Brigham and Women's Hospital
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Case of Unknown Cause of Acute Kidney Injury on Chronic Kidney Disease

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CONTINUING MEDICAL EDUCATION
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Disclosures

I have no relevant financial relationships with ineligible companies.

Challenging Case Discussion

When CKD Doesn't Behave as Expected

- Progressive kidney dysfunction in a patient with established CKD
- Recognizing when to look beyond ‘natural’ progression of underlying disease
- Diagnostic reasoning in AKI / subacute kidney injury superimposed on CKD

Learning Objectives

-Develop a structured differential diagnosis for (sub)acute kidney injury superimposed on chronic kidney disease, including recognition of findings that suggest a process other than progression of underlying CKD.

-Evaluate the potential contributions of medications, supplements, and dietary exposures to worsening kidney function, and distinguish expected kidney function changes from clinically significant kidney injury.

-Identify clinical scenarios in which kidney biopsy may provide essential diagnostic information and alter management in patients with unexplained AKI on CKD.

Case Introduction

73-year-old man with…

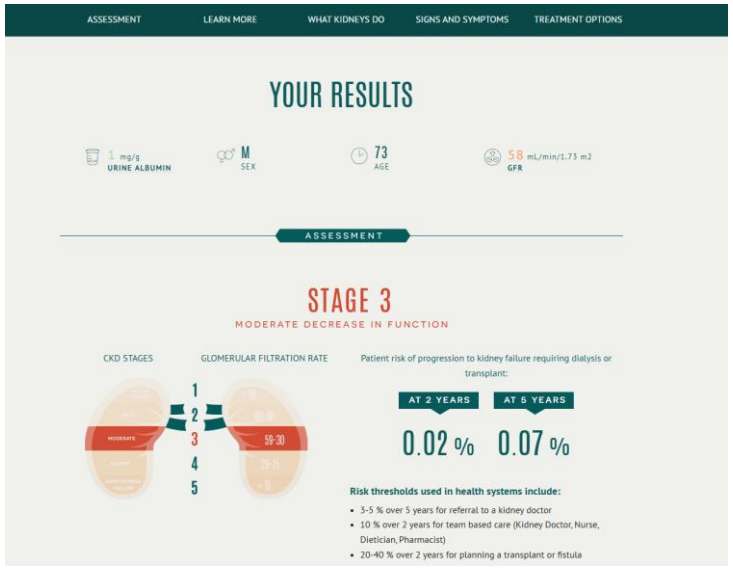
Past medical history:

CKD stage 3a in the setting of
-Remote prostate cancer (s/p beam radiation)
-Hypertension
-Obesity
-Type 2 diabetes mellitus (off meds, lifestyle)
-Afib

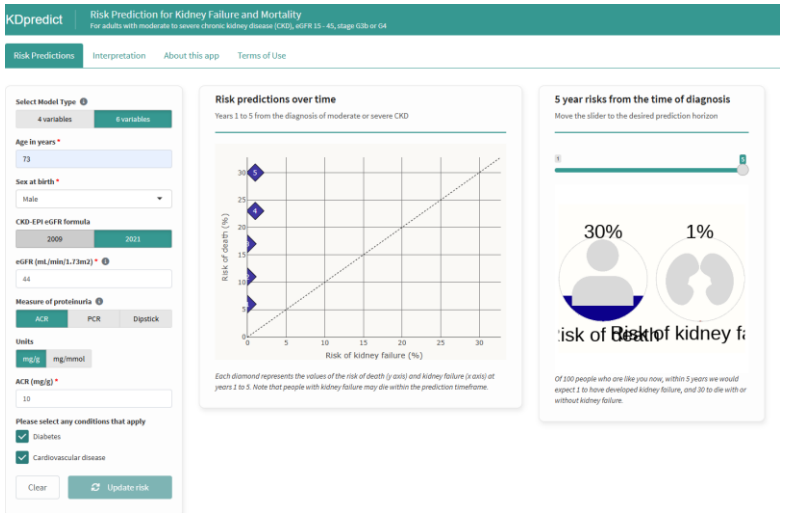
Baseline creatinine: 1.3 mg/dL for decades
*eGFR-Cr (50s)
Urine: Bland, no cells, no proteinuria.

Current medications: ACE inhibitor, Statin, PPI, Eliquis, Metoprolol, Lasix, Glucosamine, D3, omega fatty acids, MVWM

kidneyfailurerisk.com = < 1% 5 yr ESRD risks



https://kdpredict.com= mortality 30% vs kidney failure 1%



Clinical Course

Stable CKD attributed to comorbidities and patient elected to follow with PCP, return to nephrology if issues.
During routine follow up, PCP noted Cr started to elevate after years of stability.
Routed back to nephrology (5-year gap)…

Creatinine trend (*over past several months*):

Time	Creatinine	eGFR
Baseline	1.3	56
Follow-up	1.6	44
	1.8	38
	2.1	32
	2.4	27
Last	2.9	21

Questions:
Is this expected?
Is this DKD progression?
Does the trajectory fit?
Is this hemodynamic (from medications)?

Remains highly engaged with his health.
Recent additions to his regimen include Ozempic (semaglutide, GLP1RA), Jardiance (empagliflozin, SGLT2i), Kerendia (finerenone, ns-MRA).
Recent bouts of diarrhea (unclear cause- eating healthy plant forward diet).

Decline in kidney function in various populations

Reference	Population	*N*	GFR decline
	Healthy		
Slack TK[216]	Healthy kidney donors	141	0.40 ml/min/year
Rowe JW et al.[217]	Healthy males	293	0.90 ml/min/1.73 m^2/year (CrCl)
Lindeman RD[218]	Healthy males	254	0.75 ml/min/year (CrCl)
Halbesma N et al.[219]	PREVEND cohort (all participants)	6894	0.55 ml/min/1.73 m^2/year
Imai E et al.[220]	Annual health exam participants in Japan	120,727	0.36 ml/min/1.73 m^2/year
Matsuchita K et al.[221]	Atherosclerosis Risk In Communities Cohort	13,029	0.47%/year (median)
Kronborg J et al.[222]	Healthy adults from Norway	4441	1.21 ml/min/1.73 m^2/year (men) 1.19 ml/min/1.73 m^2/year (women)
	With comorbidity		
Lindeman RD[218]	Males with renal/urinary tract disease	118	1.10 ml/min/year (CrCl)
Lindeman RD[218]	Males with hypertension	74	0.92 ml/min/year (CrCl)
Halbesma N et al.[219]	PREVEND cohort – adults with macroalbuminuria (>300 mg/24 hours)	86	1.71 ml/min/1.73 m^2/year
Halbesma N et al.[219]	PREVEND cohort - Adults with impaired renal function (5% lowest CrCl/MDRD GFR)	68	0.05 ml/min/1.73 m^2/year
Imai E et al.[220]	Annual health exam participants in Japan with hypertension	16,722	0.3 to 0.5 ml/min/1.73 m^2/year
Imai E et al.[220]	Annual health exam participants in Japan with proteinuria (⩾1+ dipstick proteinuria)	2054	0.6 to 0.9 ml/min/1.73 m^2/year
	Older adults		
Hemmelgarn B et al.[223]	Males age >65 with diabetes	490	2.7 ml/min/1.73 m^2/year
Hemmelgarn B et al.[223]	Males age >65 without diabetes	2475	1.4 ml/min/1.73 m^2/year
Hemmelgarn B et al.[223]	Females age >65 with diabetes	445	2.1 ml/min/1.73 m^2/year
Hemmelgarn B et al.[223]	Females age >65 without diabetes	3163	0.8 ml/min/1.73 m^2/year
Keller C et al.[224]	Cardiovascular Health Study	4128	1.83 ml/min/1.73 m^2/year (based on cystatin C-based eGFR)

Abbreviations: CrCl, creatinine clearance; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; PREVEND, Prevention of Renal and Vascular End-Stage Disease.

Decline in kidney function in CKD populations

Study	Study population	N	Baseline GFR ml/min/1.73 m^2	Mean Follow-up years	GFR decline Mean (SD) or (95% CI) ml/min/1.73 m^2/year
MDRD Study Group[226]	Study A: GFR 25-80 ml/min/1.73 m^2	28	Mean (SD) 37.1 (8.7)	1.2	3.7 (7.6)
	Study B: GFR 7.5-24 ml/min/1.73 m^2	63	15.0 (4.5)		4.3 (4.7)
Klahr S et al.[227]	Study 1: GFR 25-55 ml/min/1.73 m^2		Mean (SD)	2.2 years	
	- Usual protein, usual MAP	145	37.6 (9.0)		4.5 (3.7 – 5.3)
	- Usual protein, low MAP	149	38.2 (8.6)		3.3 (2.5 – 4.1)
	- Low protein, usual MAP	140	38.9 (8.8)		3.3 (2.5 – 4.2)
	- Low protein, low MAP	151	39.7 (9.1)		2.3 (1.5 – 3.0)
	Study 2: GFR 13-45 ml/min/1.73 m^2				
	- Low protein, usual MAP	62	18.7 (3.1)		4.9 (3.8 – 5.9)
	- Low protein, low MAP	67	18.8 (3.3)		3.9 (3.2 – 4.7)
	- Very low protein, usual MAP	61	18.3 (3.7)		3.6 (2.8 – 4.4)
	- Very low protein, low MAP	65	18.4 (3.5)		3.5 (2.6 – 4.5)
Wright J et al.[228]	African Americans with hypertension and GFR 20-65 ml/min/1.73 m^2		Mean (SD)	4 years	Mean (SE)
	- Low MAP	380	46.0 (12.9)		2.21 (0.17)
	- Usual MAP	374	45.3 (13.2)		1.95 (0.17)
Eriksen B[229]	GFR categories G3a and G3b (GFR 30–59 ml/min/1.73 m^2)	3047	Median (IQR) 55.1 (50.8 – 57.9)	Median 3.7 years	Mean 1.03 ml/min/1.73 m^2/year
Jones C et al.[230]	Nephrology referrals with GFR categories G3a-G5 (GFR < 60 ml/min/1.73 m^2)	726	Median (IQR) 29 (18-38)	Median (IQR) 2.9 years (1.3 – 4.1)	Median 0.35 ml/min/1.73 m^2/year
Levin A et al.[231]	Nephrology referrals with GFR categories G3a-G5 (GFR < 60 ml/min/1.73 m^2)	4231	Median 33 ml/min/1.73 m^2	Median (IQR) 2.6 years (1.6-3.6)	Mean 2.65 ml/min/1.73 m^2/year

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; GFR, glomerular filtration rate; IQR, interquartile range; MAP, mean arterial pressure; MDRD, Modification of Diet in Renal Disease; SD, standard deviation; SE, standard error.

Kidney Int Suppl (2011). 2013 Jan;3(1):63-72

Initial Diagnostic Framework

Possible explanations

-**Progression** of diabetic kidney disease (outside of the expected ranges)

-**Prerenal** / **Hemodynamic** = Medication/ Volume effects
- -Hemodynamic effect of ACE inhibitor (established med, no recent changes)
- -Hemodynamic effect of SGLT2 inhibitor (recent change, GFR changes expected)
- -Hemodynamic/ volume effect (diuretic + above + GI losses + new GLP1RA + nsMRA)

-**Postrenal** = obstruction/ urological history
- - no symptoms
- - imaging

-**Intrinsic**
- -Sustained pre-renal/ hemodynamic insult = ATN
- -Glomerular disease
- -Tubulointerstitial disease
- -Vascular

Medication Review

Notable therapies:

-ACE inhibitor
-SGLT2 inhibitor
-GLP1 receptor agonist
-ns MRA
-PPI
-OTC – rare NSAIDs, vitamin C gummies

Question: Which medications could plausibly contribute?

SGLT2- inhibition and initial change in eGFR

Table 1. - Randomized controlled trials reporting an initial dip of eGFR

Trial Name	Agent Studied	Primary Outcomes	Observed Early Drop in eGFR
CREDENCE ([8])	Canagliflozin	Reduction in the composite risk of ESKD, doubling serum creatinine level, or death from renal or cardiovascular causes (HR, 0.70; 95% CI, 0.59 to 0.82), compared with placebo.	5 ml/min per 1.73 m^2
DAPA-CKD ([9])	Dapagliflozin	Reduction in the risk of 50% eGFR decline, ESKD, or death from renal or cardiovascular causes (HR, 0.61; 95% CI, 0.51 to 0.72), compared with placebo.	4 ml/min per 1.73 m^2
EMPEROR-Reduced ([5])	Empagliflozin	Reduction of the risk of cardiovascular death or hospitalization for worsening heart failure (HR, 0.75; 95% CI, 0.65 to 0.86), compared with placebo.	4 ml/min per 1.73 m^2
EMPA-REG Outcome ([11])	Empagliflozin	Canagliflozin decreased the risk of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (HR, 0.86; 95% CI, 0.74 to 0.99), compared with placebo.	3–4 ml/min per 1.73 m^2
CANTATA-SU ([12])	Canagliflozin	Canagliflozin slowed the progression of kidney disease compared with glimepiride in patients with type 2 DM ($P<0.01$ for each canagliflozin group versus glimepiride).	3–6 ml/min per 1.73 m^2

CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; HR, hazard ratio; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in CKD; EMPEROR-Reduced, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction; EMPA-REG Outcome, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; CANTATA-SU, Canagliflozin Treatment and Trial Analysis–Sulfonylurea; DM, diabetes mellitus.

Expected Kidney Function Changes

Medication	Expected Kidney Effect	When Should I Worry?
ACE inhibitor / ARB	Small early creatinine rise (often <10–20%; ≤30% acceptable)	>30% creatinine rise within ~4 weeks, persistent decline, hyperkalemia, hypotension
SGLT2 inhibitor	Early eGFR dip (~3–6 mL/min/1.73 m^2), then stabilization and slower long-term decline	Continued decline beyond the expected early dip, volume depletion, AKI
GLP-1 receptor agonist	No predictable eGFR dip	GI losses, dehydration, poor oral intake; rare AIN reported
Non-steroidal MRA (finerenone)	No predictable eGFR dip; mild BP lowering	Volume depletion, hypotension, hyperkalemia, intercurrent illness, especially with concomitant ACEi/ARB + SGLT2i + diuretics
PPI	No expected benign creatinine change	Acute interstitial nephritis (often with subtle or absent classic features)

Progressive decline so far after initiation is not the typical pattern.

Additional History and Evaluation

Plan: Volume assessment, medication/ supplementation review,
repeat BMP, UA/ urine ACR, renal ultrasound.

No: No frank hypotension, minimal NSAID use, no obstructive symptoms, acute diarrheal illness resolved, taking better po
Yes: Reports increased attention to diet; weight loss efforts; “juicing like mad” (spinach smoothies); over-the-counter gummy vitamin (C).
Urinalysis: Trace protein, no hematuria, no casts ; UACR: low, stable
Serum: Cr rising, some anemia, no hemolysis, no eosinophilia, normal calcium and lytes
Imaging: unrevealing

Question: What diagnoses remain?

AKI/ Subacute Kidney Injury on CKD: Reframing the Differential and Additional Evaluations

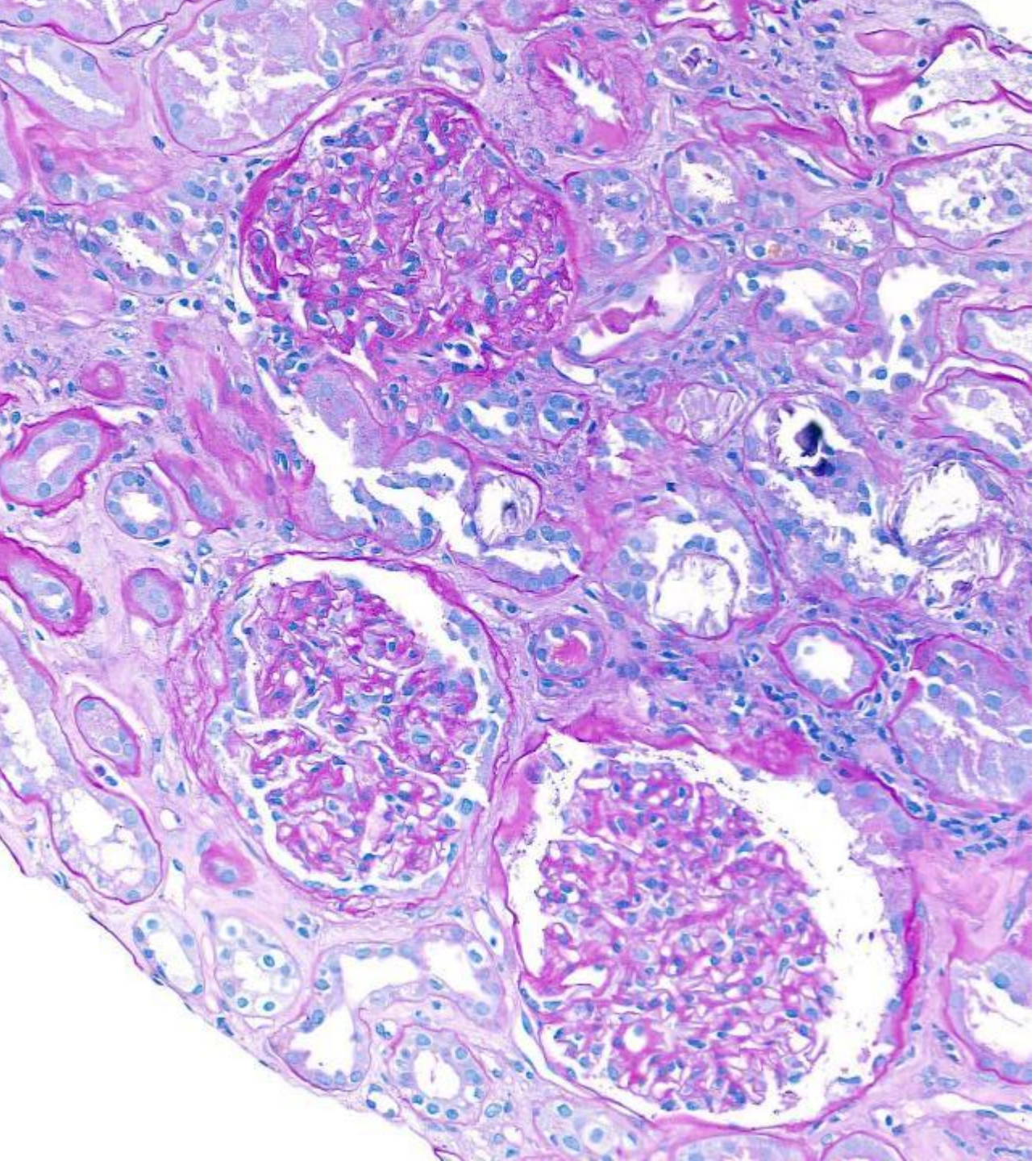
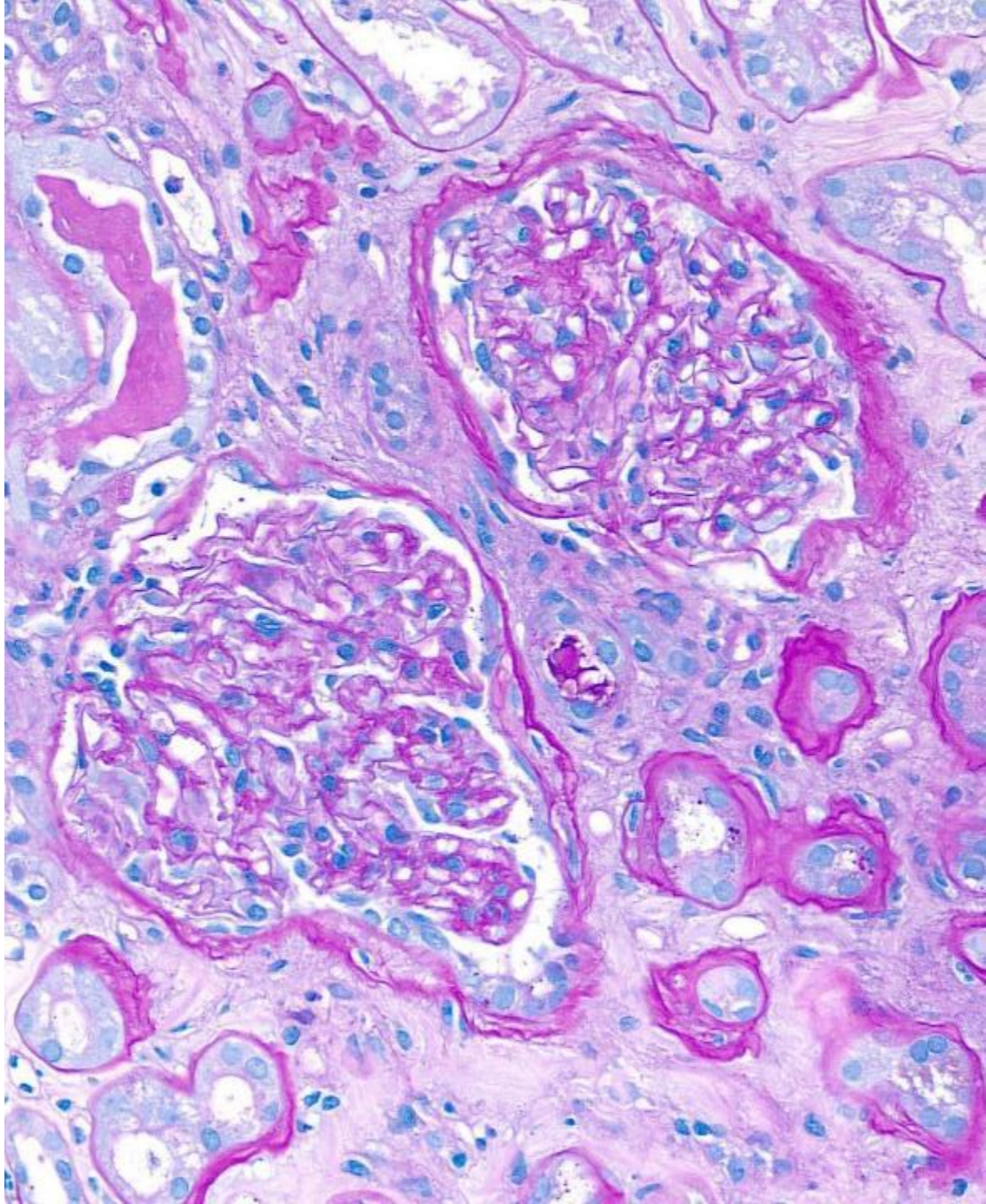
Hemodynamic/ pre-renal:
Potentiating meds/ volume losses (meds temporarily held, pushed po, no clear stabilization of function)
Postrenal: unlikely given history and findings (ultrasound negative).

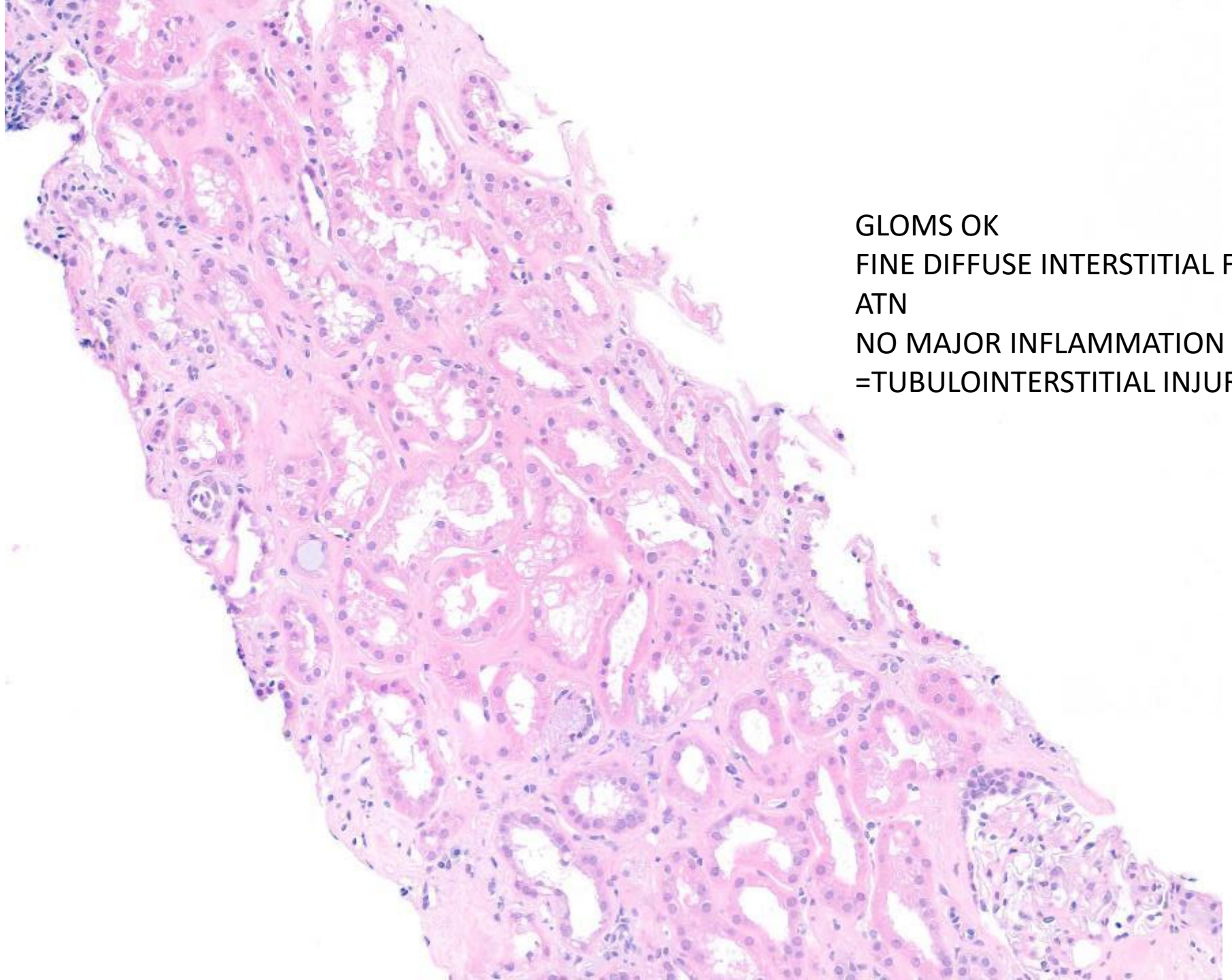
Intrinsic:
ATN (sustained hemodynamic insult, relative hypotension, ? toxin, inflammation)
Tubulointerstial disease (AIN- drug induced, crystal nephropathy, auto-immune)
Glomerular and vascular disease (Renal clinic sent serologies which returned normal - ANCA / GBM/ ANA/ Complements/ PLA2R / SPEP/SFLC/ viral serologies; furthermore, no evidence for large vessel disease, atheroembolic disease, MAHA/ TMA)

Would biopsy change management ?

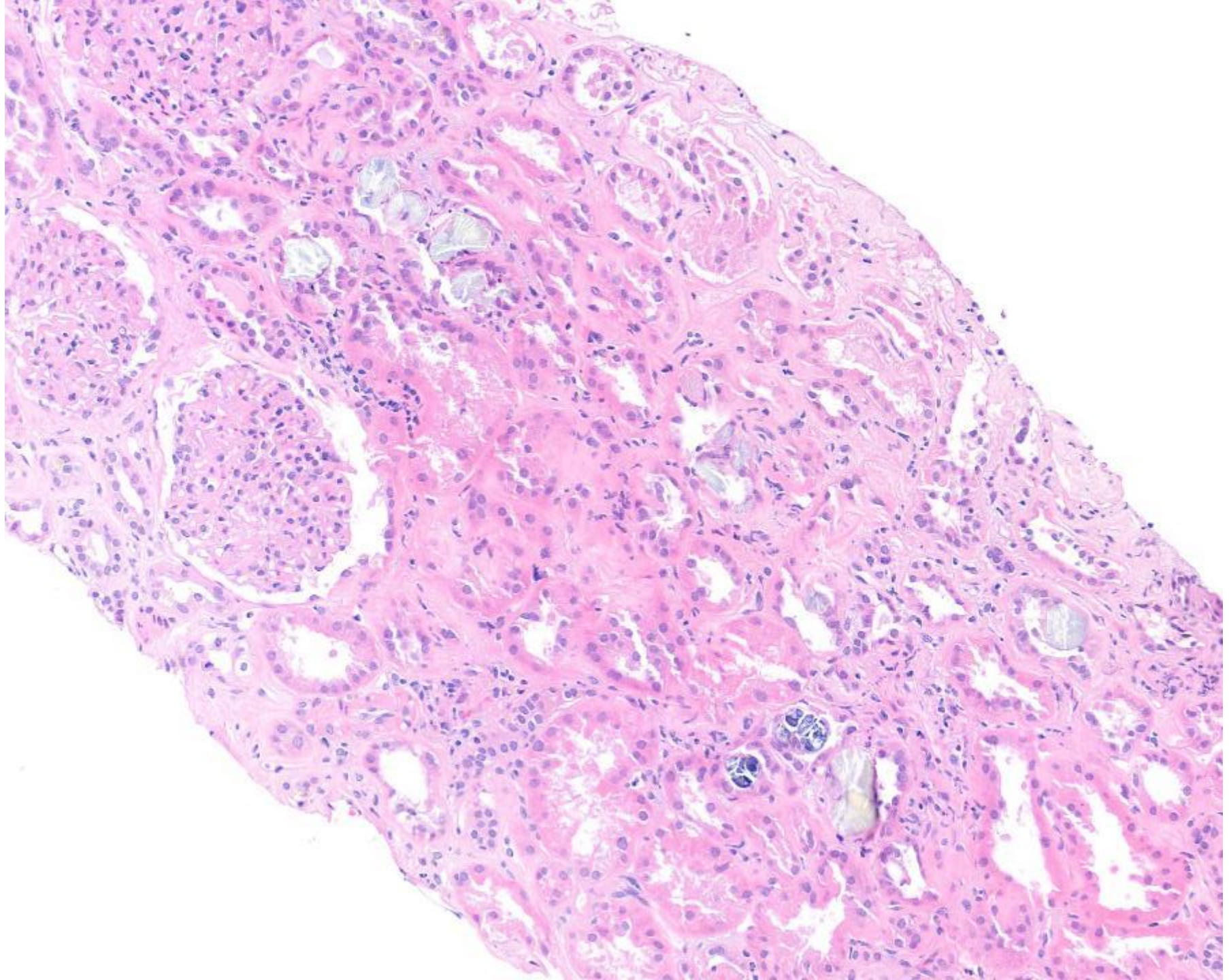
When Should We Consider Kidney Biopsy?

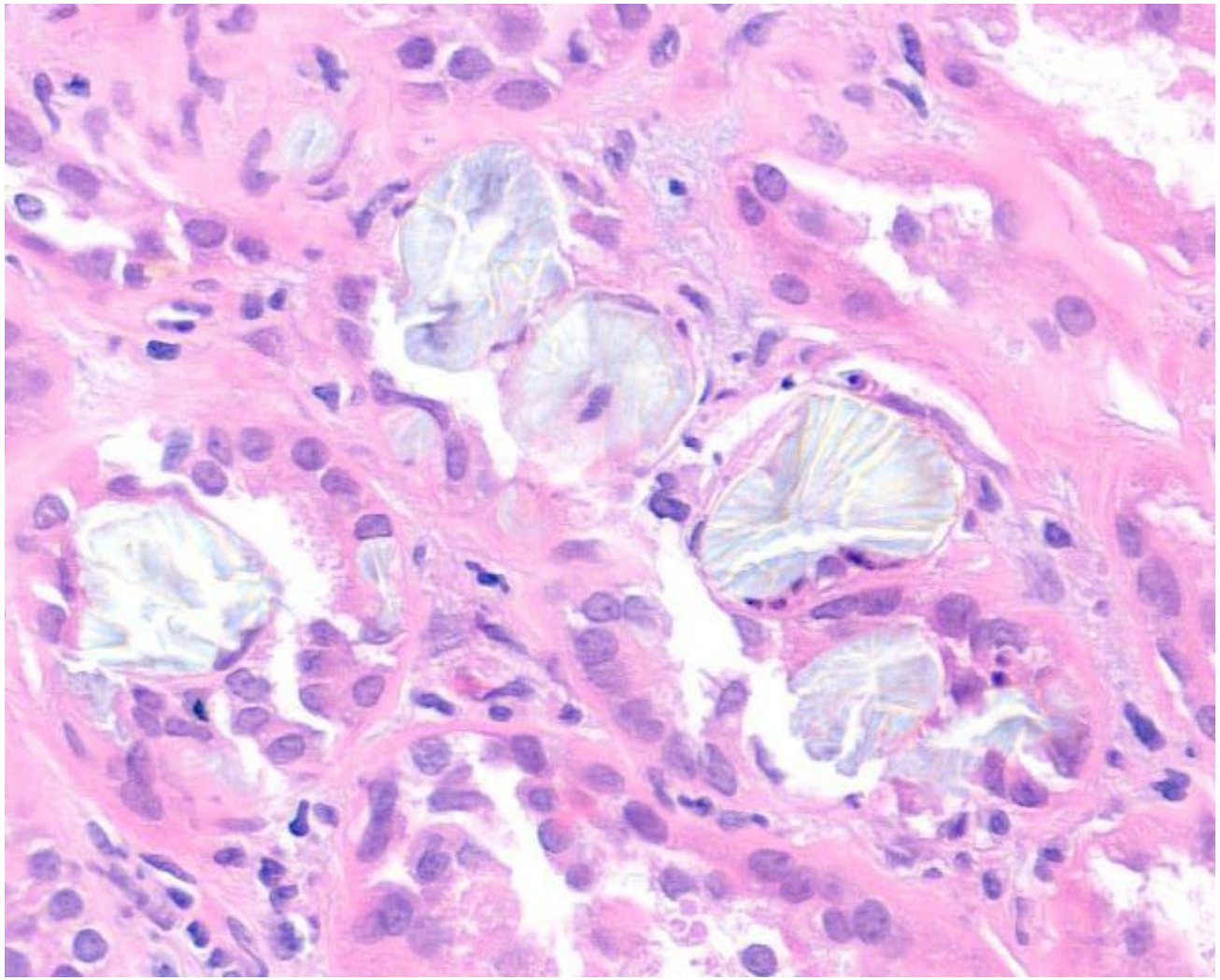
Potential indications:
Rapid decline in kidney function
Unexplained AKI
Clinical course inconsistent with presumed diagnosis
Diagnostic uncertainty likely to alter management

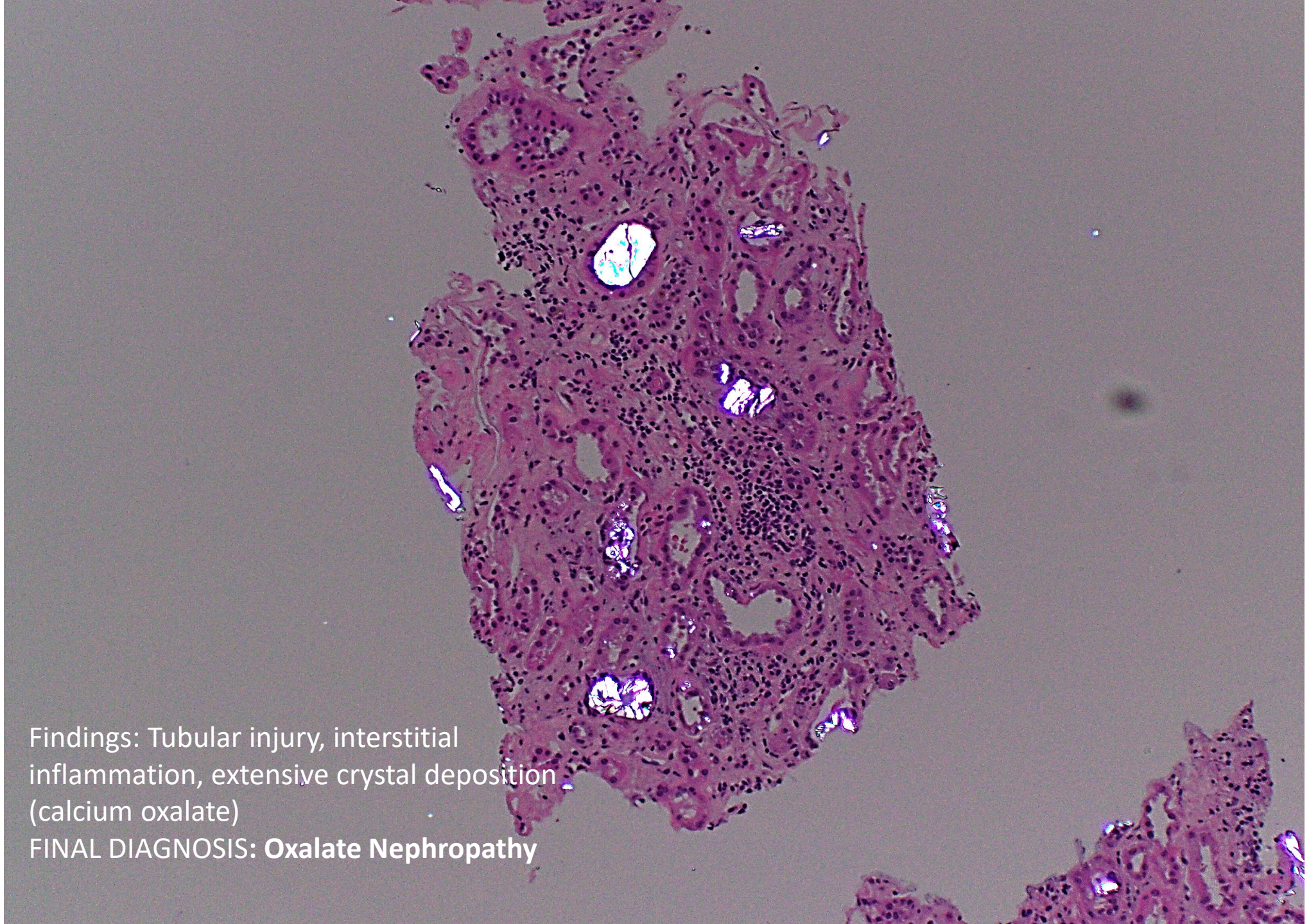





GLOMS OK
FINE DIFFUSE INTERSTITIAL FIBROSIS
ATN
NO MAJOR INFLAMMATION
=TUBULOINTERSTITIAL INJURY







Findings: Tubular injury, interstitial inflammation, extensive crystal deposition (calcium oxalate)

FINAL DIAGNOSIS**: Oxalate Nephropathy**

Oxalate Nephropathy

HOW? Major pathways for hyperoxaluria *Risk for crystal formation, urolithiasis, deposition*

Primary hyperoxaluria (inherited disorders of glyoxylate metabolism, rare)

Secondary hyperoxaluria (Enteric hyperoxaluria, most common)

-Risks bariatric surgery, chronic diarrhea, pancreatic insufficiency, IBD

-Excess oxalate ingestion (spinach, nuts, rhubarb, green smoothies, vitamin C)

WHO gets AKI?

CKD

Volume depletion

High oxalate burden

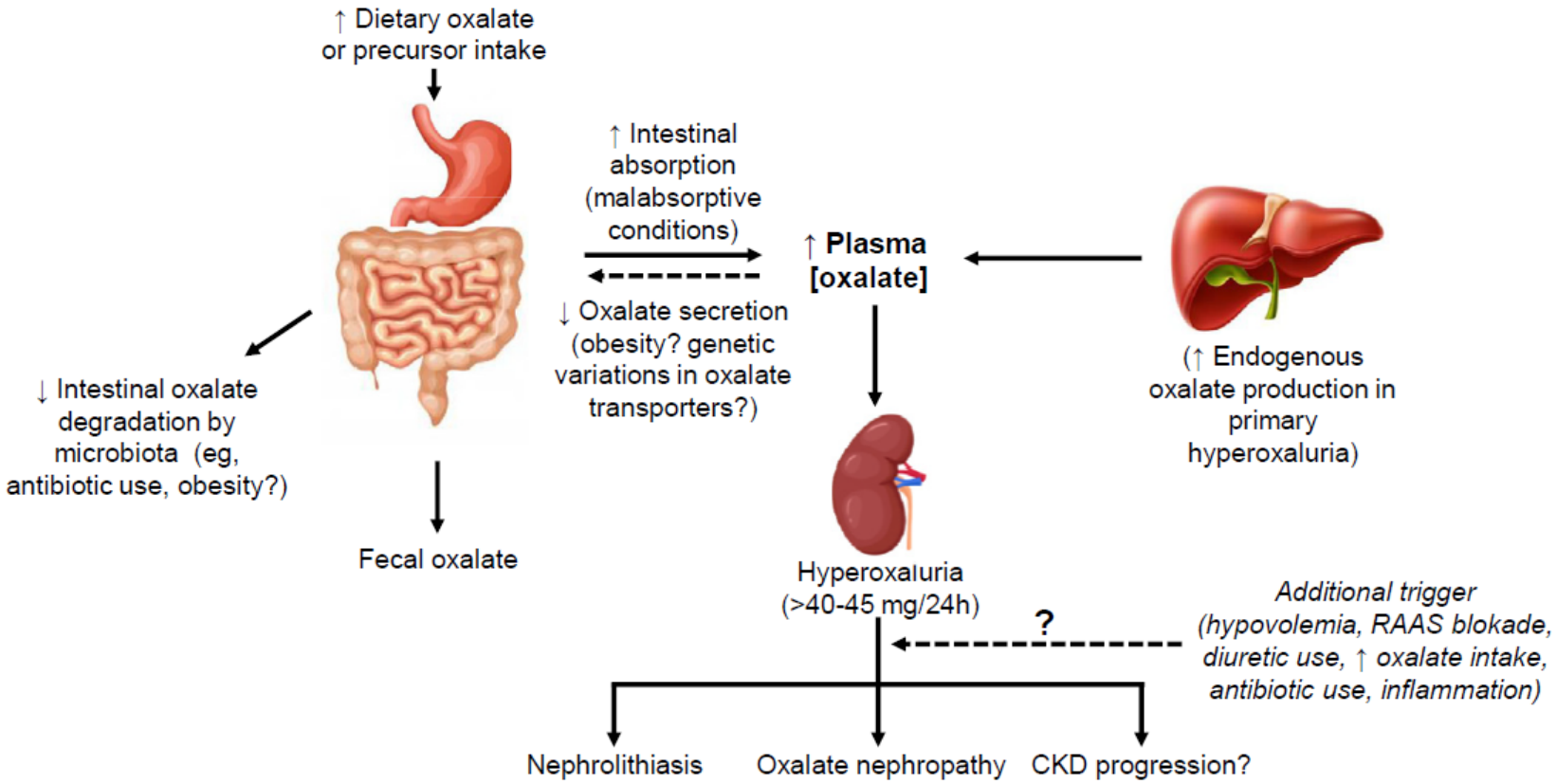
WHEN to suspect?

Progressive AKI, unrevealing urine, GI disease, bariatric surgery, exposures (spinach smoothies, vitamin C)

WHAT to do?

Remove any offending exposures, correct volume, treat enteric disease, reduce intestinal oxalate absorption – calcium with meals, low oxalate diet. *Recovery often may be incomplete.

Oxalate Nephropathy



Returning to the Case

Notable features

-Kidney function decline exceeded expected trajectory

-Medication effects did not fully explain findings (but likely potentiated them AND in this case, harm outweighed potential renal benefits)

-Bland sediment did not guide us, biopsy established the diagnosis

Clinical course

Dietary modifications enacted and urinary oxalate measures showed efficacy. Slowly, SGLT2i added back. Other meds off still. Renal function slightly improved (Cr now ~2).

Before Calling It "CKD Progression"

- Does the trajectory fit?
- Do medications explain it?
- Cross check supplements and diet?
- Could consultation and biopsy help?

BRIEF TAKE HOME NOTES

✓ Does the rate of eGFR decline fit the expected trajectory?
✓ Are medication-related changes (ACEi, ARB, SGLT2i, diuretics) occurring in the expected time course?
✓ Have medications, supplements, and dietary exposures been reviewed?
✓ Does the urine sediment or laboratory evaluation suggest an alternative diagnosis?
✓ Would establishing a tissue diagnosis change management?

•AKI (or subacute kidney injury) on CKD requires systematic reassessment
•Expected medication-related GFR changes have recognizable patterns
•Supplements and dietary practices can contribute to kidney injury
•Kidney biopsy remains invaluable in unexplained AKI
•Oxalate nephropathy is uncommon but often diagnosable when suspected

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