

These tubules look funny...

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Case courtesy of Prof Jim Yong

EM photos courtesy of Prof
Murray Killingsworth



THE 47TH ANNUAL SCIENTIFIC MEETING

of the Australasian Division of the
International Academy of Pathology

Disclosure of Relevant Financial Relationships

no relevant financial relationships

History

84F, referred to renal physician for increasing serum creatinine to 205 $\mu\text{mol/L}$, baseline 100 $\mu\text{mol/L}$.

Background of colorectal cancer, type 2 diabetes on metformin

Investigations

Autoimmune screen negative

Hepatitis screen negative

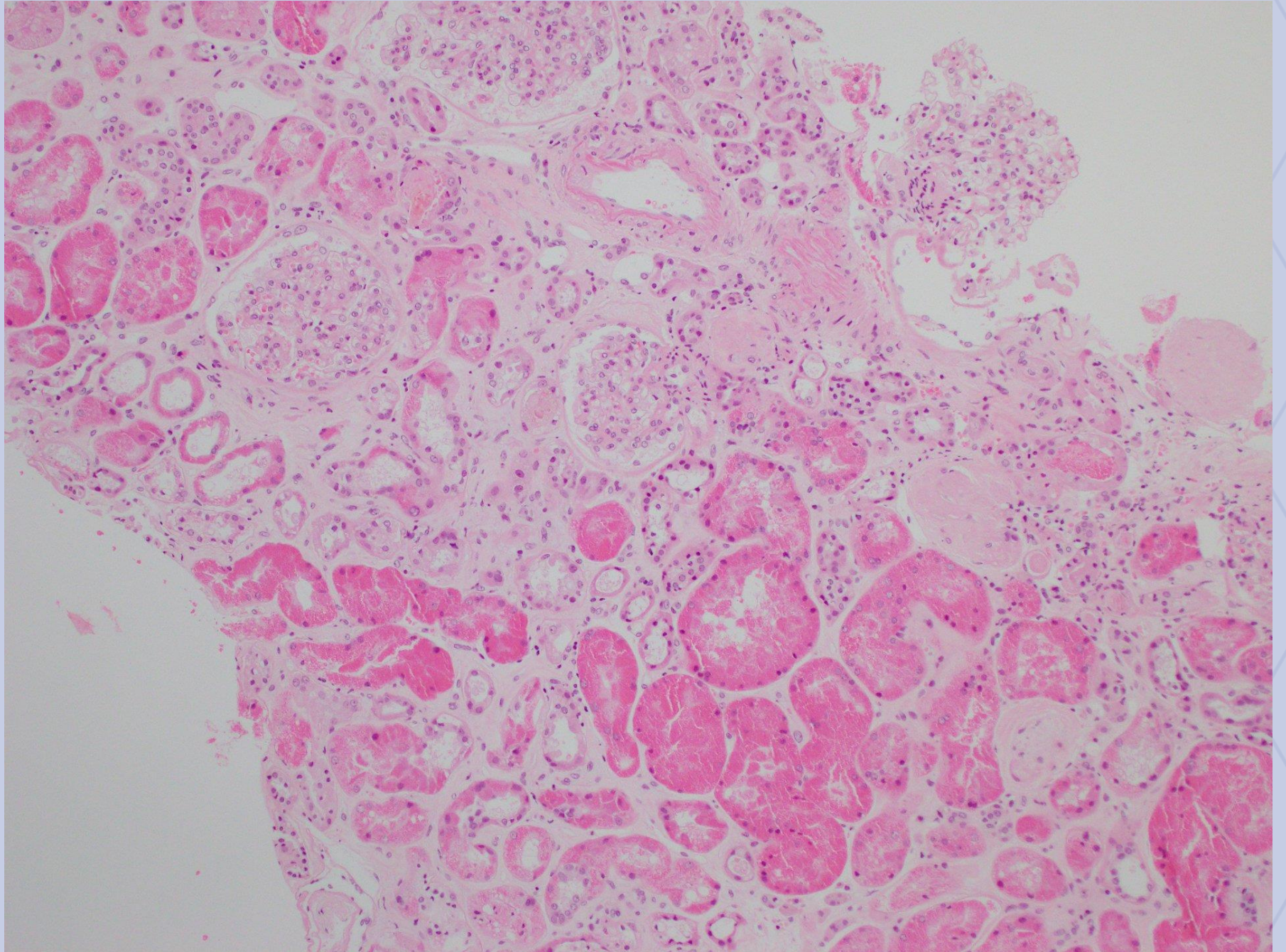
Myeloma screen negative

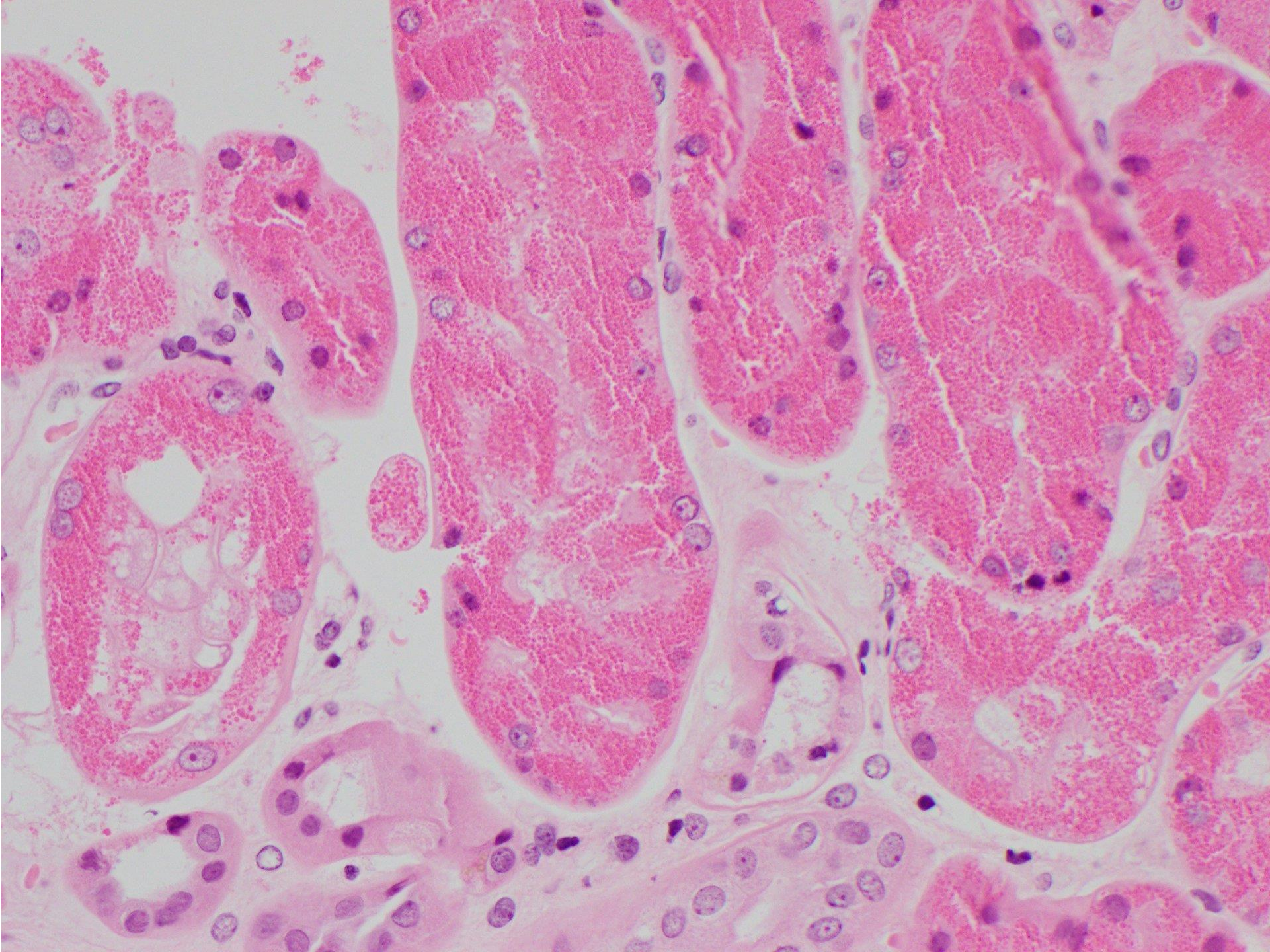
Microscopic haematuria: urine RBC $11 \times 10^6/L$

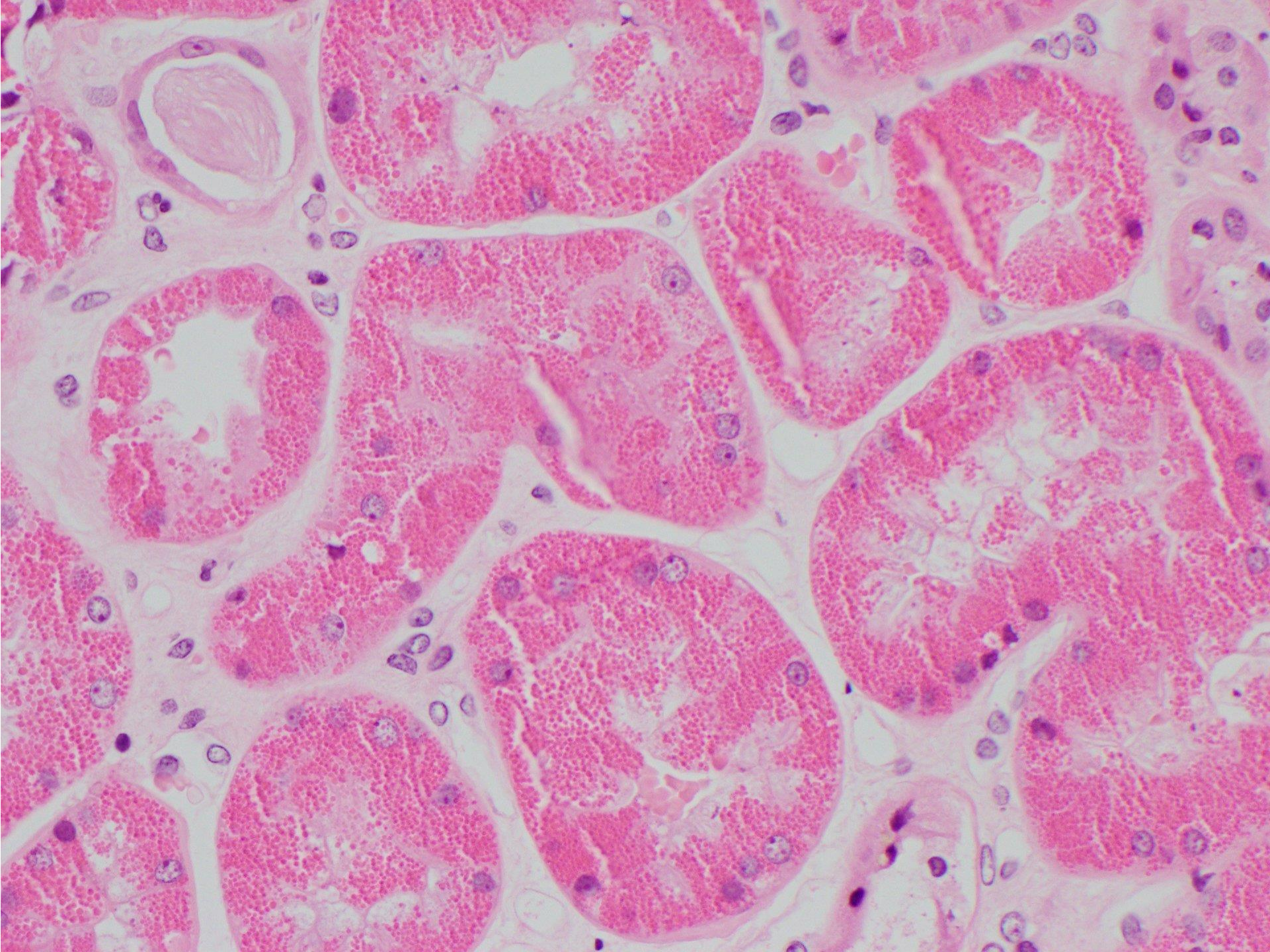
Mild proteinuria: albumin/creatinine ratio 15mg/mmol

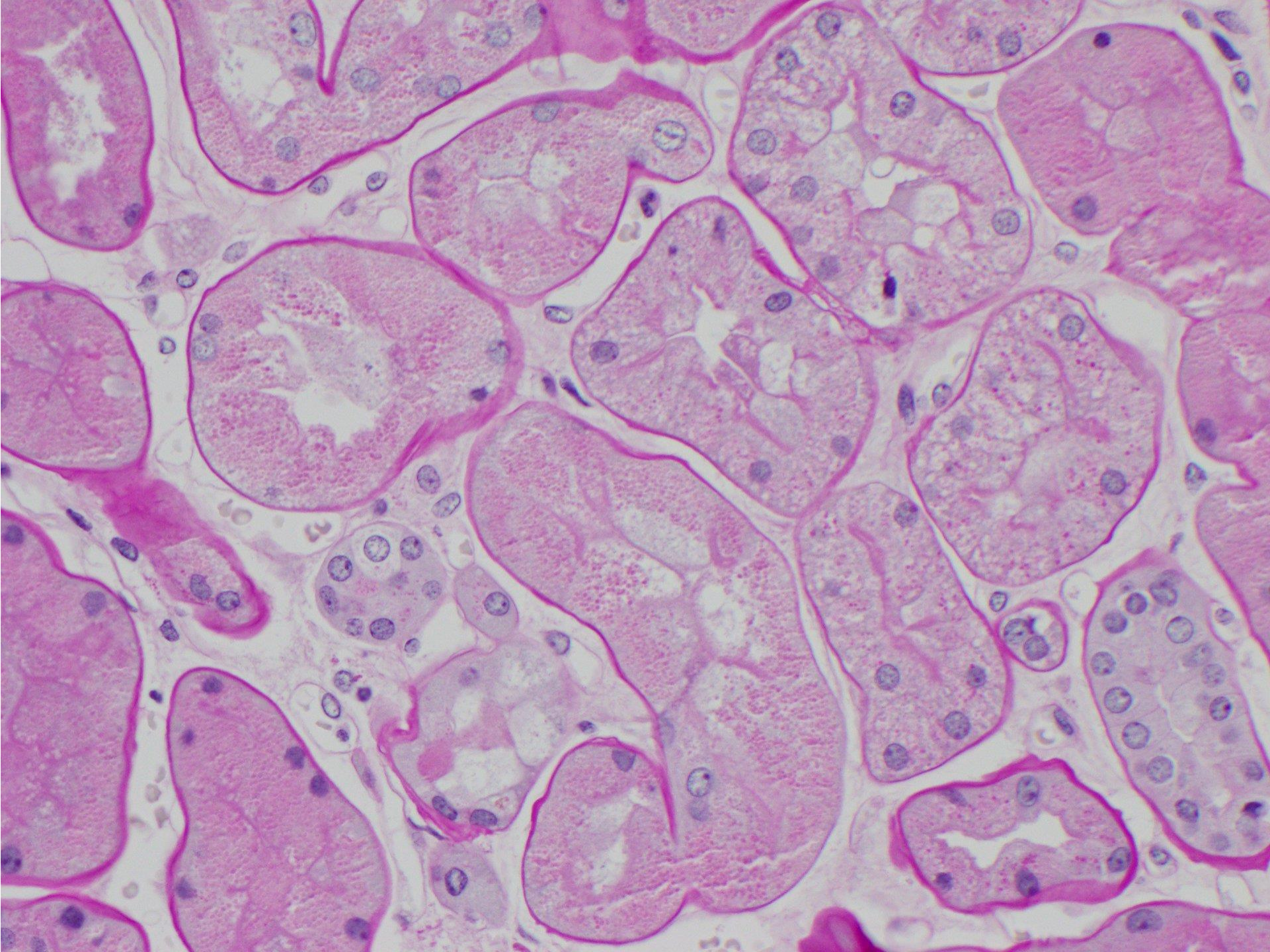
Blood count: Hb 103g/l, WCC $8.0 \times 10^9/L$, Platelet $113 \times 10^9/L$,
monocytes $1.5 \times 10^9/L$, blood film comments: hypogranulated and
hypossegmented neutrophils

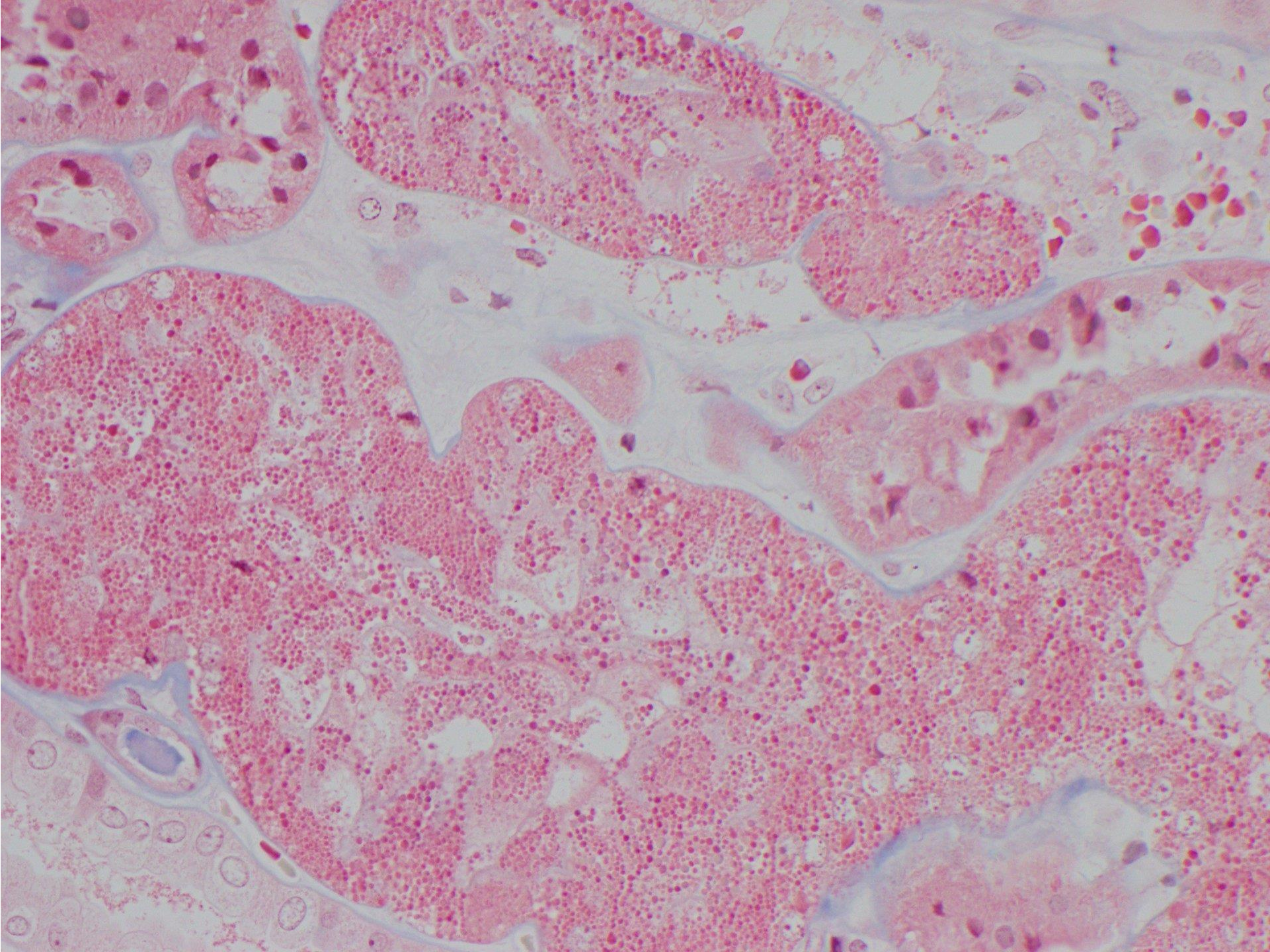
Renal biopsy

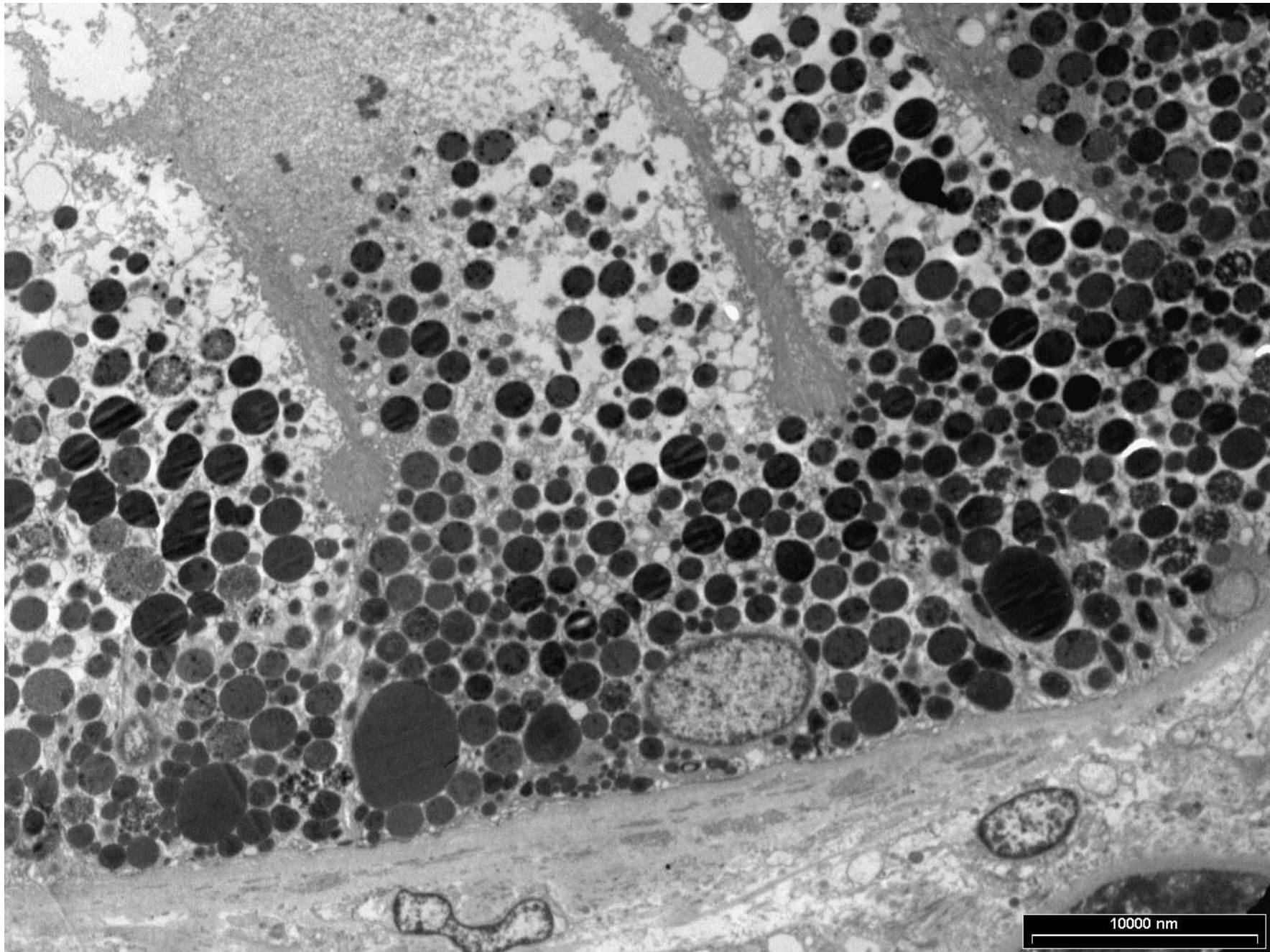


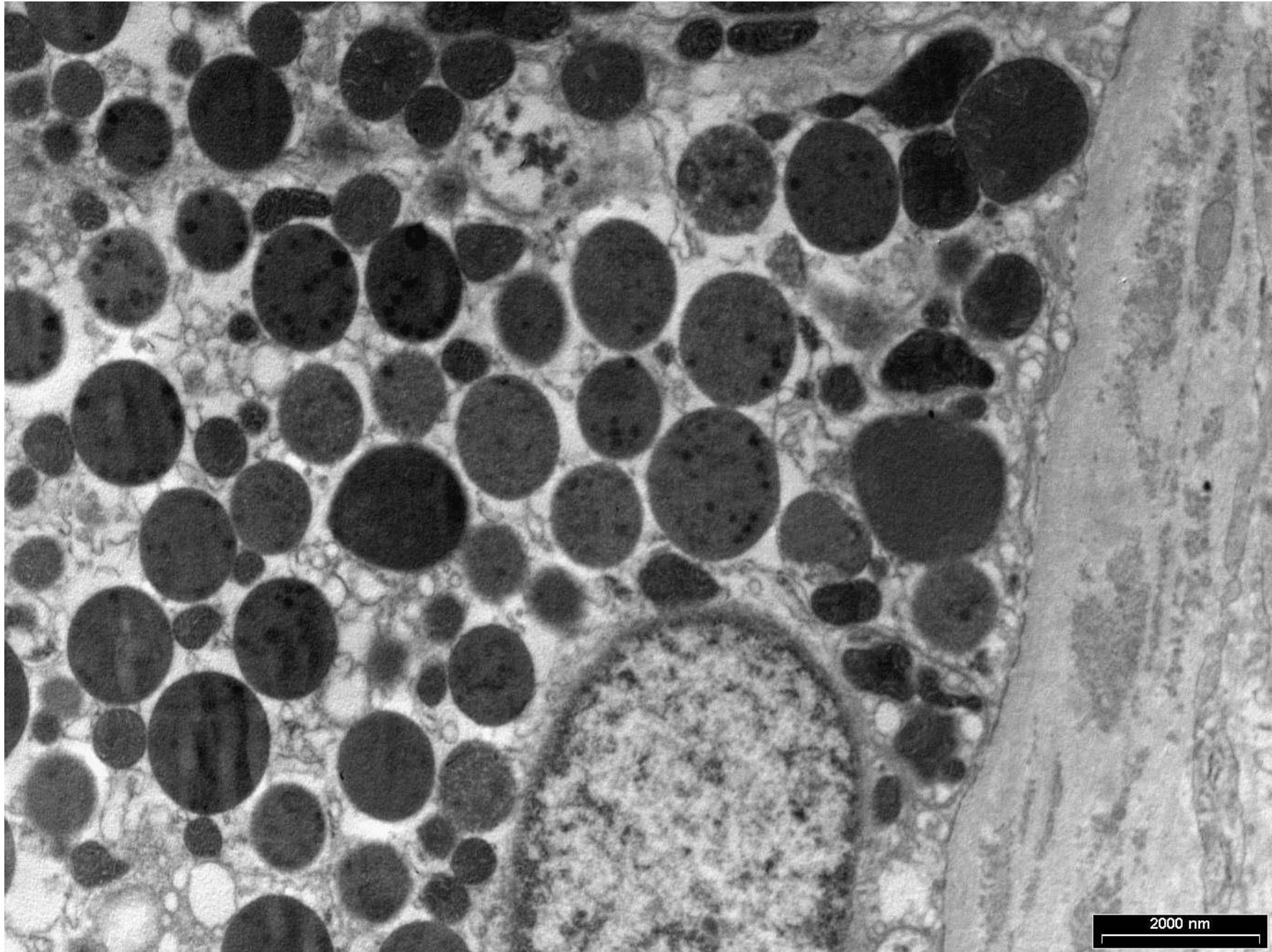












Renal biopsy

Light microscopy: Proximal tubules show prominent intracytoplasmic protein resorption droplets

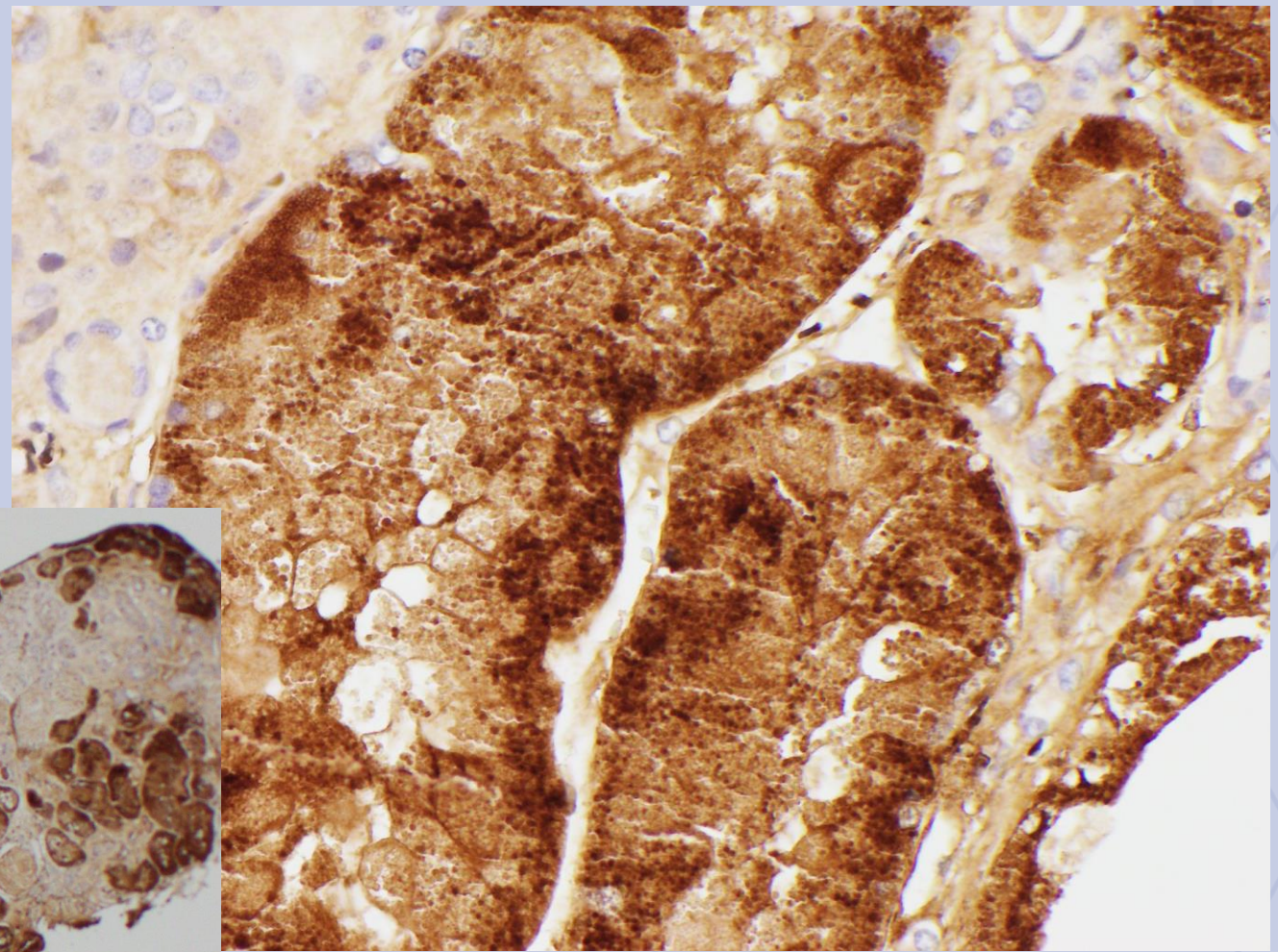
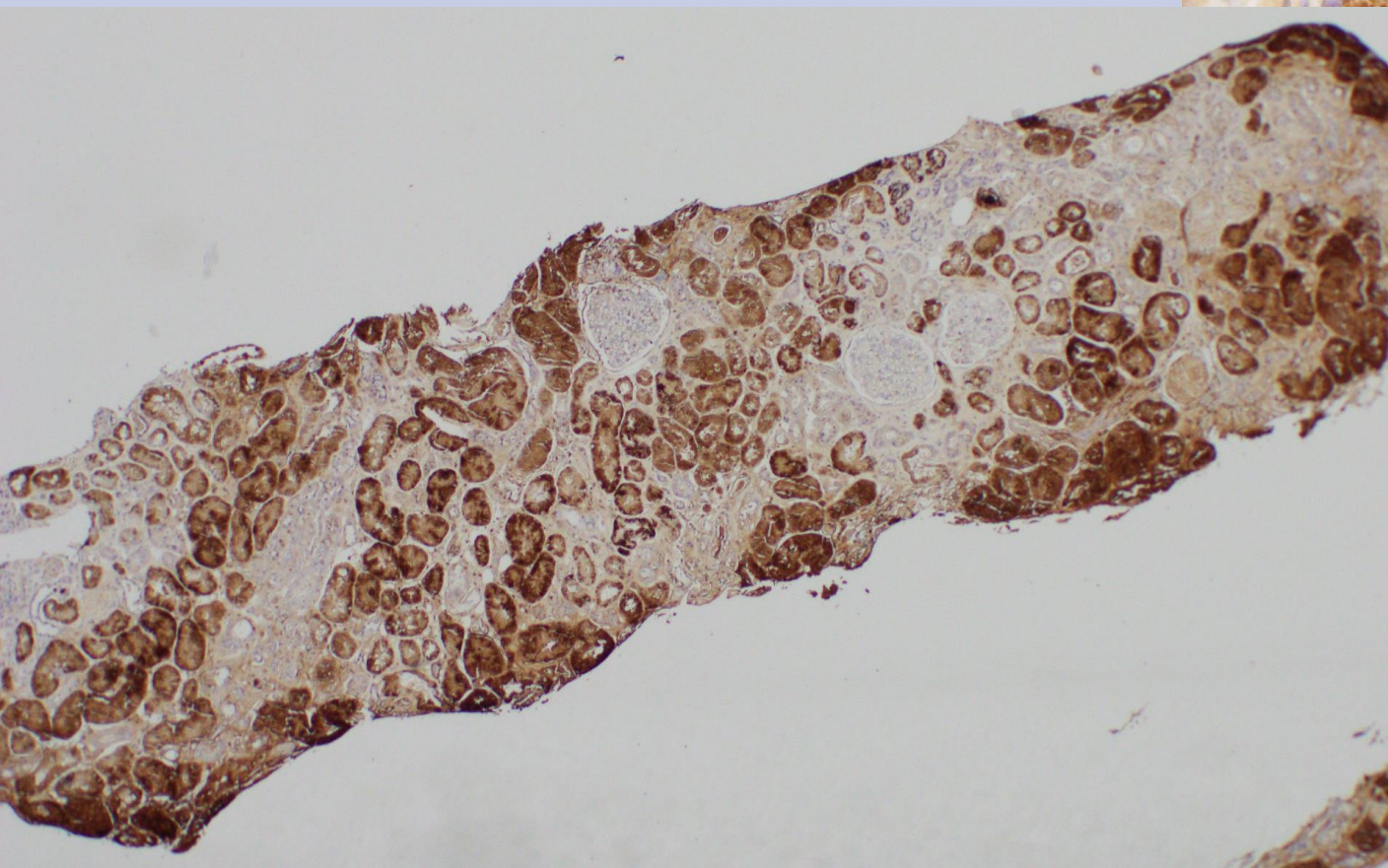
IF: negative

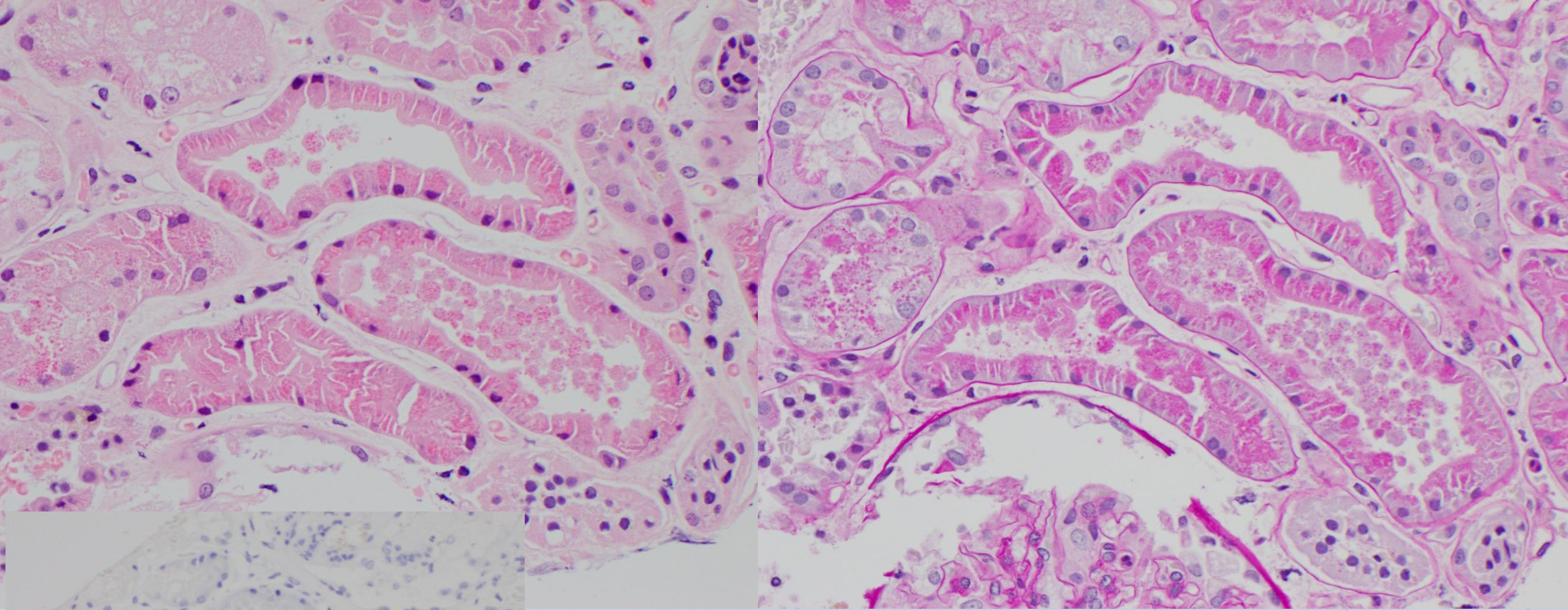
EM: prominent phagolysosomes in tubular cell cytoplasm



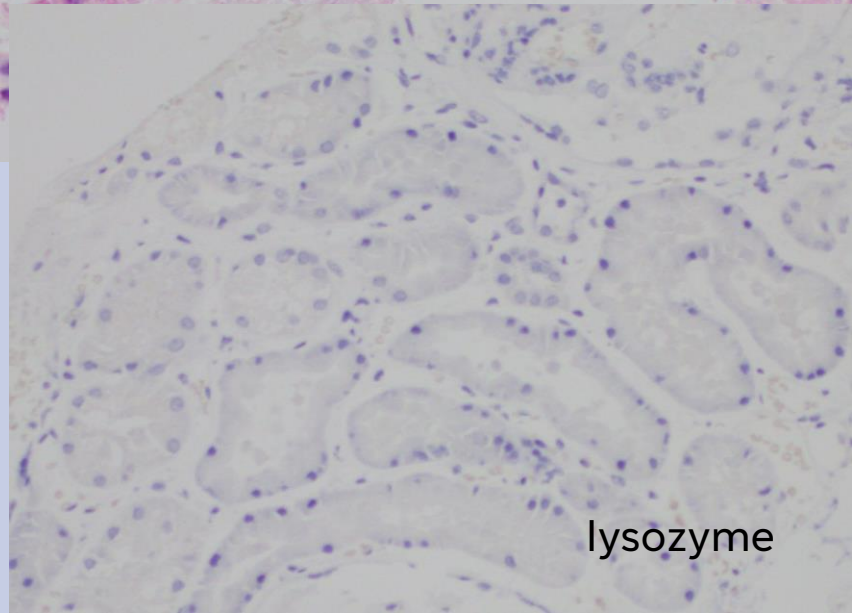
Could the patient have chronic myelomonocytic leukaemia (CMML) and have lysozyme induced nephropathy?

Lysozyme IHC





A patient with nephrotic syndrome,
due to minimal change disease



lysozyme

Bone marrow aspirate and trephine

Moderately cellular

Left shifted and dysplastic granulopoiesis

12% blasts & promonocytes

16% monocytes with dysplasia

Features in keeping with chronic myelomonocytic leukaemia (CMML)

Lysozyme

A cationic bactericidal enzyme produced by monocytes/macrophages and neutrophils, can cleave the peptidoglycan cell walls of bacteria, and is present in body secretions such as saliva, nasal secretion and tears.

It is filtered at the glomerulus and resorbed in the proximal tubules, where it is degraded in phagolysosomes.

Increases serum enzymes levels found in:

- Acute and chronic myeloid and monocytic leukaemias

- Increased monocyte/macrophage activity:

 - Sarcoidosis (can be used to monitor disease activity, more sensitive than ACE)

 - Tuberculosis

 - Inflammatory reactions with reactive monocyte/macrophage activity: rheumatoid arthritis, acute bacterial infection

- Renal failure (reduced renal excretion of lysozyme)

Increased urinary levels can be found in:

- Increased serum lysozyme

- Renal tubular dysfunction (due to impaired resorption and increased urinary excretion)

TABLE 1. Serum and urinary lysozyme levels in patients with hematologic disorders

Diseases	Number of cases	Serum lysozyme ($\mu\text{g/ml}$)	Urine (mg/day)	Number of patients with lysozymuria
		Mean \pm S.D. (range)	Mean (range)	
Normal	45	6.5 \pm 1.5 (2.5-9.0)	0	0
Leukemia				
Monocytic	44	48.1 \pm 27.7 (17.0-150.0)	938 (80-3910)	44
Acute myeloblastic	17	7.8 \pm 3.6 (2.7-14.5)	0.6 (0-4)	5
Acute paramyeloblastic	16	12.8 \pm 6.5 (4.5-29.0)	0.9 (0-5)	6
Acute lymphoblastic	13	2.7 \pm 1.2 (1.0-4.6)	0	0
Chronic myelocytic	13	16.7 \pm 6.4 (10.4-30.0)	12 (0-110)	9
Chronic lymphocytic	6	2.5 \pm 1.3 (1.2-4.5)	0	0
Malignant lymphoma	39	8.0 \pm 3.1 (3.4-15.0)	0.1 (0-3)	5
Multiple myeloma	8	9.1 \pm 3.5 (4.3-14.5)	0.4 (0-2)	2
Polycythemia vera	8	15.1 \pm 8.6 (6.0-32.0)	1.0 (0-7)	4
Aplasia	15	6.0 \pm 2.5 (2.6-13.0)	0.1 (0-2)	3

Chronic myelomonocytic leukemia (CMML)

Myeloid neoplasm with myelodysplastic and myeloproliferative features

71-76, M>F

Peripheral blood monocytosis $\geq 0.5 \times 10^9/L$ and $\geq 10\%$

Dysplastic features of myeloid lineages on bone marrow examination

Anaemia, thrombocytopenia, variable leukocytosis (depends if MD or MP features dominate)

Subgroups:

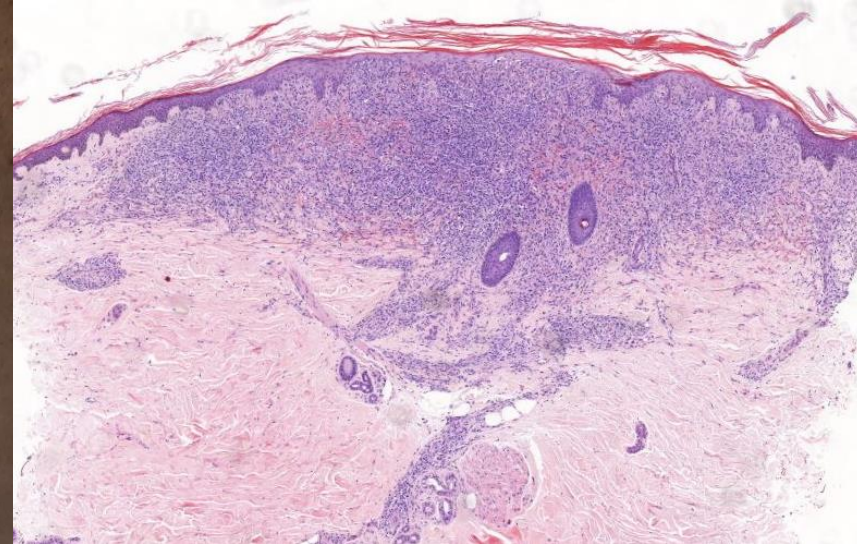
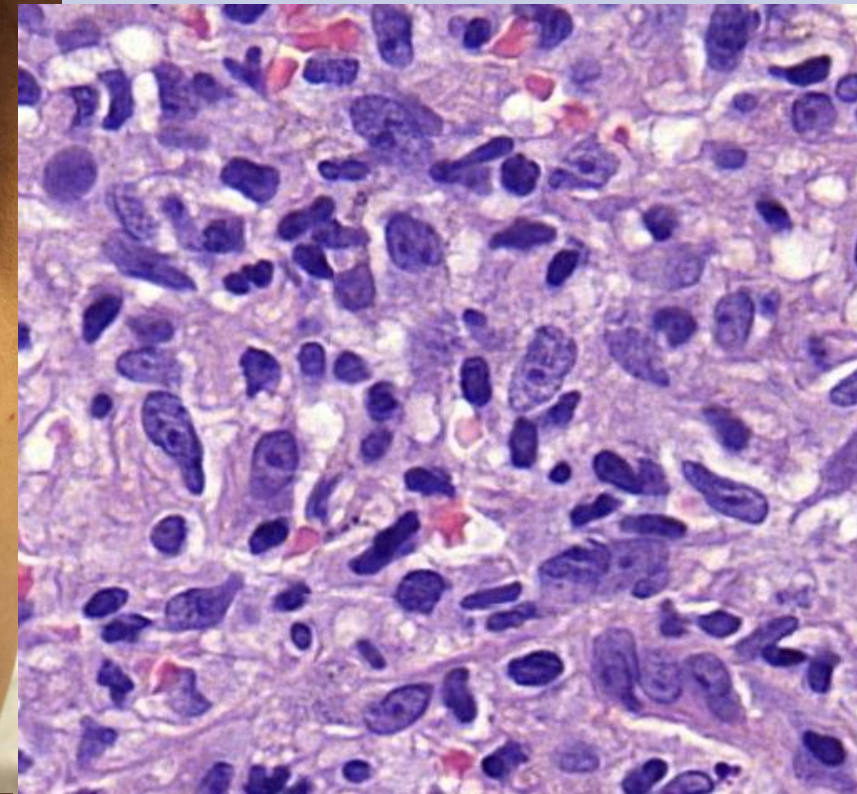
CMML-1: <5% blasts & promonocytes in the blood or <10% in bone marrow.

CMML-2: 5-19% blasts & promonocytes in the blood or 10-19% in bone marrow.

Pathway	Gene
Epigenetic regulation	TET2
	ASXL1*
	DNMT3A
	EZH2*
	IDH1
	IDH2
	BCOR*
Spliceosome	SRSF2*
	U2AF1*
	SF3B1*
	ZRSR2*
	CBL*
Cellular signaling	KRAS*
	NRAS*
	NF1
	JAK2
	RUNX1*
	SETBP1*
Other	

CMML – dendritic cell proliferations

Cutaneous dendritic cell proliferations can include mature plasmacytoid dendritic cell proliferation, blastic plasmacytoid dendritic cell neoplasm (BPDCN), indeterminate dendritic cell tumours.



CASE REPORT

Journal of CUTANEOUS PATHOLOGY

Atypical cutaneous histiocytic eruption in a patient with chronic myelomonocytic leukemia: A case report

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Lysozyme induced nephropathy

Caused by overproduction of lysozyme by neoplastic monocytes in CMML and other myelomonocytic neoplasms.

Lysozyme is freely filtered by the glomerulus and taken up into phagolysosomes.

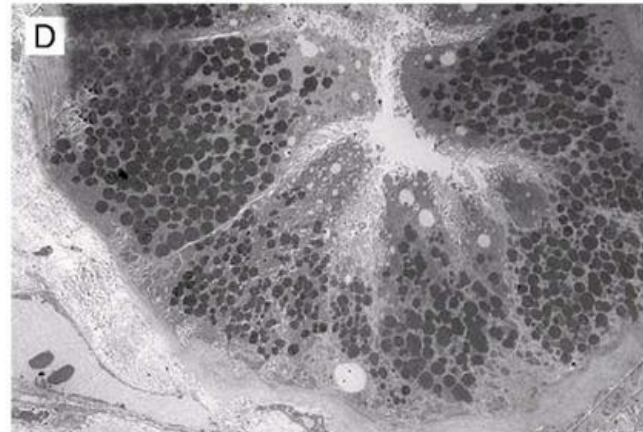
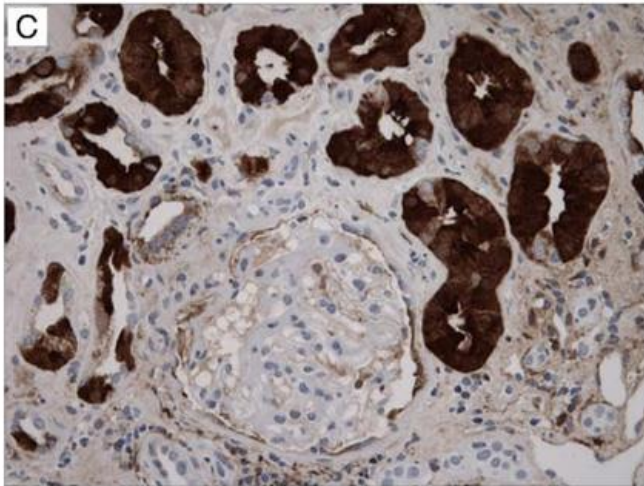
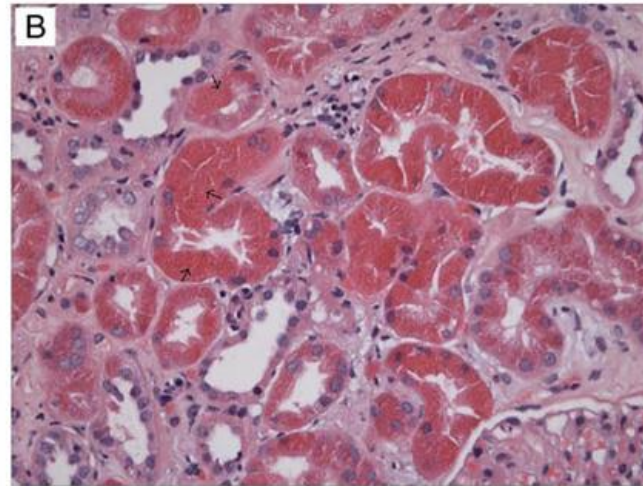
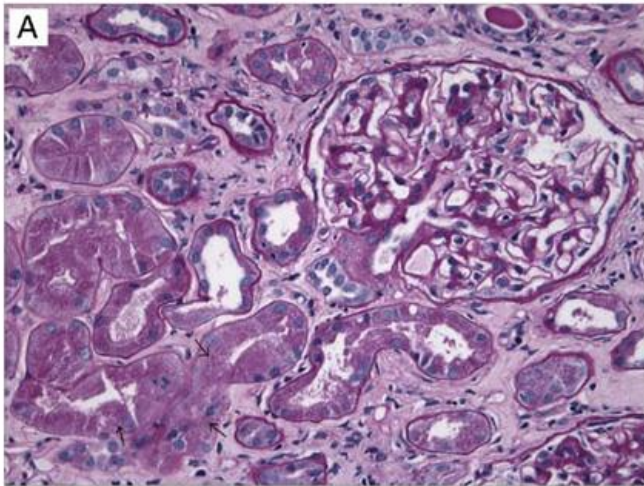
Lysozyme is directly toxic to tubular epithelial cells; and being cationic, can also cause potassium wasting and hypokalaemia.

Patients present with renal impairment, and have elevated serum and urinary lysozyme levels.

Elevated urine lysozyme (lysozymuria) gives rise to a non-albumin proteinuria. On urine EPG, lysozyme migrates to the γ -globulin region, but no paraprotein would be detected on the IEPG.

Lysozyme induced nephropathy

Rare condition, three cases in recent decades



KI REPORTS ————— NEPHROLOGY
KIReports.org

Lysozyme-Induced Nephropathy

Dominick Santoriello¹, Laurie May Andal², Robert Cox³, Vivette D. D'Agati¹ and Glen S. Markowitz¹

The Netherlands Journal of Medicine

CASE REPORT

Progressive kidney failure in chronic myelomonocytic leukaemia: don't forget lysozyme damage

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A Forgotten Cause of Kidney Injury in Chronic Myelomonocytic Leukemia

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Diagnosis and progress

Diagnosis: lysozyme induced nephropathy, in the setting of CMML.

Metformin switched to gliclazide

Started on azacitidine, repeat marrow 6 months later showed 5% blasts/promonocytes

Blood counts remained stable for next two years

Serum creatinine down to $123\mu\text{mol/L}$

Summary

CMML and other monocytic leukaemias may overproduce lysozyme, leading to lysozyme induced nephropathy and renal impairment.

The histology and electron microscopy findings are distinctive, and positive immunohistochemical stain for lysozyme supports the diagnosis.

Think of this when there are prominent protein resorption droplets, and the patient does not have significant proteinuria, or has proteinuria that is non-albuminuria (could be lysozymuria).

References

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