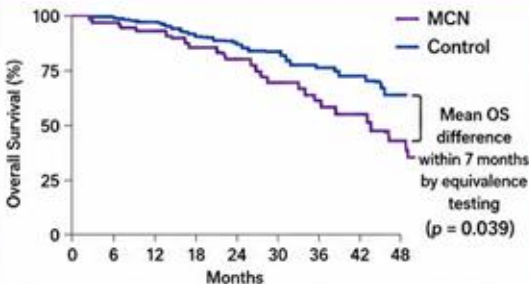
Controls



98.2%

No difference in OS at 6 months between MCN and controls

OVERALL SURVIVAL (OS) AT ~3 YEARS



At a median follow-up of ~3 years, mean MCN OS was within 7 months of control by equivalence testing.

RAPID HEMATURIC AND PROTEINURIC RESPONSE

Median time to major reduction

Involved Free Light Chain (iFLC)



83.1%

achieved major
iFLC reduction
within 1 month

Proteinuria



3.9 g/d

median reduction
in proteinuria
within 1 month

Most iFLC and proteinuria reduction occurred within 1 month of treatment.

SUMMARY OF KEY FINDINGS



Excellent 6-month renal recovery:
ORR 76.1%; CR 32.6%



No early mortality: 6-month OS 100% in MCN



Mean OS at ~3 years within 7 months of controls
($p = 0.039$ by equivalence testing)



Rapid hematologic and proteinuric response
within 1 month



Outcomes achieved with modern anti-myeloma
therapies (bortezomib, anti-CD38+ mAb)



CONCLUSION: We report excellent 6-month renal recovery without early mortality in MCN patients treated with modern anti-myeloma therapies. Prospective studies focused on MCN are urgently needed to further improve the renal CR rate.

Modern therapy >>>>> PLEX

Real-world cohort data confirm no advantage: several retrospective data and ongoing emulsion trial(**to be published soon**)



Modern chemotherapy achieves rapid FLC reduction independently: Bortezomib- and daratumumab-based regimens now reliably achieve the rapid FLC lowering that was previously the rationale for PLEX.

Studies (some published, some abstracts)

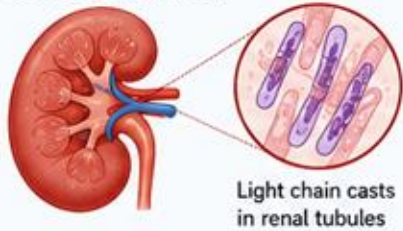
Study / Design	Population & N	PLEX protocol	Key comparator	Primary endpoint	Result
Zucchelli 1988 — single-center RCT	29 pts, ARF due to MM, Bence-Jones >1 g/d; 24 dialysis-dependent	PLEX + steroids + cytotoxic + HD as needed	Peritoneal dialysis + steroids + cytotoxic	Renal recovery & survival	Positive: 13/15 stopped dialysis vs 2/14; 1-yr survival 66% vs 28% (p<0.01)
Clark 2005 (Canadian MRC) — RCT, 14 centers, open-label	104 pts, ARF at MM onset; no biopsy requirement	5–7 exchanges (50 mL/kg, 5% albumin) over 10 d	Conventional therapy alone	Composite: death, dialysis dependence, or GFR <30 at 6 mo	Negative: 57.9% vs 69.2% (diff 11.3%, 95% CI –8.3 to 29.1; p=0.36)
MERIT (UK) — RCT (details via Hughes 2025 secondary report)	78 newly diagnosed MCN pts	7 sessions over days 1–14 (≥4 within days 1–7)	No PLEX; backbone VAD or thalidomide-based	Alive & dialysis-independent at 100 d	Negative: no difference; no difference in FLC reduction by day 15
Boone 2026 (JCO/ASCO abstr 7575) — retrospective, multicenter, propensity-matched (TriNetX)	5,454 NDMM w/ AKI + FLC >1,500 mg/L; 248 per matched arm	PLEX within 7 d of diagnosis (81% plasma exchange, 19% plasmapheresis)	No PLEX; modern-era therapy (38% PI each arm)	Dialysis dependence at 90/180 d	Negative overall: 90 d 16.1% vs 18.1% (OR 0.87); mortality/ICU similar. Signal in FLC >5,000: Cr <2.0 at 90 d 77% vs 63% (p=0.02)

Plasma Exchange and Daratumumab for Myeloma Cast Nephropathy

Two Target Trial Emulations in 25 U.S. Academic Cancer Centers

BACKGROUND

Multiple myeloma light chain cast nephropathy (LCCN) is often treated with plasma exchange (PLEX) or the anti-CD38 monoclonal antibody, daratumumab. However, rigorous studies supporting these therapies for LCCN are limited.



METHODS



Design: Two target trial emulations using data from 25 U.S.-based academic cancer centers



Population: Patients with newly diagnosed multiple myeloma and biopsy-proven LCCN



Primary outcome (at 90 days): Kidney recovery = alive, not on kidney replacement therapy (KRT), and ≥ 1 stage improvement in AKI severity



Secondary outcomes: Kidney recovery at 60 and 180 days



Analysis: Multivariable logistic regression with propensity score overlap weights to adjust for confounders

STUDY DESIGN: TWO TARGET TRIAL EMULATIONS



PLEX TARGET TRIAL



PLEX received

n = 158 (28.8%)



No PLEX

n = 391 (71.2%)

Early PLEX initiation (≤ 14 days encouraged)



DARATUMUMAB TARGET TRIAL



Daratumumab received

n = 136 (28.7%)



No daratumumab

n = 338 (71.3%)

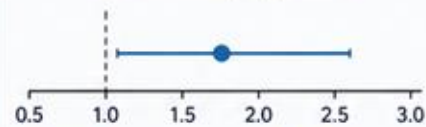
Early daratumumab initiation (≤ 14 days encouraged)

PRIMARY OUTCOME: KIDNEY RECOVERY AT 90 DAYS

PLEX vs No PLEX

OR 1.48 (95% CI 0.96–2.29)

Not statistically significant



Favors
No PLEX

Favors
PLEX

Daratumumab vs No Daratumumab

OR 1.46 (95% CI 0.84–2.56)

Not statistically significant



Favors
No Dara

Favors
Daratumumab

SECONDARY OUTCOMES: KIDNEY RECOVERY



Assessed at
60 days



Primary outcome
assessed at
90 days



Assessed at
180 days

KEY RESULTS



Kidney recovery at 90 days
(primary outcome)

Treatment	OR (95% CI)	P value
PLEX vs No PLEX	1.48 (0.96–2.29)	0.08
Daratumumab vs No Daratumumab	1.46 (0.84–2.56)	0.18



Subgroup analyses for PLEX



Newly diagnosed MM
vs relapsed disease

Higher odds of
kidney recovery
at 90 days



Stage 3 vs stage 1 or 2 AKI
at LCCN diagnosis

Higher odds of
kidney recovery
at 90 days



Sample sizes

PLEX target trial: 549 eligible
158 (28.8%) received PLEX

Daratumumab target trial: 474 eligible
136 (28.7%) received daratumumab

CONCLUSION



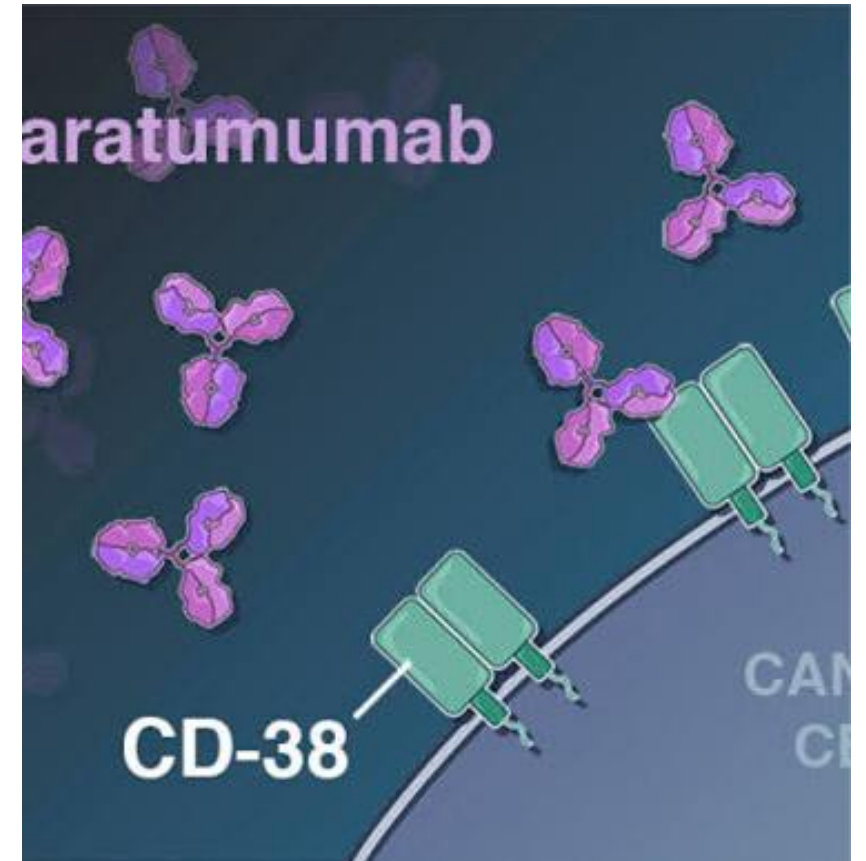
Neither plasma exchange
nor daratumumab was
associated with kidney
recovery at 90 days.

Can PLEX be harmful?

PLEX may remove therapeutic monoclonal antibodies (e.g., daratumumab), potentially undermining anti-myeloma therapy (*opinion and inference*)

Daratumumab is a fully human IgG1κ monoclonal antibody that binds CD38. Large monoclonal antibodies are among the drug classes most efficiently cleared by TPE precisely because of their high molecular weight and predominantly intravascular distribution.

A single plasma-volume exchange lowers total IgG by roughly 34% per session, and IgG falls by ~50% after two–three sessions; IgG is the slowest immunoglobulin to re-equilibrate/recover because of its large intravascular fraction. As an exogenous IgG1, daratumumab would be removed in parallel with endogenous IgG





And?

Procedural risks and resource burden:
Vascular access complications, hypotension, coagulopathy, infection risk, and significant cost/resource utilization.

Delays in systemic therapy should be avoided

What my opponent will show?



Biopsy-proven cast nephropathy subgroup may benefit:

Leung et al. found that 75% of patients with biopsy-proven cast nephropathy who achieved $\geq 50\%$ FLC reduction with PLEX recovered renal function (single center, 2008-- >17 years ago— old chemotherapies)

Possible benefit with extreme FLC burden:

A large 2026 propensity-matched cohort (n=5,454) found that patients with FLC >5,000 mg/L treated with PLEX were significantly more likely to achieve creatinine <2.0 mg/dL at 90 and 180 days (p=0.02 and p=0.006, respectively). (not published data yet, but this study also showed no overall survival and or dialysis dependency)

What do the societies say?

NCCN guidelines state that systemic therapy should not be delayed for extracorporeal FLC removal, which "may have a limited role".

International Myeloma Working Group (IMWG, 2023) —Supportive care plus high-dose dexamethasone and bortezomib-based regimens are the cornerstone of management. The IMWG explicitly concludes that **mechanical approaches (including plasma exchange and high-cutoff hemodialysis) do not increase overall survival**, and centers renal recovery on rapid FLC reduction with modern triplet/quadruplet regimens (proteasome inhibitor + IMiD + anti-CD38).

American Society for Apheresis (ASFA) — assigns myeloma cast nephropathy a **Category II** indication with a **Grade 2B** recommendation,

No KDIGO or any renal society guidelines



Summary

- Current evidence and guidelines support prioritizing **rapid initiation of bortezomib-based ($\pm$ daratumumab) anti-myeloma therapy** as the cornerstone of cast nephropathy management.
- PLEX is not routinely recommended but may be considered in select cases — particularly with biopsy-proven cast nephropathy and very high FLC burden — provided it does not delay chemotherapy.
- Harm perhaps?





Thank you

- @kdjhaveri
- kjhaveri@northwell.edu

**Dr. Leung what would you
advise?**

Clone Wars Case Debate Case: PLEX or NO Plex

FOR

Nelson Leung

Head of OncoNephrology Section, Division of Nephrology and Hypertension

David L. and Colleen B. Kessenich Professor of Multiple Myeloma

Mayo Clinic

Dr. Kenar Jhaveri



Documents

Peer Review

✓ Web of Science Core Collection (394)

Author Position

All Publications

Filters

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394 results

1

Article

When the Podocyte Speaks First

Kuruvada, KM; Gries, F; (...); Jhaveri, KD

Jul 2026 | KIDNEY360 7(7), pp.1651-1654

We report the case of a 23-year-old woman who developed minimal change disease (MCD) in the postpartum period. Kidney biopsy findings were consistent with MCD, with positive anti-nephrin immunostaining. Her clinical course was complicated by multiple relap ... Show more

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12

References

2

Article

Chronic Kidney Disease After Radical Cystectomy for Carcinoma Bladder: Incidence, Predictors, and Implications for Long-Term Surveillance

Deewan, A; Parthasarathy, R; (...); Rajja, A

Jun 2026 (Early Access) | INDIAN JOURNAL OF SURGICAL ONCOLOGY

IntroductionDecline in renal function after Radical Cystectomy (RC) for bladder cancer, besides cancer recurrence and progression, is an important prognostic factor for survival. Although several studies worldwide have investigated the decline in renal function after ... Show more

30

References

0

Verified peer reviews

1

Verified editor records

0

Awarded grants

Web of Science Core Collection metrics

40

H-Index

394

Publications

7,150

Sum of Times Cited

5,496

Citing Articles

6,794

Sum of Times Cited without self-citations

5,365

Citing Articles without self-citations

20

Sum of Times Cited by Patents

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PUBLICATION DATE

☐ 1 year

☐ 5 years

☐ 10 years

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TEXT AVAILABILITY

☐ Abstract

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5 results

<< < Page 1 of 1 > >>



1

Cite


Parameters Associated With Renal Recovery and Survival in Myeloma Patients With Acute Renal Failure to **Cast Nephropathy**.

Ludwig H, Dimopoulos MA, Terpos E, Bernhard S, Theodorakakou F, Beksac M, Cengiz-Seval G, Leung N, Arcaini L, Mangiacavalli S, Bridoux F, Agis H, Chaidos A, Gay F, Roccatello D, Hilbe W, Havasi A, Derudas D, Klomjit N, **Jhaveri KD**, De La Rubia Comos J, Kastritis E. *Am J Hematol*. 2026 Jan;101(1):56-69. doi: 10.1002/ajh.70104. Epub 2025 Oct 24.

PMID: 41134013 [Free PMC article](#).

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Acute renal failure due to **cast nephropathy** (CAN) is a severe complication of multiple myeloma (MM). Here, we aimed to identify parameters associated with renal outcomes and survival in newly diagnosed MM patients with CAN-related acute renal failure and to validate ...



2

Cite


High-Cutoff Hemodialysis in Myeloma **Cast Nephropathy**.

Jhaveri KD, Niesvizky R.

JAMA. 2017 Dec 5;318(21):2085-2086. doi: 10.1001/jama.2017.18710.

PMID: 29209704 No abstract available.

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First use of PLEX in MM

- 29 yo male
- Scr = 13.8 mg/dL
- Melphalan alone
- Patient discontinued dialysis and return to work after 9 months

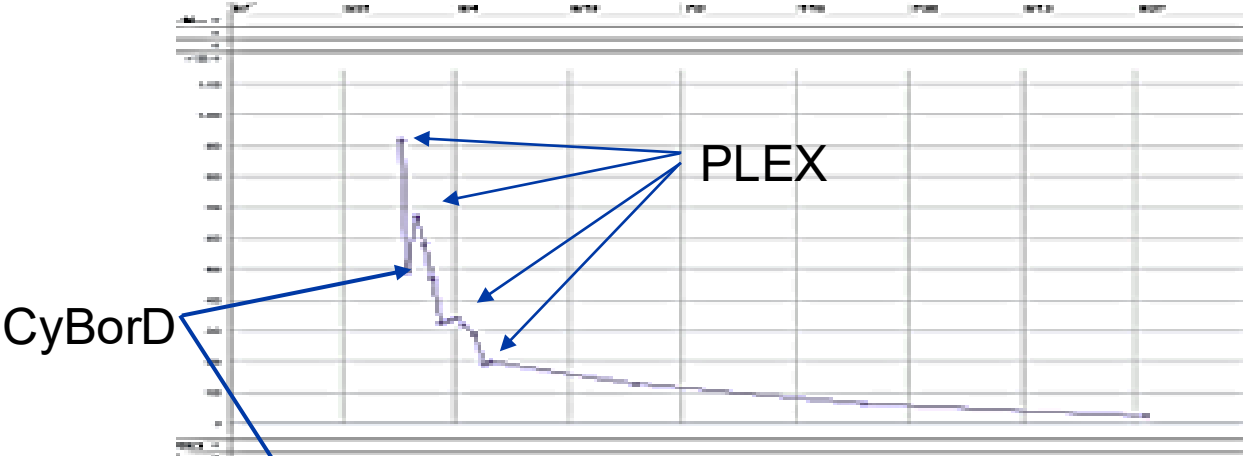
Arguments against PLEX

1. It is ineffective at removing
FLC



Patient with presumed LCCN

Lambda FLC



Scr



FLC reduction with extracorporeal devices

	Conventional HD/ PD, N = 148	HCO-HD, N = 550	MCO-HD, N = 55	Adsorption, N = 151	PLEX, N = 257	HDF (n = 29)
Publications	[6, 9, 10, 13–17]	[9, 10, 13, 15, 16, 18–38]	[38]	[17, 39–52]	[5–8, 20, 53–62]	[14, 18, 39]
Reduction in FLC for each session, mean±SD	Median 21±8% (in 102 of 148 patients) 21±10 (in 101 patients)	62±15% (among 344 of 550) 62±15% (among 299 patients)	70% for <i>kappa</i> and 37% for <i>lambda</i>	39±16% (among 59 of 151 patients) 39±15 (among 56 patients)	35±13% (among the 52 patients) 55±24 (among six patients)	63±10% 63±10% (among 29 patients)
Reduction in FLC after the first cycle, mean±SD	Mean 70±6% (in 56 of 148 patients) 71±1 (among 55 patients)	88±11% (among 246 of 550) 89±6 (among 224 patients)	Not available	60±13% (among 110 of 151) 60±13% (among patients)	72±19% (among 78 of patients) 86±7% (among 40 patients)	Not available
Renal recovery, mean %	31% (among 94 patients with available data) 33% (in 80 patients)	58% (among 371 patients with available data) 56% (among 330 patients)	92%	52% (among 126 patients with available data) 52% (among 126 patients)	50% (among 233 patients) 84% (among 25 patients)	53% among 16 patients with available data)
Patient survival, mean % (short-term, usually within 3–6 months of follow-up)	18% (among 55 patients with available data) 18 (among 55 patients)	53% (among 167 patients with available data) 53% (among 164 patients)	62%	76% (among only 31 patients with available data) 76% (among only 31 patients)	73% (among the 165 patients) 96% (among 26 patients)	59% (among 16 patients with available data)

Arguments against PLEX

1. It is ineffective in removing FLC
2. Clinical trials are inconclusive

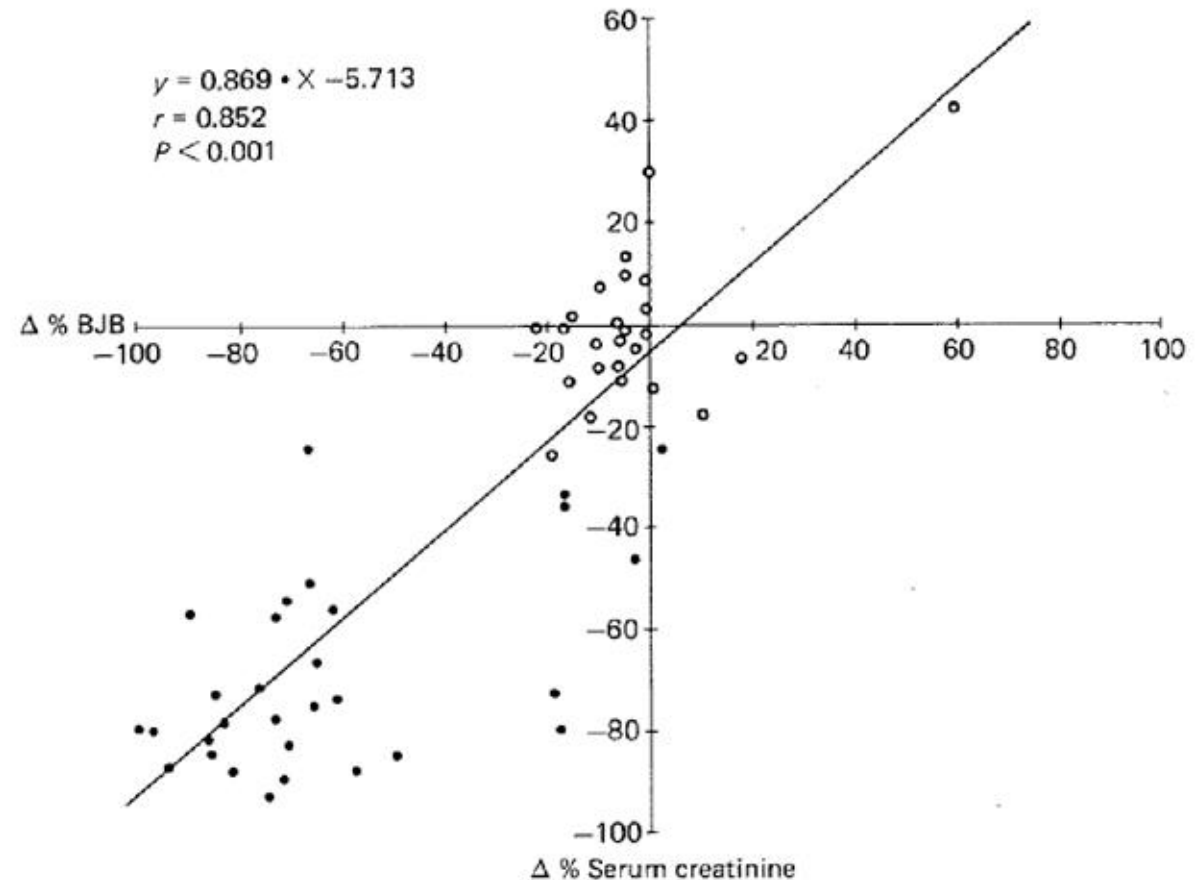


Results of Plasma Exchange Trials

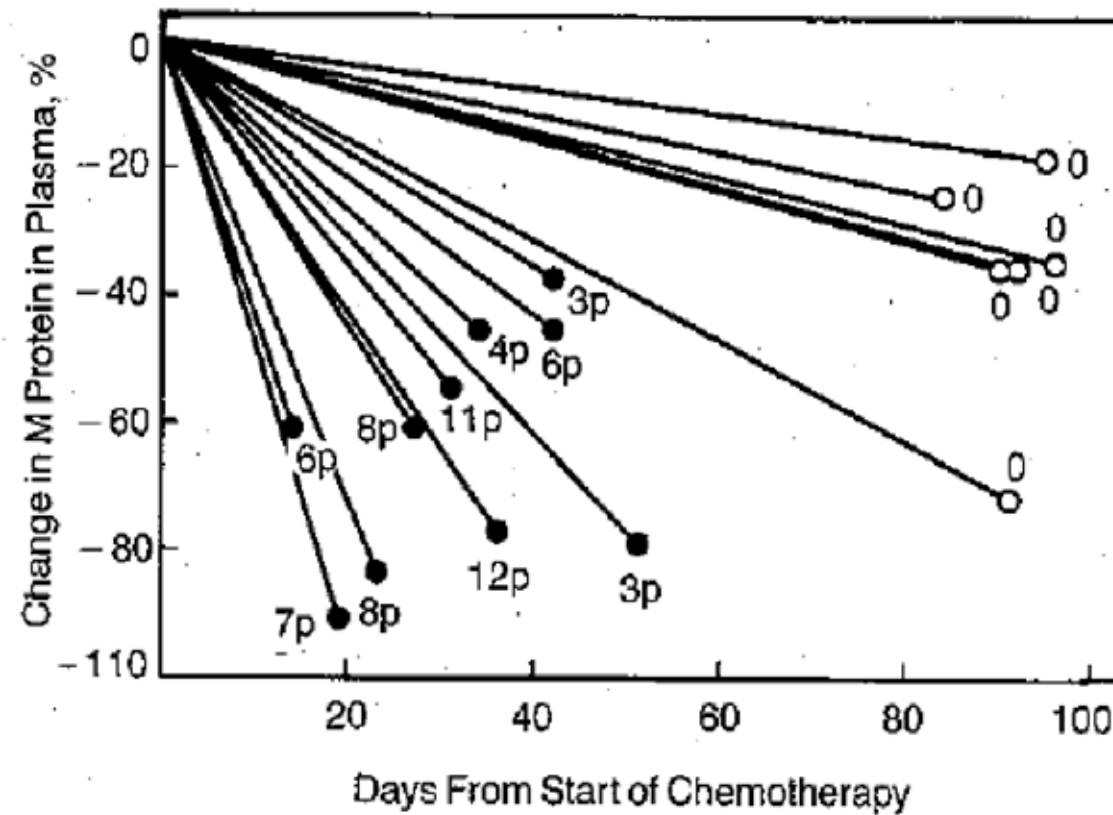
	Zucchelli	Johnson	Clark	Behrens
Patients	29	21	104	78
Biopsy	58.6%	76%	<i>few</i>	<i>unknown</i>
Dialysis	82.8%	57.1%	27.9%	61.5%
PLEX	5 daily, 7, 10	3x/wk	5-7/10 day	7 / 14 days
Chemo	CTX methylpred	MP	VAD	VAD
Renal response	84.6% v 18.2%	63.6% v 50%	57.9%* v 69.2%*	<i>unknown</i>
Dialysis ind	84.6% v 18.2%	42.8% v 0	66.7% vs 50%	44.7% vs 52.5%

Zucchelli Randomized Trial HD + PLEX vs PD

- Urine BJP reduction
 - PLEX 4.43 → 0.81 g/d
 - Control 3.23 → 2.98 g/d
- Renal function recovery
 - PLEX – 11/13
 - Control – 2/11



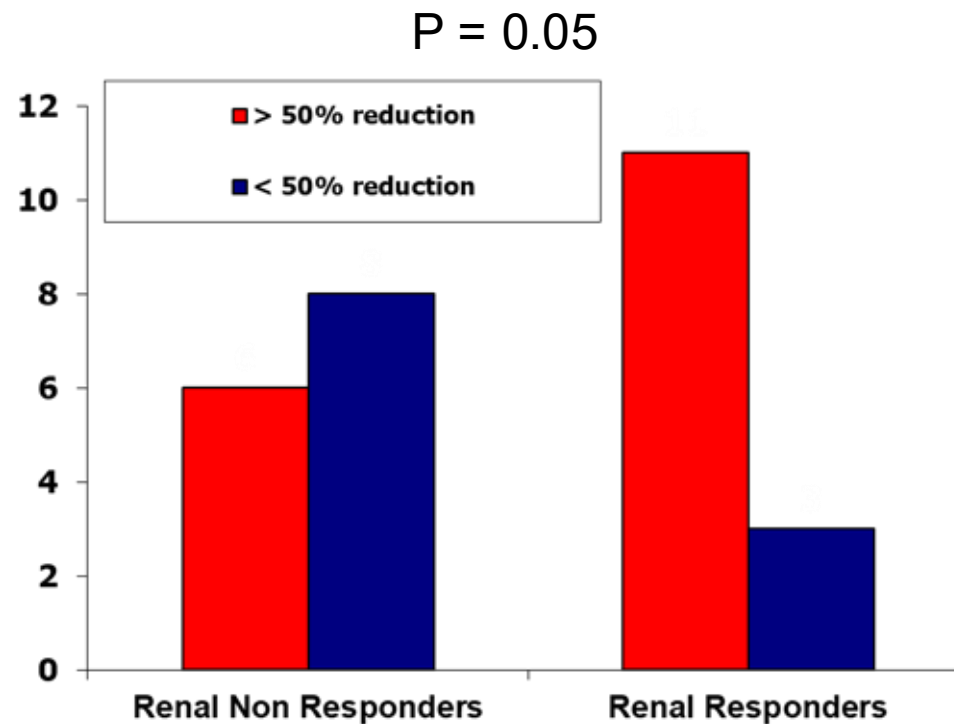
Reduction of M-protein with and without PLEX



Results of Plasma Exchange Trials

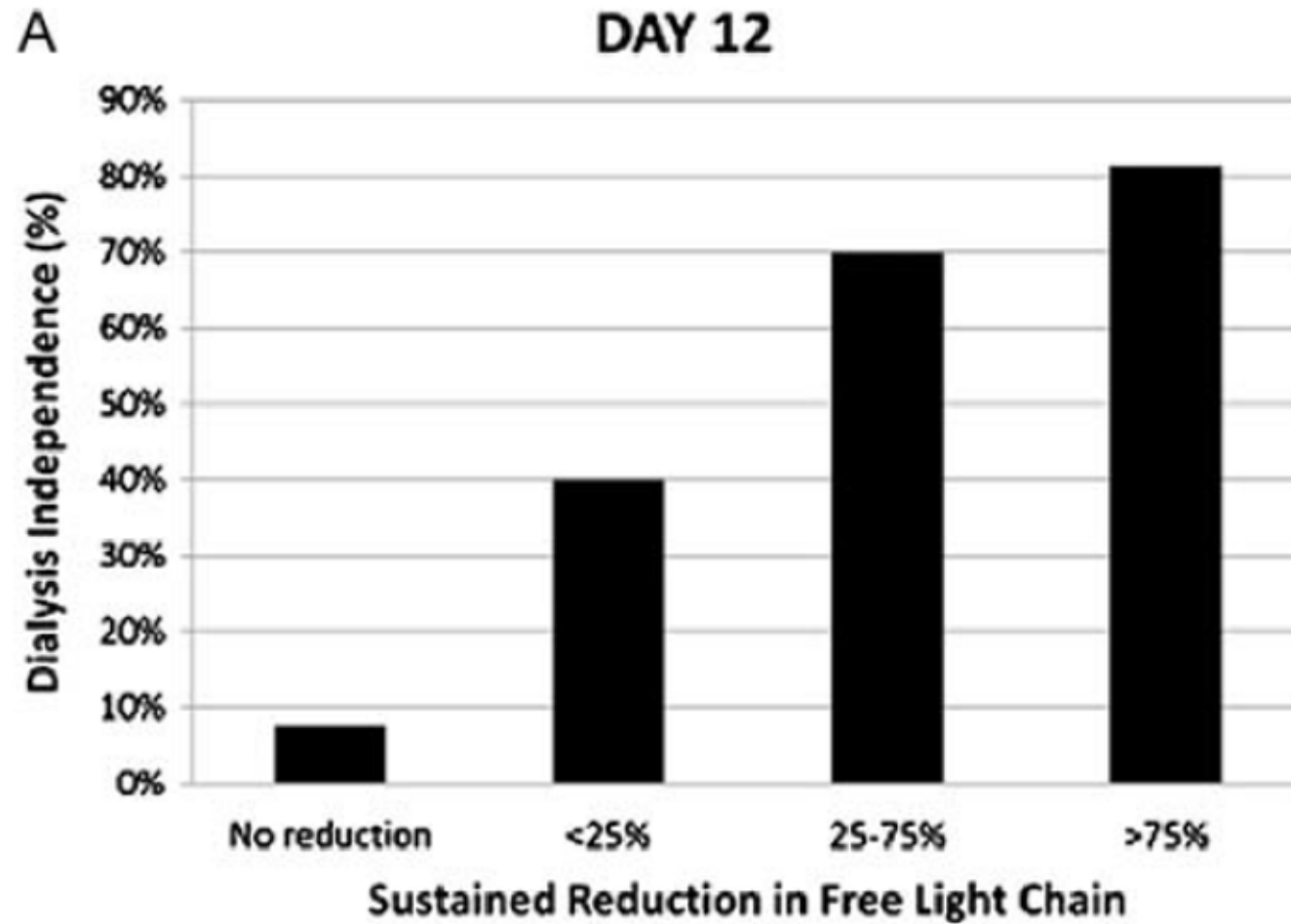
	<u>Zucchelli</u>	<u>Johnson</u>	<u>Clark</u>	<u>Behrens</u>
Patients	29	21	104	78
Biopsy	58.6%	76%	few	unknown
Dialysis	82.8%	57.1%	27.9%	61.5%
PLEX	5 daily, 7, 10	3x/wk	5-7/10 day	7/ 14 days
Chemo	CTX methylpred	MP	VAD	VAD
Renal response	84.6% v 18.2%	63.6% v 50%	57.9% v 69.2%	unknown
Dialysis ind	84.6% v 18.2%	42.8% v 0	66.7% vs 50%	44.7% vs 52.5%
Hem response	decreased BJP	decreased BJP	not mentioned	not mentioned

Improvement of acute renal function in patients with MM



- Factor associated with renal recovery
 - sFLC was reduced by 50%
 - Cast nephropathy

Renal recovery after HCO dialyzer



Variables associated with kidney recovery

	No. of Patients	No. of Events	Bivariable Analysis		Multivariable Analysis	
			Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Age group, y						
65	63	30	1 [Reference]	.72		
≥65	31	16	0.85 (0.36-2.02)			
Monoclonal gammopathy of undetermined significance						
No preexisting	76	38	1 [Reference]	.67		
Preexisting	18	8	0.80 (0.28-2.25)			
Chronic kidney disease						
No preexisting	83	40	1 [Reference]	.69		
Preexisting ^a	11	6	1.29 (0.36-4.56)			
Type of myeloma ^b						
Light chain	45	16	1 [Reference]	.02	1 [Reference]	.03
Whole immunoglobulin	49	30	2.62 (1.14-6.05)		2.75 (1.11-6.80)	
Light chain isotype						
κ	51	24	1 [Reference]	.69		
λ	43	22	1.18 (0.52-2.66)			
Cytogenetics						
Standard risk	46	23	1 [Reference]	>.99		
High risk ^c	12	6	1.00 (0.28-3.56)			
Baseline serum-free light chain level, mg/L ^d						
<3000	20	13	1 [Reference]	.13		
3000-5999	26	11	0.39 (0.12-1.32)			
6000-11 999	17	10	0.77 (0.20-2.92)			
≥12 000	18	12	0.40 (0.12-1.32)			
After first chemotherapy cycle, level of involved serum-free light chain, mg/L ^e						
>500	59	23	1 [Reference]	.01	1 [Reference]	.049
≤500	35	23	3.00 (1.25-7.18)		2.51 (1.00-6.33)	
Randomization group ^f						
Conventional hemodialysis	48	18	1 [Reference]	.02	1 [Reference]	.03
High-cutoff hemodialysis	46	28	2.59 (1.13-5.97)		2.78 (1.13-6.80)	

Factors the predicts renal response

Variable	Univariate Analyses		Multivariate Analysis	
	OR (95% CI)	P	OR (95% CI)	P
Age $\geq$ 65 years	0.43 (0.22 to 0.82)	.011		
Preexisting MGUS	1.57 (0.65 to 3.77)	.31		
Entire Ig-secreting myeloma	1.44 (0.79 to 2.65)	.23		
Precipitating factor	1.82 (0.99 to 3.36)	.055		
Known preexisting CKD*	0.08 (0.017 to 0.36)	.001	0.59 (0.47 to 0.75)	< .0001
Serum creatinine at random assignment	1.00 (0.99 to 1.00)	.009		
AKIN stage 3	0.52 (0.28 to 0.97)	.039	0.86 (0.75 to 0.98)	.026
sFLC < 500 mg/L after 1 cycle of chemotherapy	1.52 (0.81 to 2.85)	.19		
sFLC response within 6 months, %				
< 50	1.00 (reference)		1.00 (reference)	
50-90	9.84 (3.02 to 32.1)	.0001	1.44 (1.14 to 1.83)	.0027
> 90	4.20 (1.19 to 14.8)	.026	1.70 (1.37 to 2.10)	< .0001
Random assignment in C-BD group	1.33 (0.73 to 2.43)	.36		

VISTA

	VMP		MP	
	Normal	RI	Normal	RI
ISS III	21%	62%	22%	54%
≤ 30 ml/min		5.5%		4.5%
Overall Response	71%	74%	35%	47%
CR	30%	30%	3%	4%
≤ 30 ml/min		37%		13%
First response	1.4m	1.0m	4.9m	3.4m
Median TTP	NE	19.9m	18.0m	16.1m
Median OS	NE	NE	NE	31.9m

* Serum Cr ≤ 2.0 mg/dl

Early daratumumab therapy improves renal outcomes in newly diagnosed patients with myeloma admitted with kidney injury

Characteristics	N = 20
Age at diagnosis, y	
Median (range)	65 (44-87)
Subgroup, n (%)	
18 to <65	10 (50)
≥65 to <75	7 (35)
≥75	3 (15)
Male, n (%)	9 (45)
Peak SCr at admission, median (range), mg/dL	6.5 (3.1-17.8)
eGFR (CKD-EPI), median (range), mL/min per 1.73 m ²	8 (2-16)
Requiring dialysis during hospitalization, n (%)	9 (45)
Peak involved sFLC at diagnosis, median (range), mg/L	6603 (1839-26 023)
HRCAs*, n (%)	
0	9 (45)
1	9 (45)
≥2	2 (10)
Extramedullary disease, n (%)	2 (10)

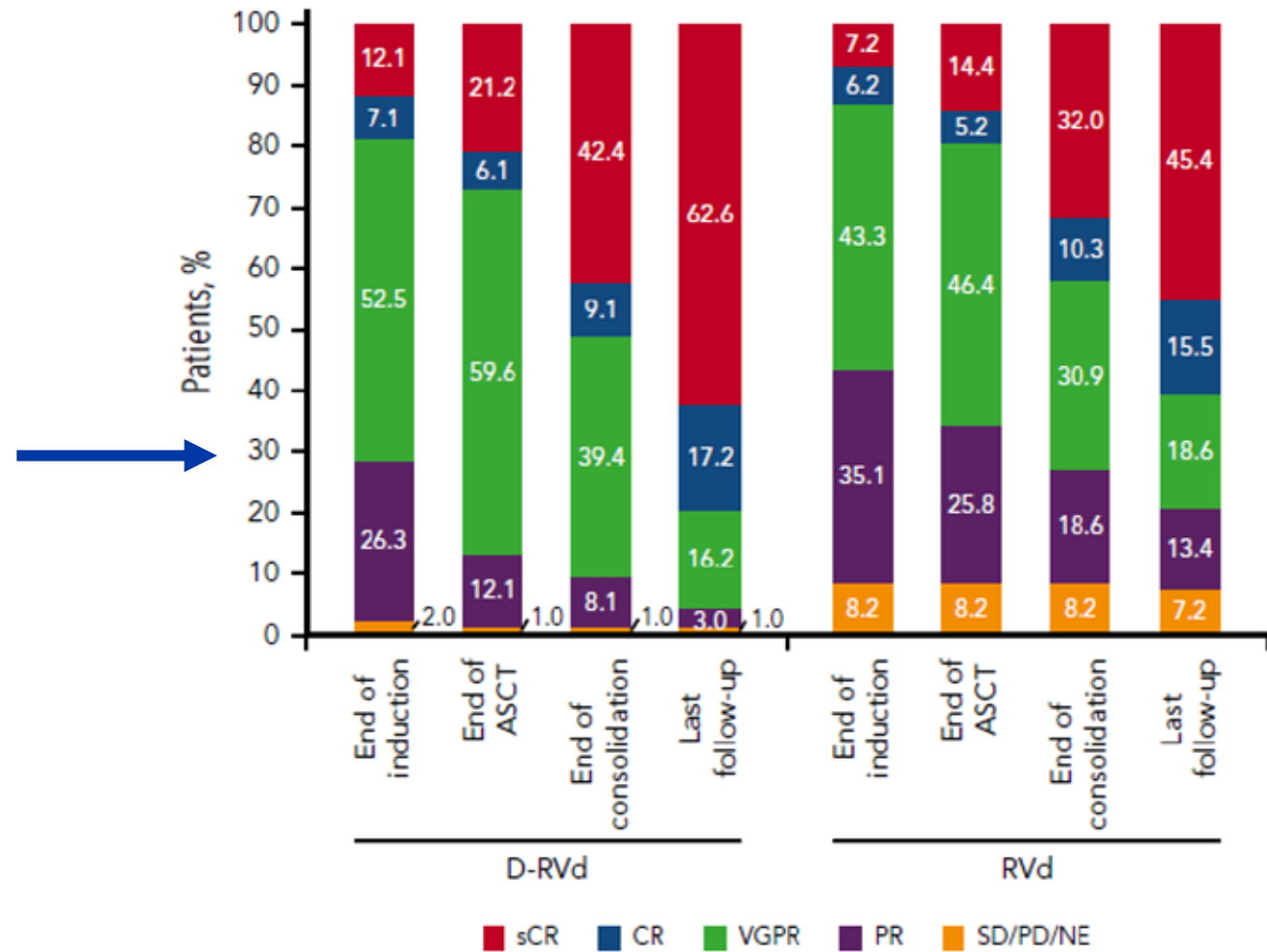
- DaraVCD – 11, DaraVD – 9
- All patients had ≥ 50% FLC reduction with a median of 3 days
- Median time to FLC ≤ 500 mg/L was 14.5 days
- ≥VGPR – 90%
- Renal response at 3m = 85%
- At 3m 4 of 9 and at 12m 6 of 9 achieved dialysis independence

Response and response time to myeloma therapies

	<u>HR</u>	<u>VGPR/CR</u>	<u>Time to HR</u>	<u>% FLC < 50 mg/dl</u>
MP	47%	13%	3.5 m	
VMP	71%	30%	1.4m	
VAD	36%	9%	ND	
PAD	75%	33%	ND	
RD	71.5%	23.4%	ND	
VD	78.3%	46.8%		75%
VRD	81.5 - 93.8%	89.2%	ND	
VCD	77.2 - 83.4%	53.3 - 56.2%		72.8%
VTD	92.3%	66.3%	ND	
DVRD	96.6 - 99%	90.9 - 95.2%	ND	

Bridoux et al. JCO 2020; Dimopoulos et al. JCO 2009; Durie et al. Lancet 2017; Moreau et al. Blood 2018; Scheid et al. Haematologica; 2014; Voorhees et al. Blood 2020

Hematologic response after D-VRD (GRIFFIN)



Question

- Since PLEX is only performed for a short time (5 – 7 sessions), did PLEX fail or did the chemotherapy fail?

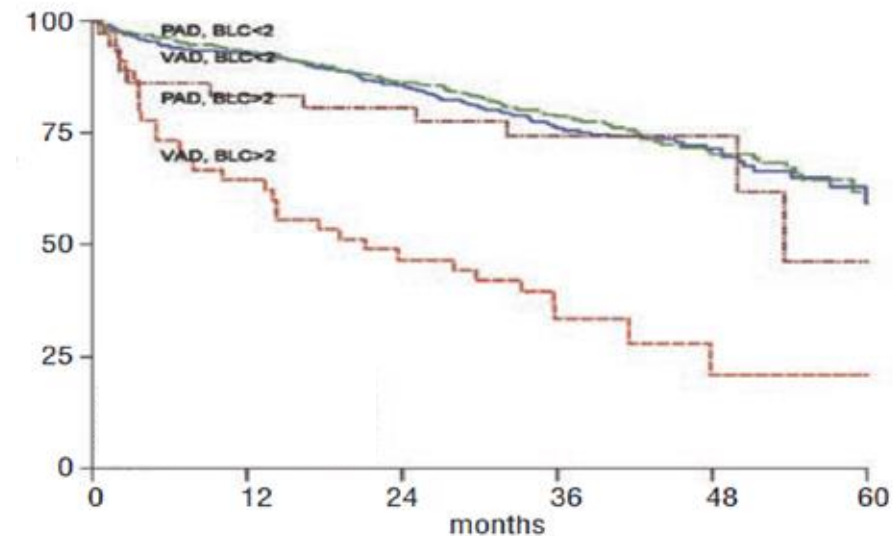
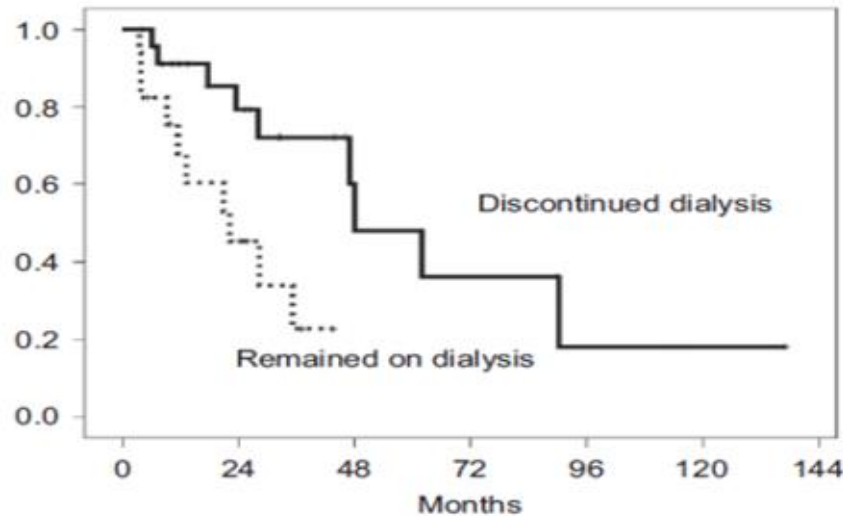
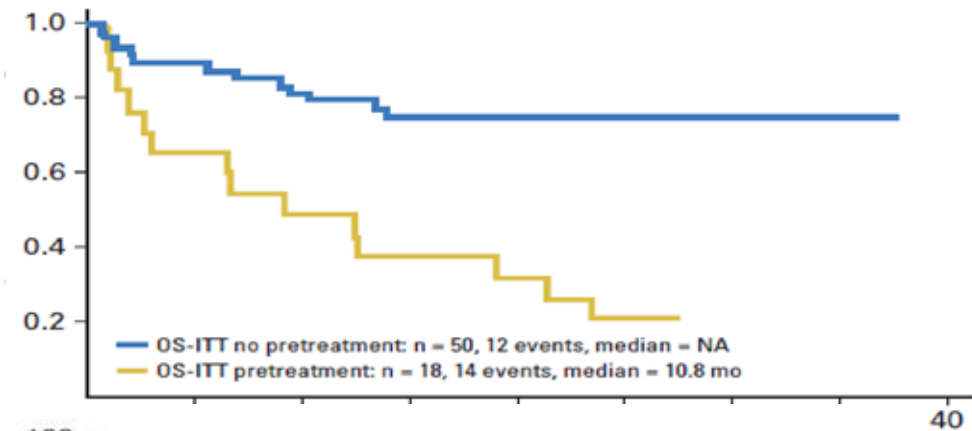
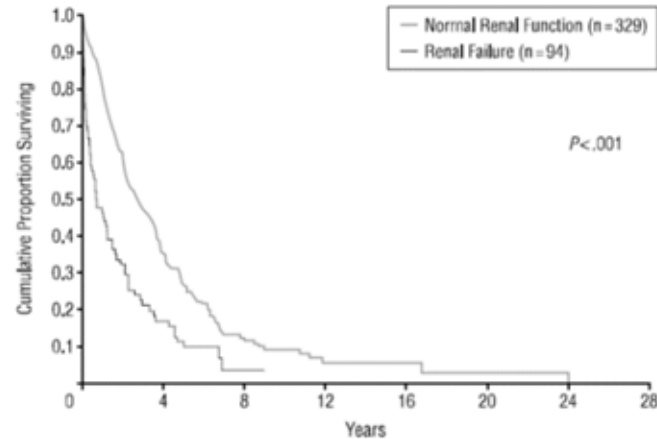
Results of Plasma Exchange Trials

	Zucchelli	Johnson	Clark	Behrens
Patients	29	21	104	78
Biopsy	58.6%	76%	few	unknown
Dialysis	82.8%	57.1%	27.9%	61.5%
PLEX	5 daily, 7, 10	3x/wk	5-7/10 day	7/ 14 days
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Renal response	84.6% v 18.2%	63.6% v 50%	57.9% v 69.2%	unknown
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Mathematical model of time to eliminate 95% of FLC

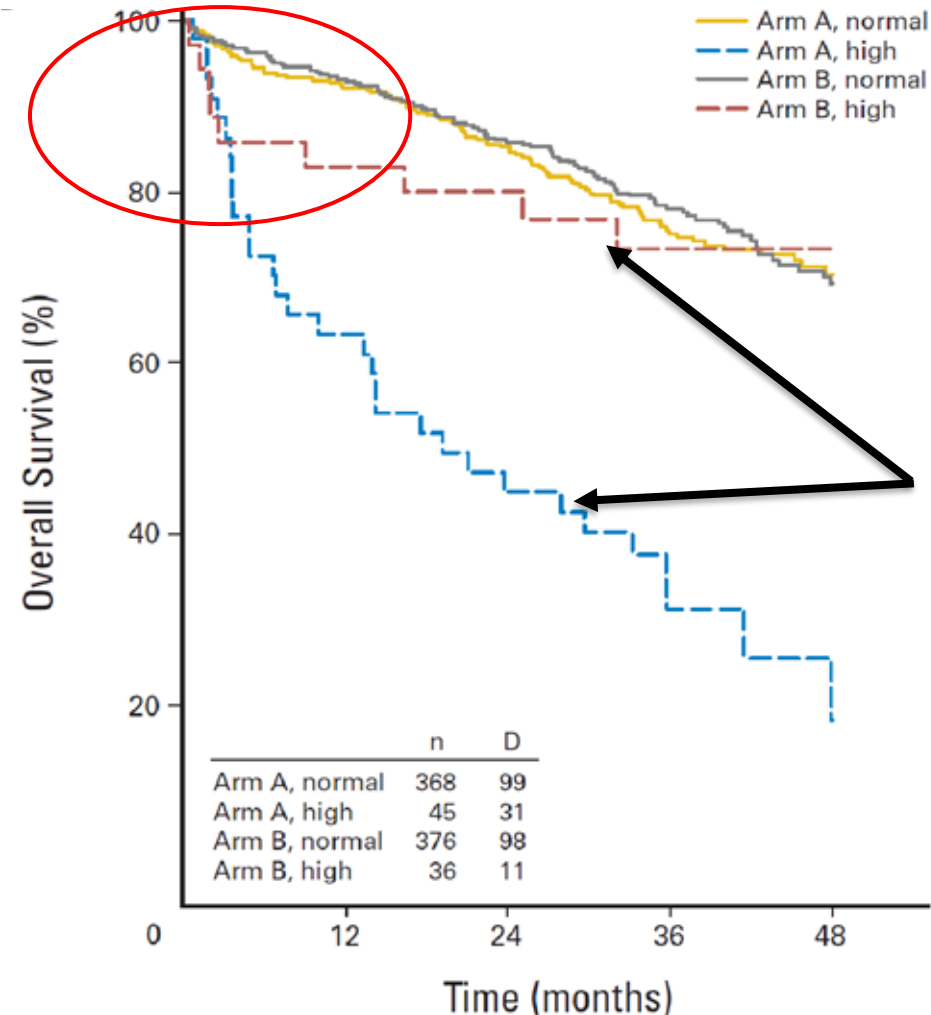
Method of FLC Removal	Percentage of FLC Removed by Intervention (and Time [D], to Reduce from 10 to 0.5 g/L) with Different Chemotherapeutic Tumor Killing Rates ^c				
	100%	10%	5%	2%	0%
None	NA (14) ¹	NA (30) ²	NA (52)	NA (121)	NA (10 g/L) ^{b 8}
PE ×6 in 10 d	29 (10)	24 (29) ³	17 (52)	9 (121)	3 (10 g/L) ^b
PE ×10 in 10 d	40 (8)	34 (29)	25 (52)	13 (121)	4 (10 g/L) ^b
HD 4 h ×3/wk	60 (7)	54 (19) ⁴	53 (31)	51 (73)	50 (3.6 g/L) ^b
HD 4 h/d	76 (4)	73 (13) ⁵	72 (23)	71 (55)	70 (1.9 g/L) ^b
HD 8 h alternate days	79 (4)	73 (13)	72 (19)	70 (47)	69 (1.5 g/L) ^{b 7}
HD 8 h/d	87 (3)	85 (7)	84 (14)	83 (29)	82 (1.0 g/L) ^b
HD 12 h/d	91 (2)	89 (5) ⁶	89 (8)	88 (16)	88 (0.7 g/L) ^b
HD 18 h/d	93 (2)	93 (3)	93 (4)	92 (8)	91 (0.6 g/L) ^b

Renal impairment impacts early mortality in patients with multiple myeloma

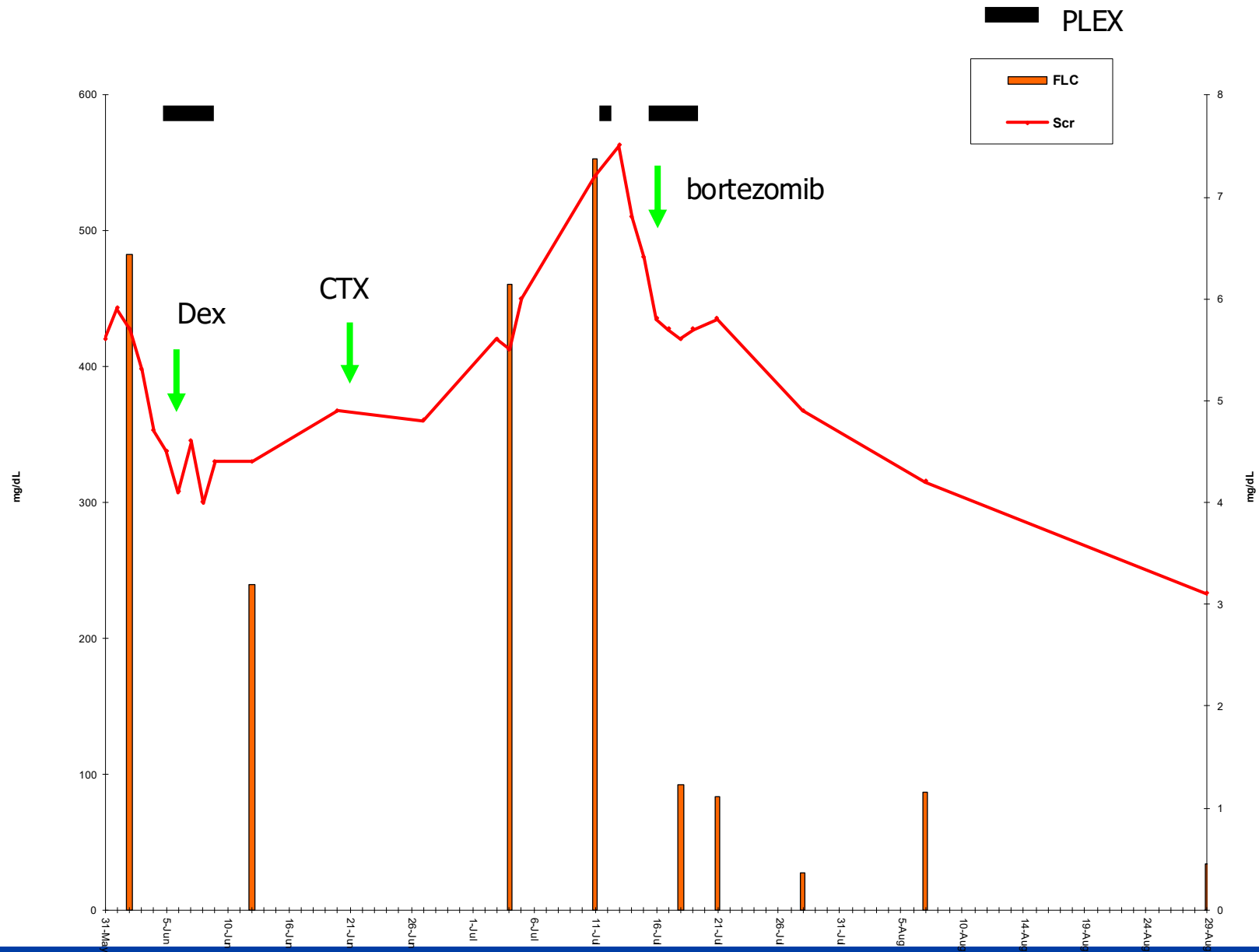


Bortezomib before and after autologous stem cell transplantation overcomes the negative prognostic impact of renal impairment in newly diagnosed multiple myeloma: a subgroup analysis from the HOVON-65/GMMG-HD4 trial

Bortezomib Adriamycin
dexamethasone (PAD)
vs Vincristine Adriamycin
dexamethasone (VAD)



Patients with high
serum creatinine



Summary

- While clinical trials have failed to consistently demonstrate a benefit, there is not a harm.
- Benefits to individualized patients cannot be excluded
- Until we have chemotherapy that is 100% effective and can eliminate FLC rapidly, extracorporeal methods of removing FLC may have a role in LCCN

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Onconeurology Team



Lourdes
Gonzales



Mireille El Ters



Carrie
Schinstock



Sandra
Herrmann



Leticia Rolon



Aleksandra Kukla

Panel Discussion: Key Questions

1

Approach Changes

Any thoughts on the new reduced EF and hypotension and how does that change your approach?

2

Ideal Trial Design

What would your ideal clinical trial for plasmapheresis look like?

3

Future & T-Cell Era

How do you see the future of plasmapheresis in LCCN evolve in the era of T-Cell engager therapies?



Thank You

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For your invaluable advice, guidance, and clinical expertise.