OXALATE NEPHROPATHY AND VITAMIN C ADMINISTRATION

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INTRODUCTION

- Oxalate nephropathy can occur as a consequence of a primary hyperoxaluria, as caused by genetic defects, or secondary, because of increased plasma oxalate levels.
- Most forms of secondary oxalate nephropathy are caused by fat malabsorption, when calcium reacts with unabsorbed bile and fatty acids instead of with oxalate, resulting in increased oxalate availability.

INTRODUCTION…

- Other secondary forms include oxalate nephropathy as a consequence of vitamin C supplementation.
- Vitamin C is a water-soluble acid that humans are unable to synthesize, and almost half of the septic patients display vitamin C deficiency, with lower vitamin C concentrations.

INTRODUCTION…

- Sepsis is associated with a higher load of oxidative stress, leading to an increased consumption of antioxidative substances such as vitamin C.
- Exerting its antioxidative effects by providing electrons, vitamin C is partially metabolized to oxalate.

INTRODUCTION…

- All around the world multiple therapeutic interventions have been tried to mitigate the disease burden associated with COVID-19 infection.
- One of treatment strategies involves high-dose vitamin C (ascorbic acid).

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OXALATE METABOLISM

- Oxalate itself then cannot be metabolized and is excreted by the kidney through both glomerular filtration and tubular secretion.
- In the tubular lumen, it binds to calcium and eventually forms calcium oxalate crystals.
- Depending on the location and concentration of the crystals, this can result in nephrocalcinosis (or oxalate nephropathy) or urolithiasis.

RISK FACTORS FOR OXALATE NEPHROPATHY

- Low urine output
  - In primary hyperoxaluria, a fluid intake of >3 L per 1.73 m2 per day is recommended to increase urine volume and decrease tubular oxalate concentration.
- Preexisting kidney injury.

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REVIEW

Overview of the possible role of vitamin C in management of COVID-19

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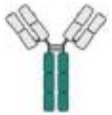
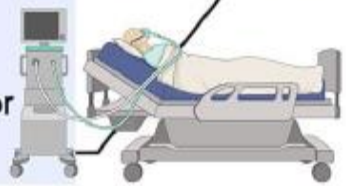
The possible beneficial effects of vitamin C in management of COVID-19

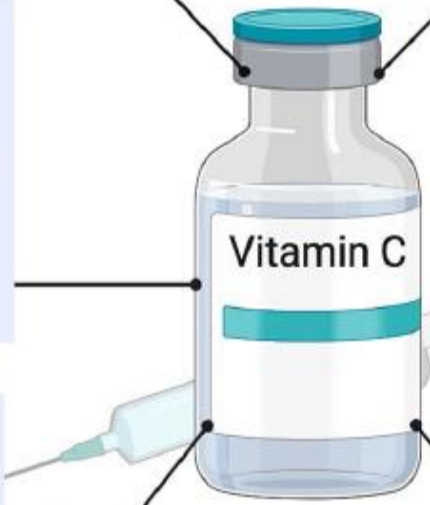
Indirect antiviral effect
Improves the host innate immunological response against viral infections

Immunomodulatory effect
Improves T-cells function and increases production of immunoglobulins, which could ameliorate the lymphopenic effect of SARS-CoV-2 infection

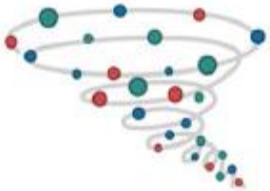


Critically-ill patients
*Decreases duration of mechanical ventilation
*shortens ICU stay
*Decreases vasopressor requirements





Anti-inflammatory effect
Decreases risk of development of cytokine storm



Antioxidant effect
*Decreases oxidative stress induced-lung inflammation and injury
*restores endothelial function which decreases risk of SARS-CoV-2 induced- endothelial dysfunction and its negative consequences .

DOSE OF VITAMIN C

- The i.v. infusion of a high dose of vitamin C has been shown to significantly reduce the proinflammatory biomarkers C-reactive protein and procalcitonin in patients with sepsis.
- Administration of 15 g/d of i.v. vitamin C for 4 days may decrease mortality in patients with sepsis-related ARDS.

Open access Protocol

BMJ Open

Intravenous high-dose vitamin C for the treatment of severe COVID-19: study protocol for a multicentre randomised controlled trial

Fang Liu, Yuan Zhu, Jing Zhang, Yiming Li, Zhiyong Peng

- A previous meta-analysis considered high doses as equalto or greater than 10 g/day. Twenty-four grams of VC in this trial is higher than the dosage of VC in previous clinical trials conducted on critically ill patients with severe infection.
- HIVC is expected to improve pulmonary function and reduce mortality for patients with COVID-19.

KI REPORTS
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Oxalate Nephropathy Caused by Excessive Vitamin C Administration in 2 Patients With COVID-19

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PATIENT 1

- 50-year-old white man hospitalized for the persistence of fever, cough, and dyspnea; an oropharyngeal/nasal swab was positive for SARS-CoV
- His medical history included arterial hypertension and Brugada syndrome.
- he had no history of kidney disease nor kidney stones.

PATIENT 1

- According to the internal protocol for COVID-19, he was started on hydroxychloroquine, lopinavir/ritonavir 200/50 mg/d (rapidly switched to darunavir-cobicistat 800/150 mg/d), and azithromycin 500 mg/d. To counteract cytokine storm, a single dose of subcutaneous tocilizumab was used. I.v. steroids and broad-spectrum antibiotic therapy were provided.
- The patient was put on enteral nutrition.

PATIENT 1

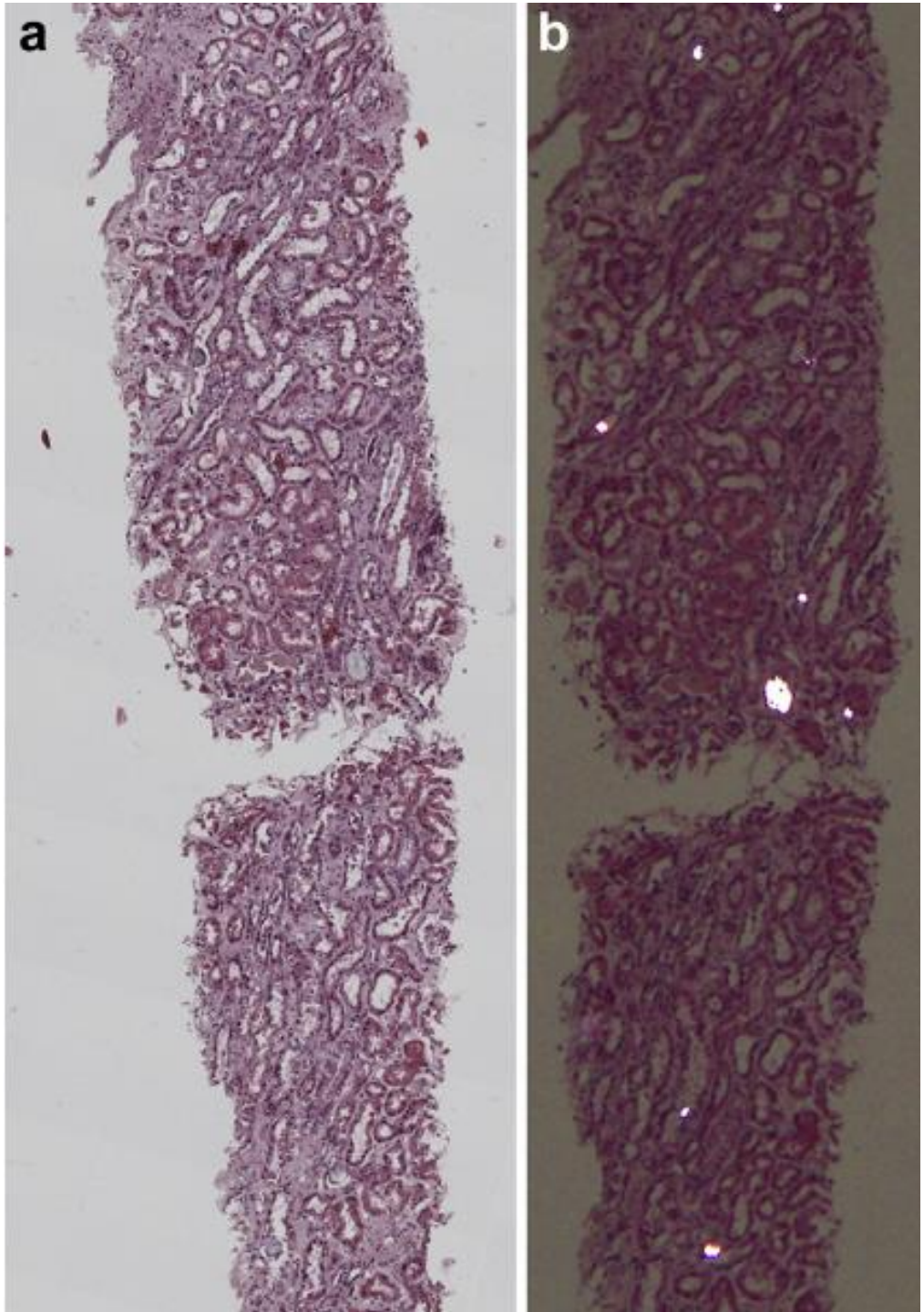
- Due to rapid deterioration of respiratory function, the patient was transferred to the intensive care unit on the same day where he was intubated and put on lung-protective mechanical ventilation.

PATIENT 1

- considering his septic status, high-dose i.v. vitamin C (50 mg/kg 4 times/d) was administered.
- The patient developed multiorgan failure with hepatic dysfunction and AKI with anuria.
- he was started on continuous venovenous hemodiafiltration

PATIENT 1

- The patient's respiratory status improved, and he was extubated by day15 from hospitalization; swabs for SARS-CoV-2 were negative from day 18.
- Despite an increase in urine output, kidney function did not show any improvement and the patient was transferred to the nephrology unit; at day 36 a biopsy specimen of the kidney was obtained.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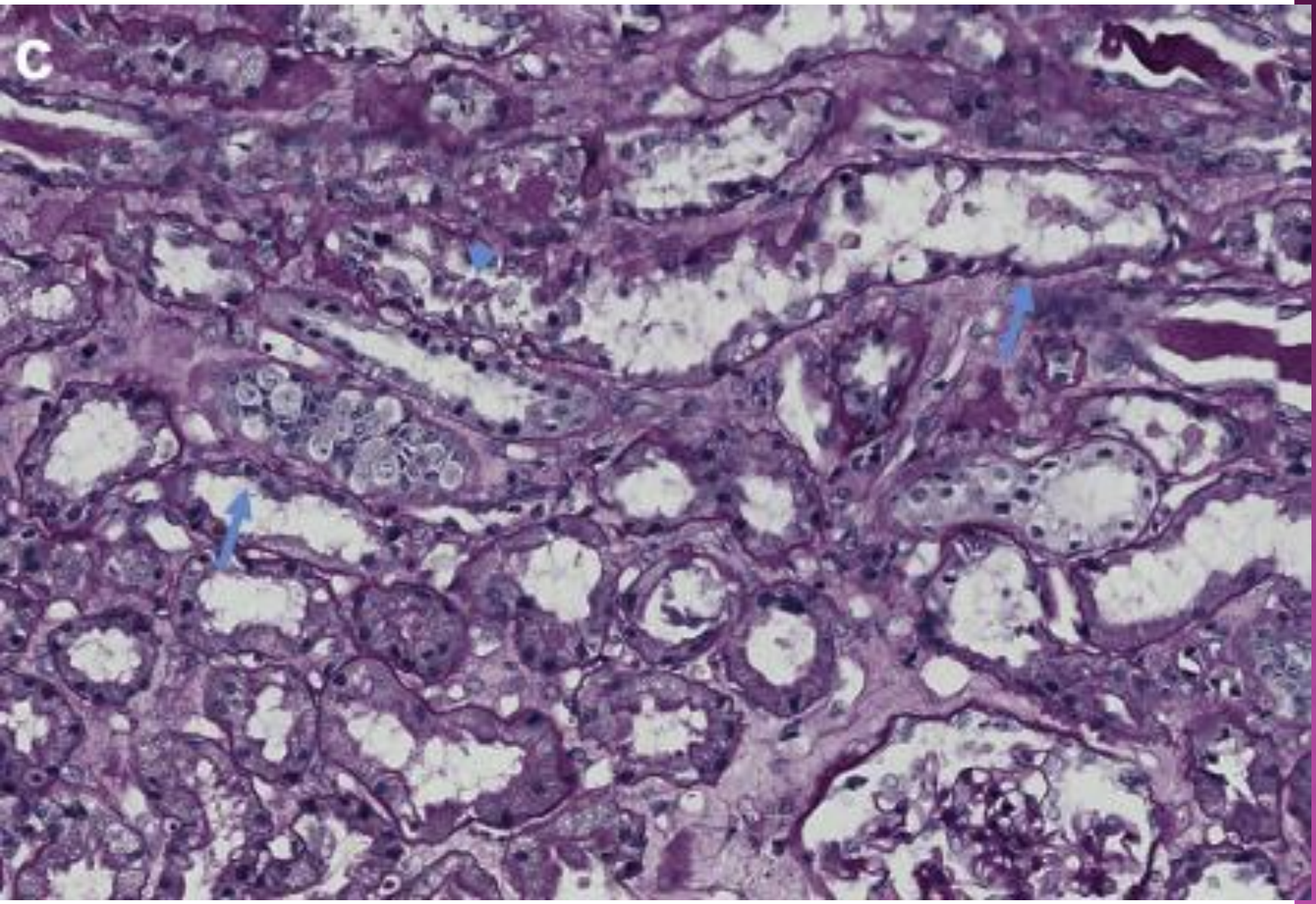
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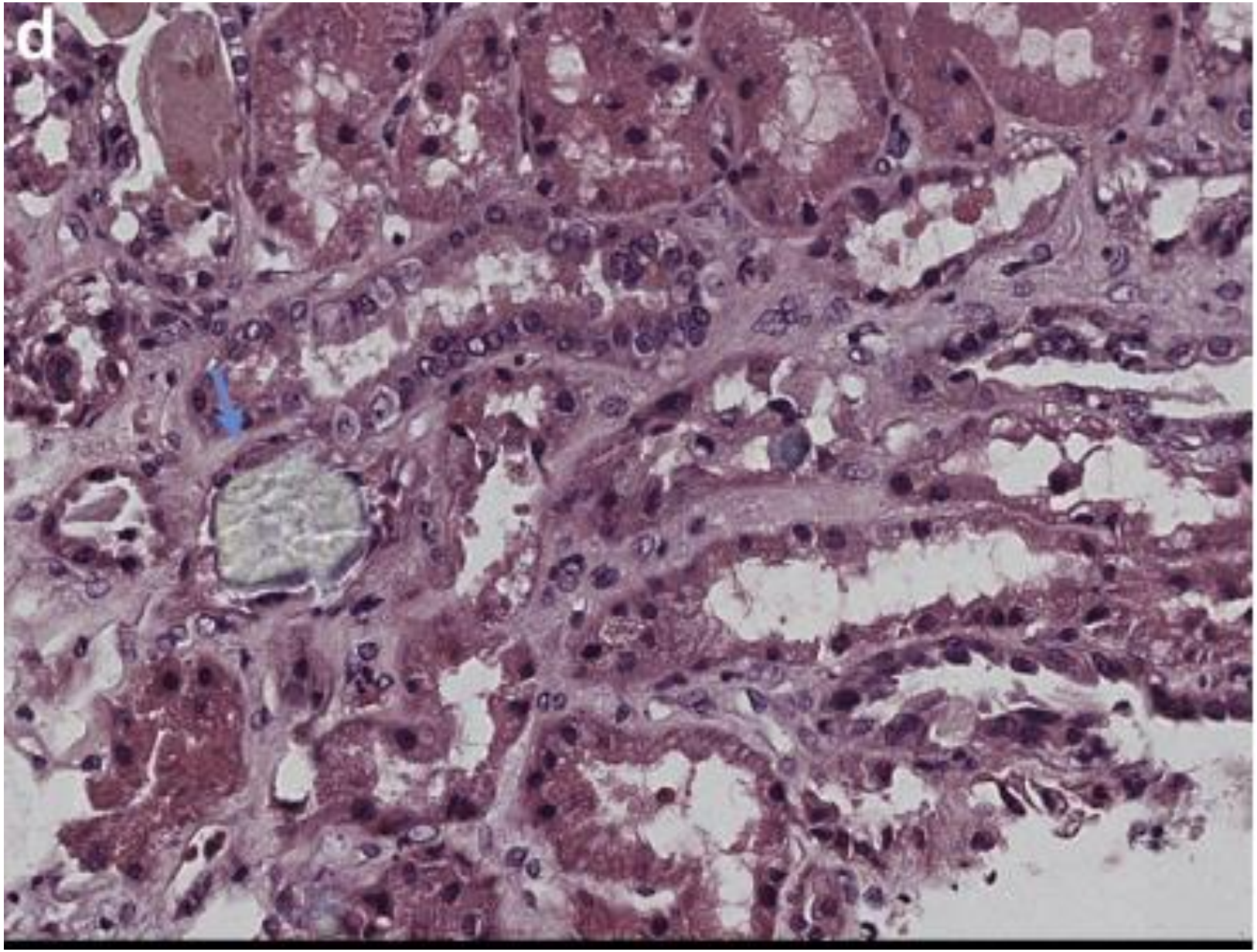
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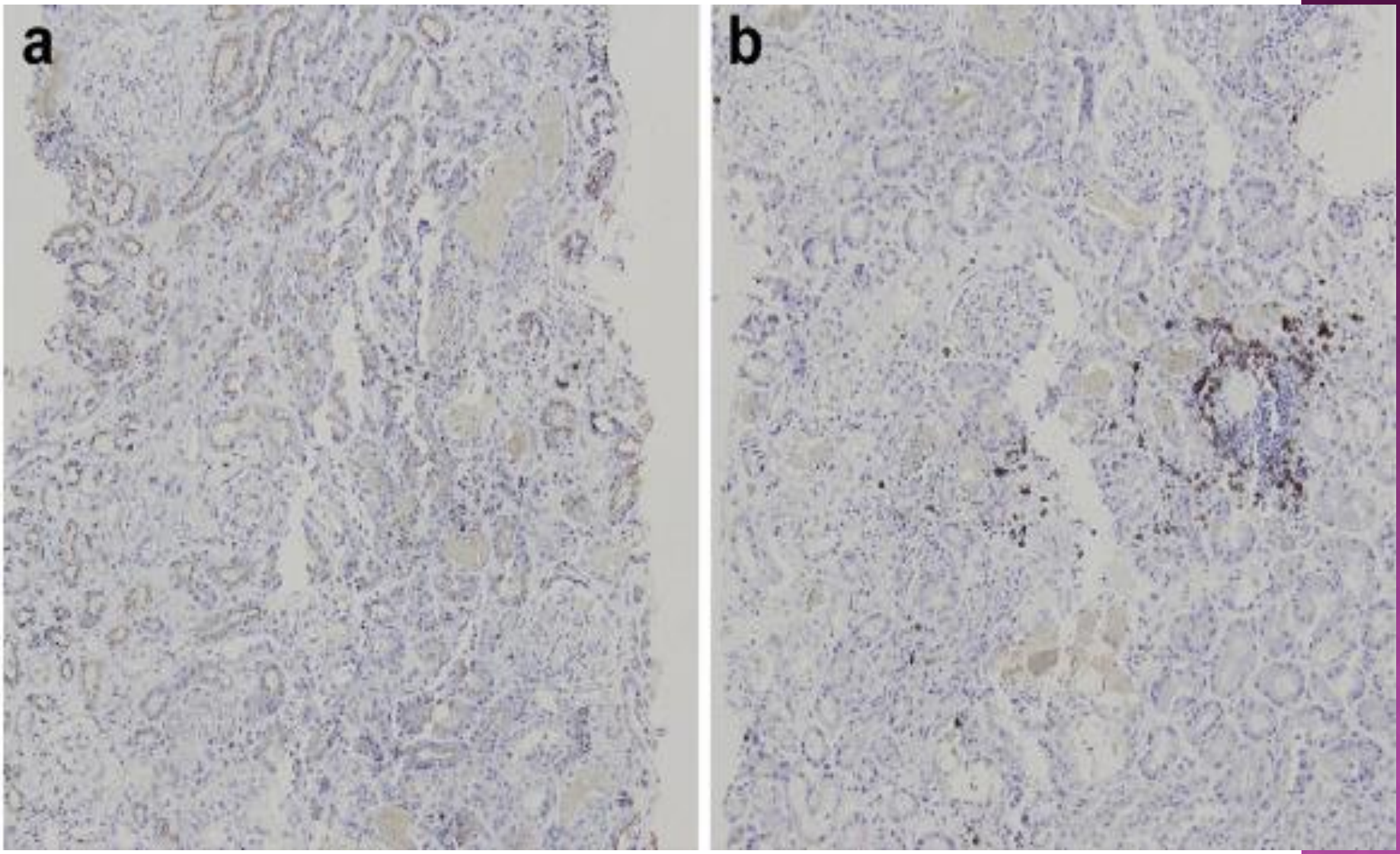
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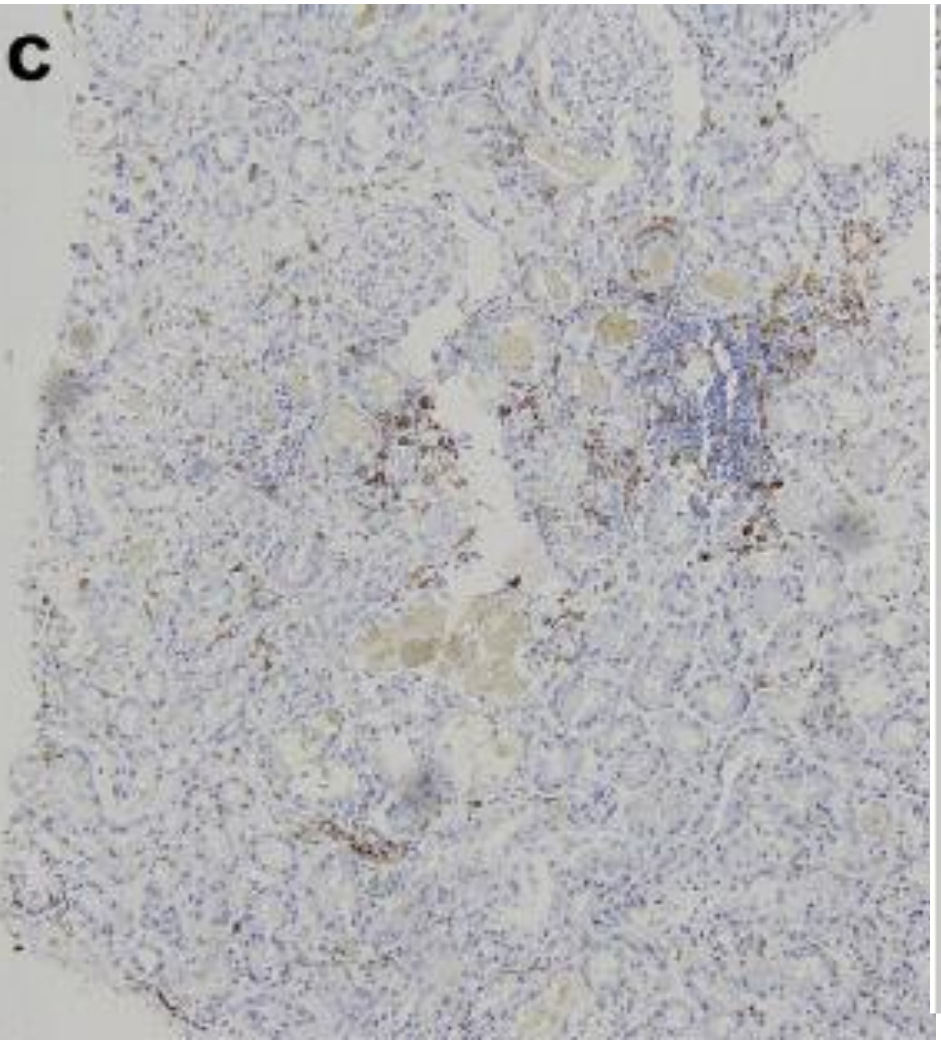
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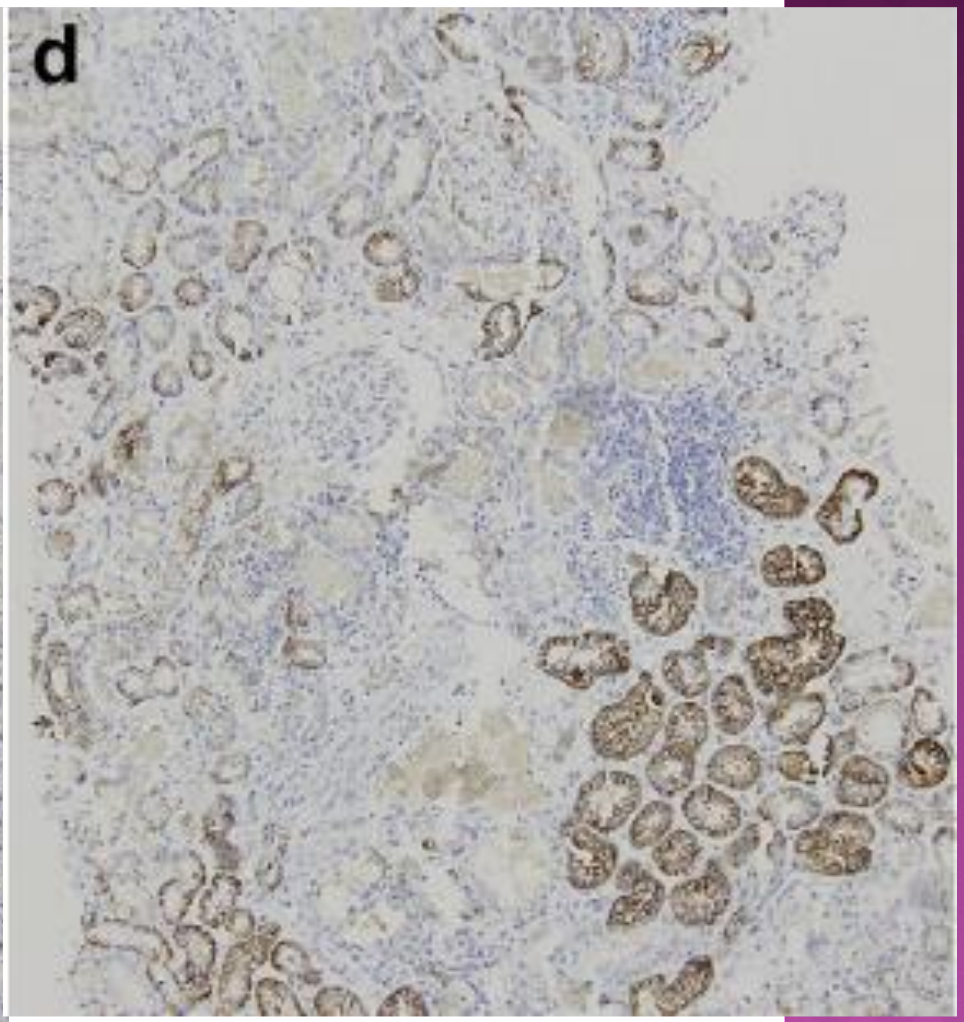
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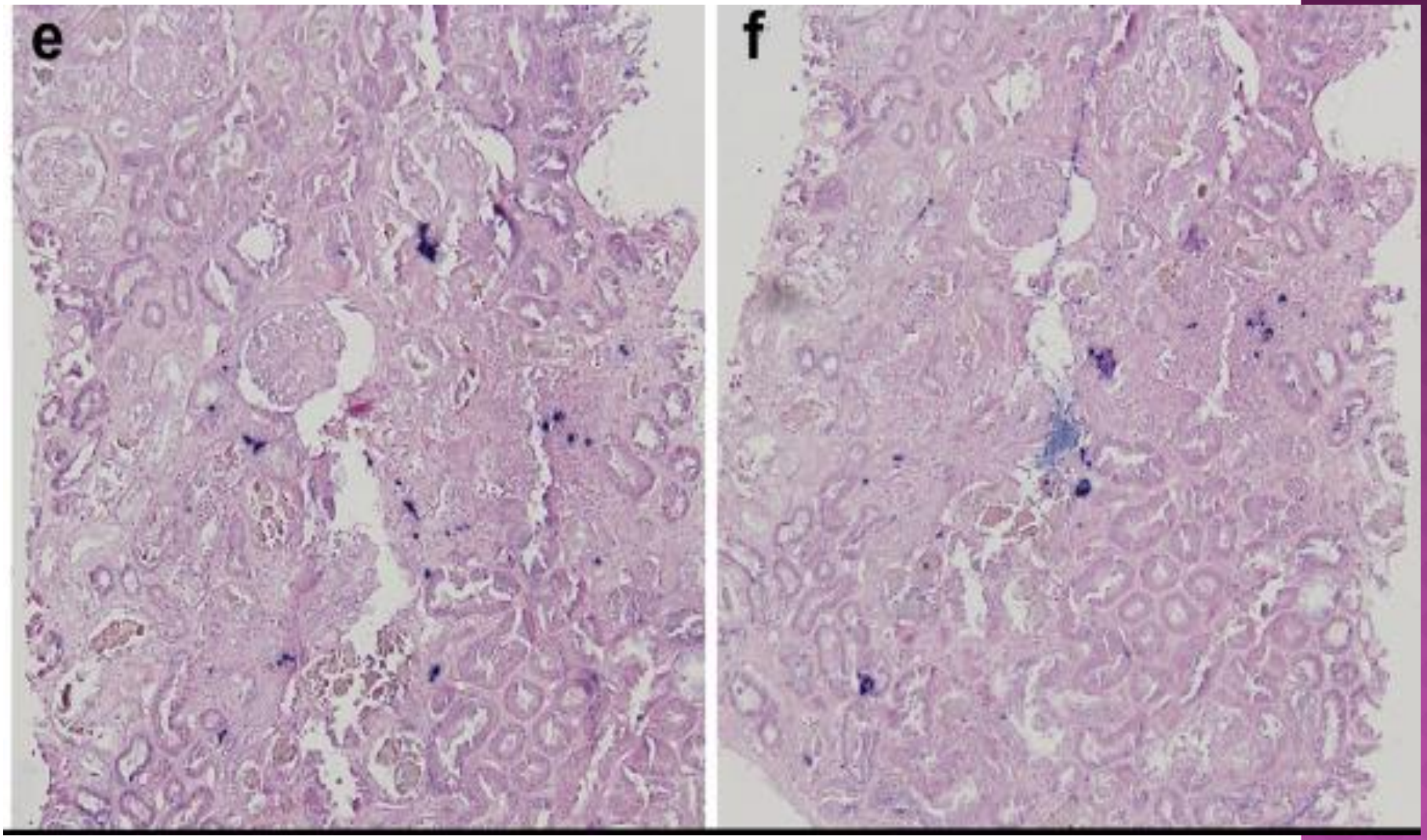
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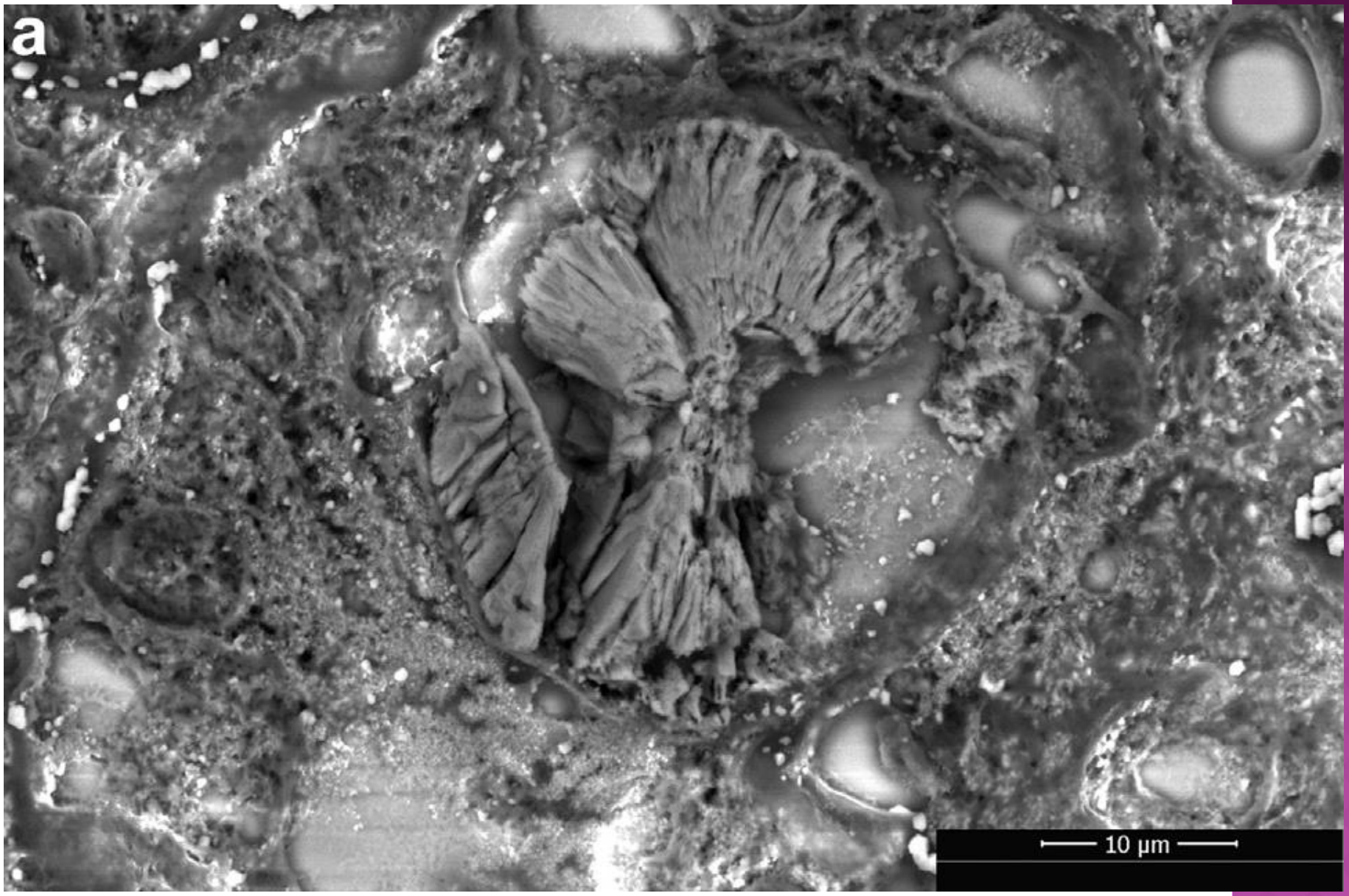
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PATIENT 1

- Extensive ATI and focal acute tubular necrosis, with degenerative and reactive aspects of tubular cells .
- Interestingly, calcium oxalate crystals (fan-shaped radially arranged translucent crystals on hematoxylin and eosin stain, birefringent when examined with polarized light) were identified in several tubular lumina.

PATIENT 2

- A 71-year-old white man who was hospitalized for fever, diarrhea, and worsening neurologic status. His medical history included type 2 diabetes mellitus treated with metformin plus long-acting insulin, arterial hypertension, hypercholesterolemia,and mild liver steatosis.
- he had no history of kidney disease or kidney stones.

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PATIENT 2

- Because of worsening respiratory failure and rapid development of ARDS, he was immediately transferred to the intensive care unit where he was intubated and put on lung-protective mechanical ventilation.
- A chest X-ray showed bilateral interstitial pneumonia and an oropharyngeal/nasal swab was positive for SARS-CoV-2.

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PATIENT 2

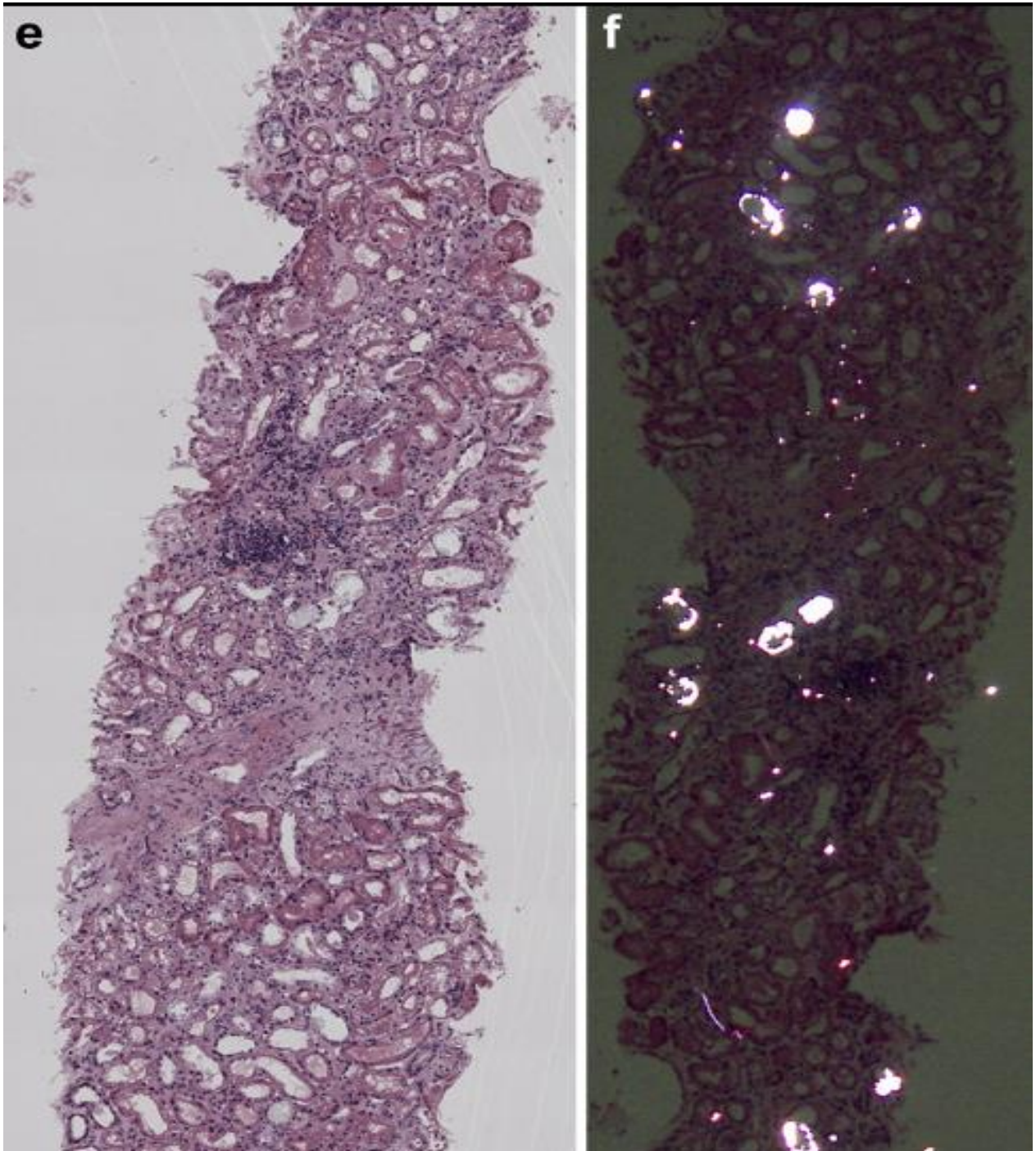
- he was started on hydroxychloroquine, darunavir-cobicistat 800/150 mg/d, and azithromycin 500 mg/d; i.v. steroids and broad-spectrum antibiotic therapy were provided.
- High-dose i.v. vitamin C (50 mg/kg 4 times/d) was administered according to internal management of septic patients.

PATIENT 2

- The clinical course was complicated by persistent hypotension with the need for inotropes.
- The patient developed progressive kidney dysfunction and needed kidney replacement treatment from day 8.
- He received 11 continuous venovenous hemodiafiltration sessions (2 of them with CytoSorb adsorber with local citrate anticoagulation and was later switched to intermittent hemodialysis.

PATIENT 2

- Despite regaining adequate diuresis, kidney function failed to improve and hemodialysis was continued; the patient was transferred to the nephrology unit, and on day 45 a biopsy specimen of the kidney was obtained.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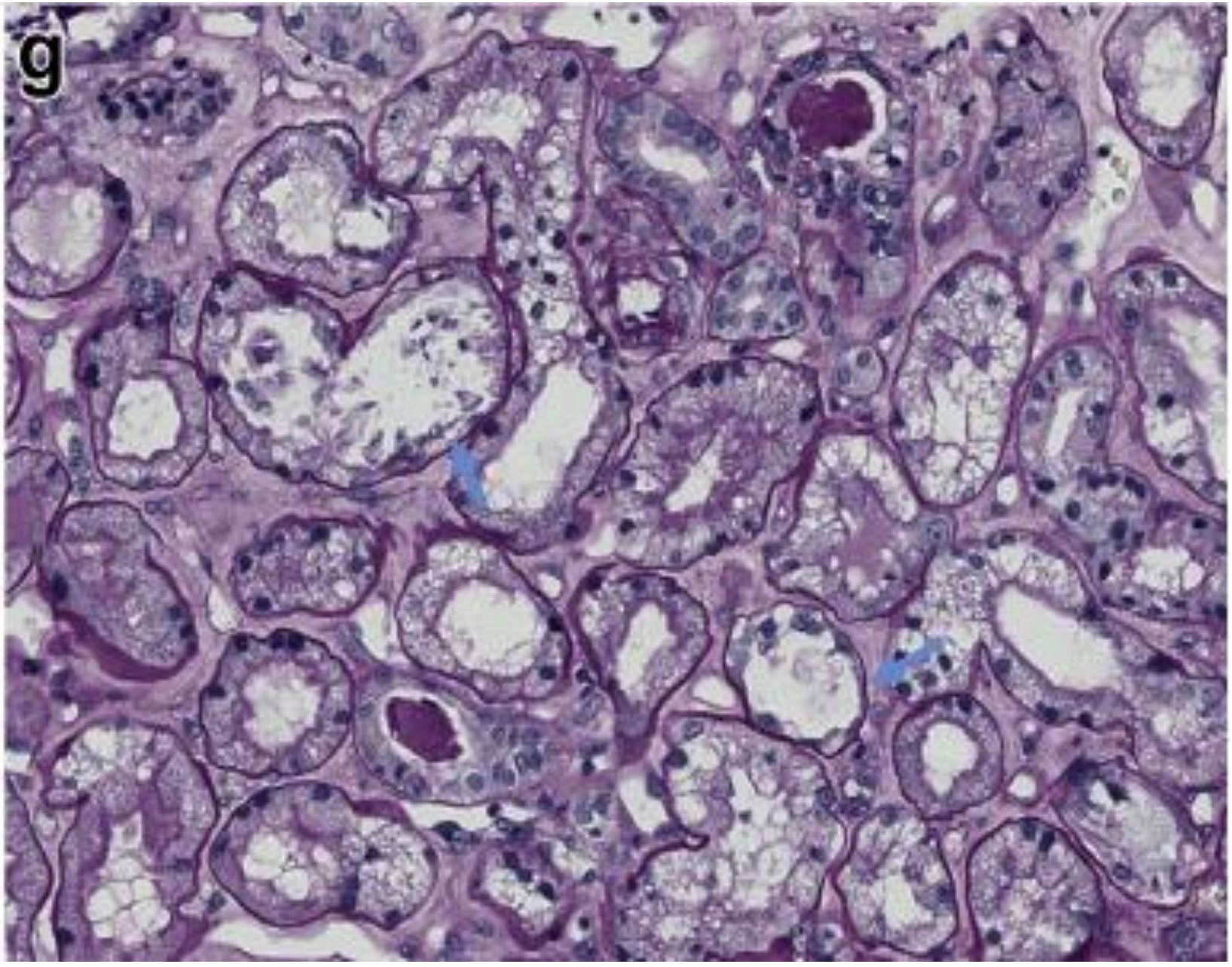
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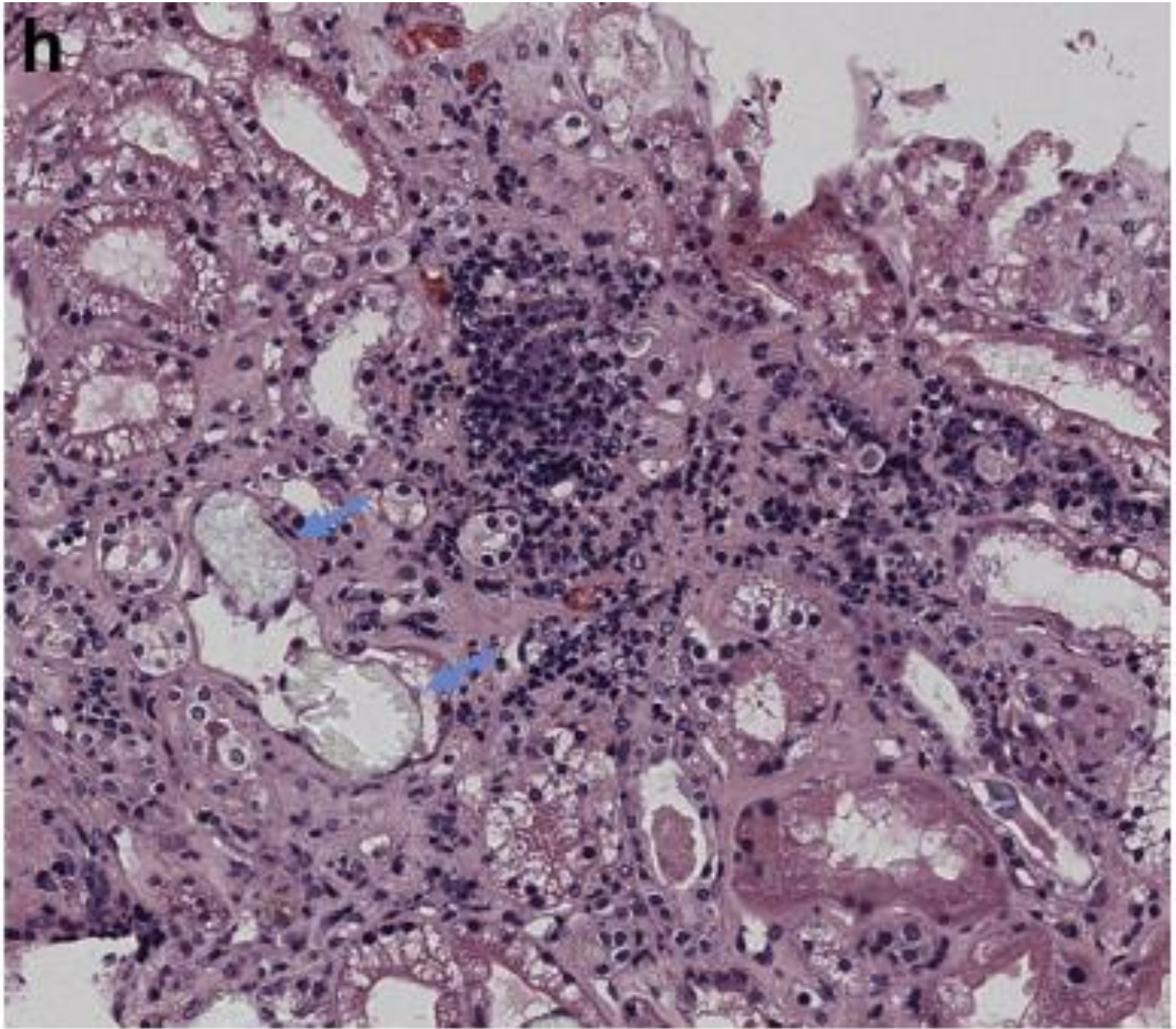
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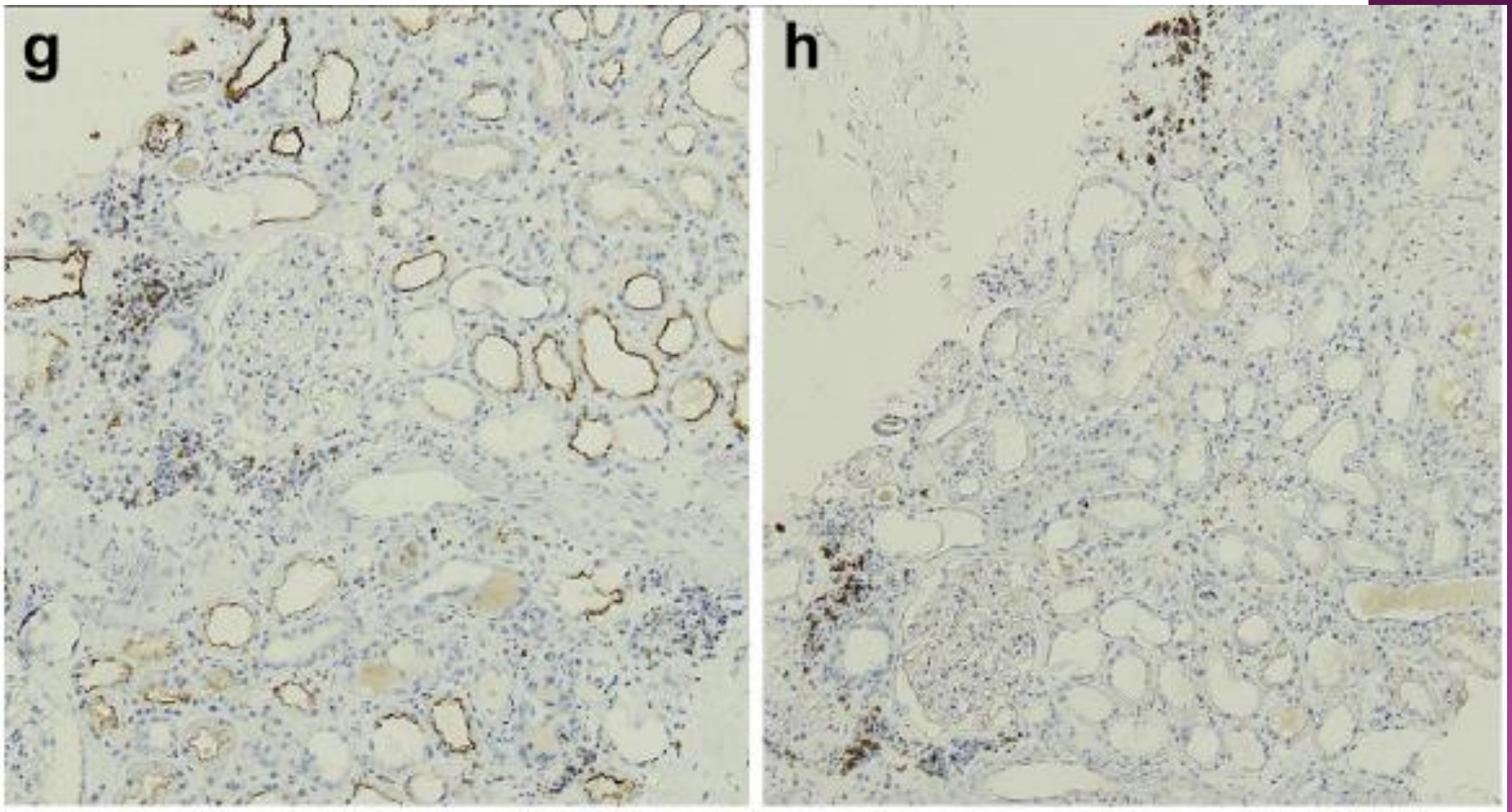
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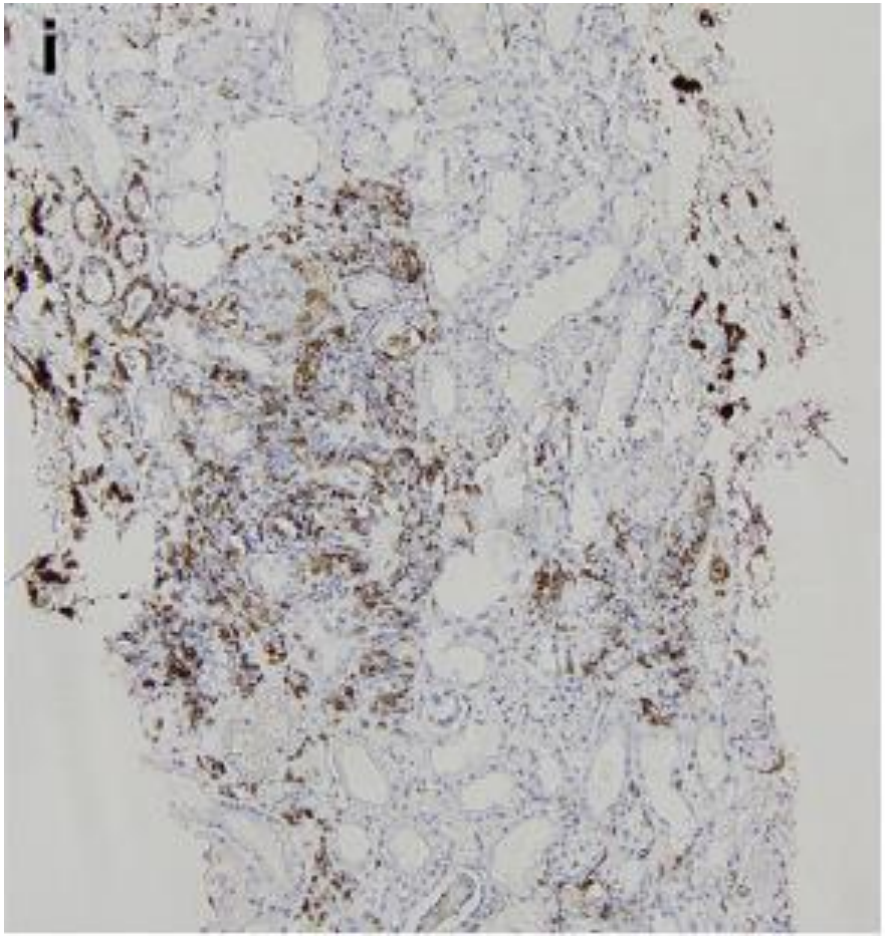
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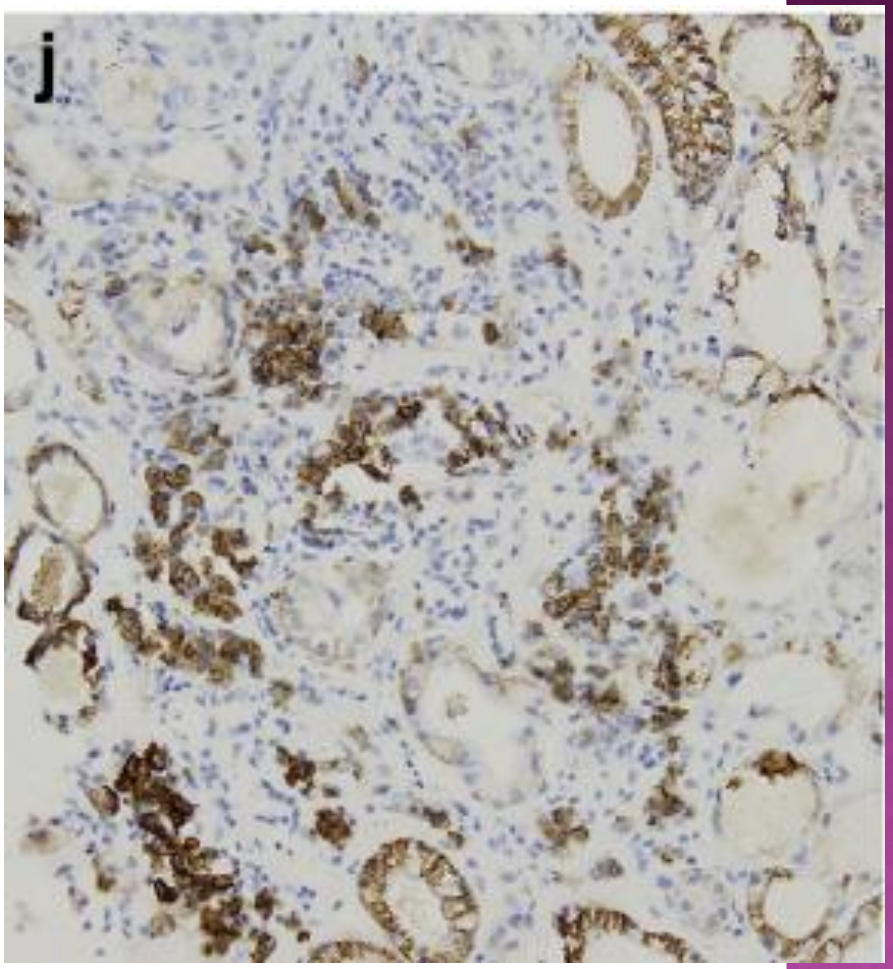
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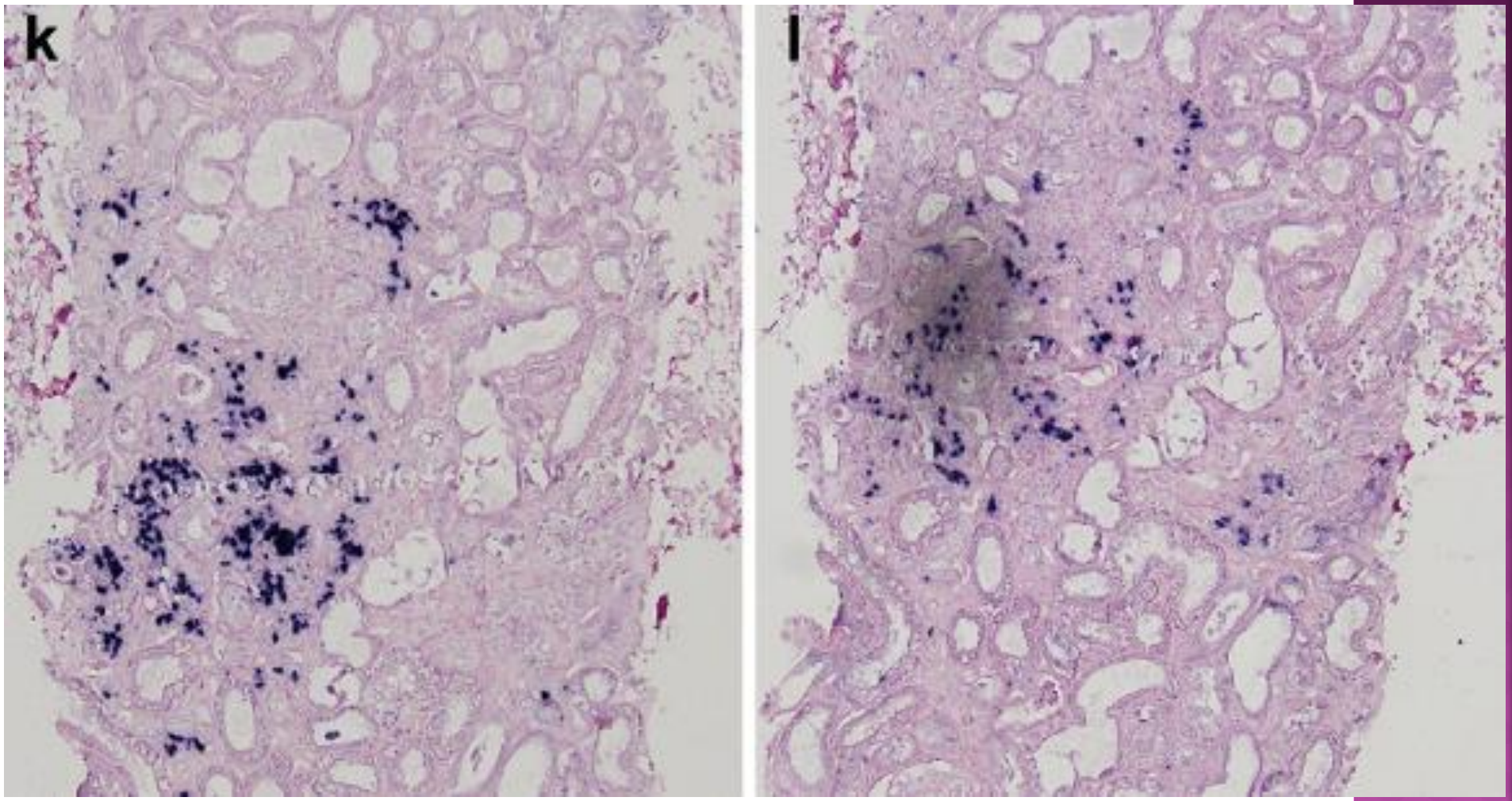
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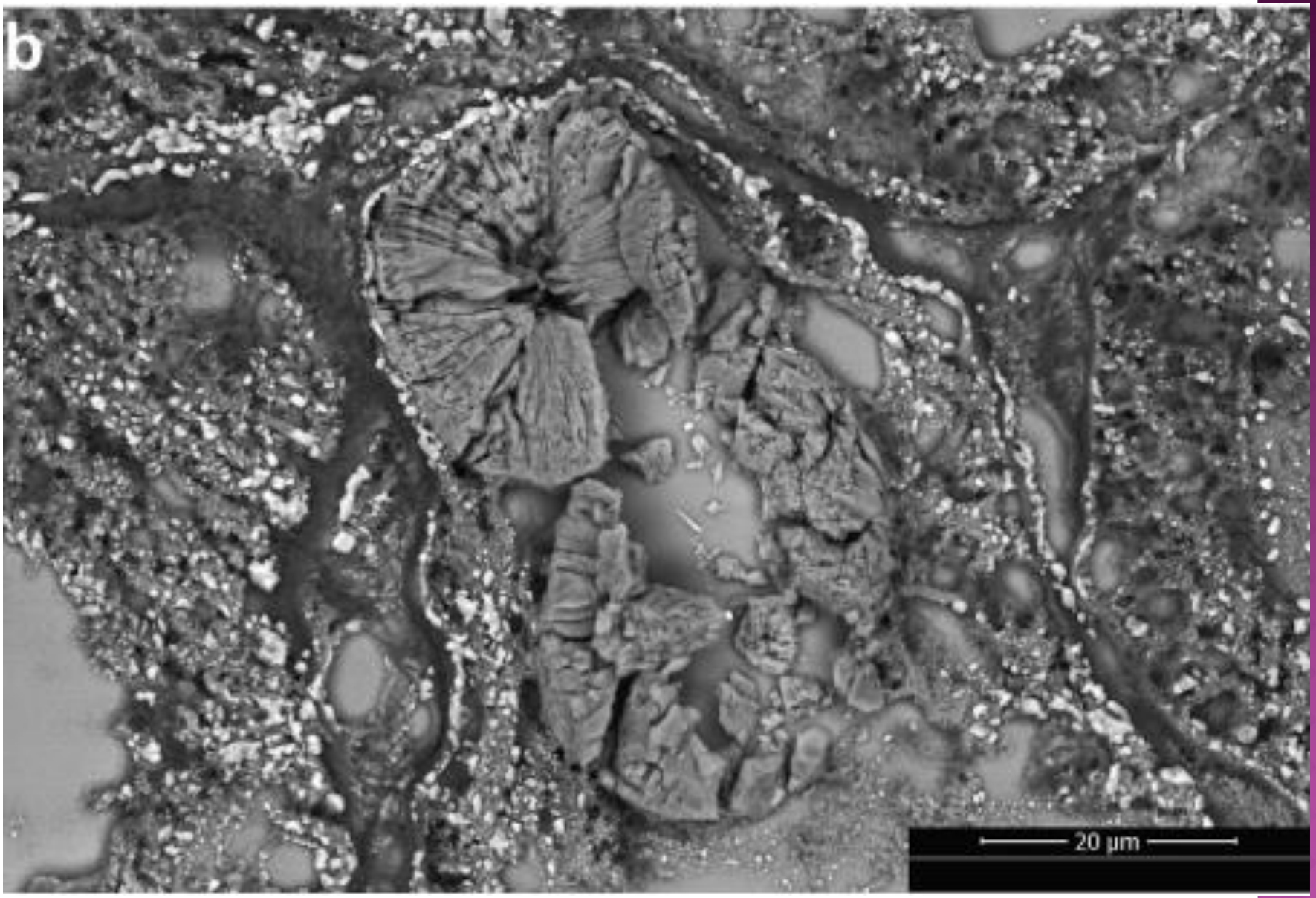
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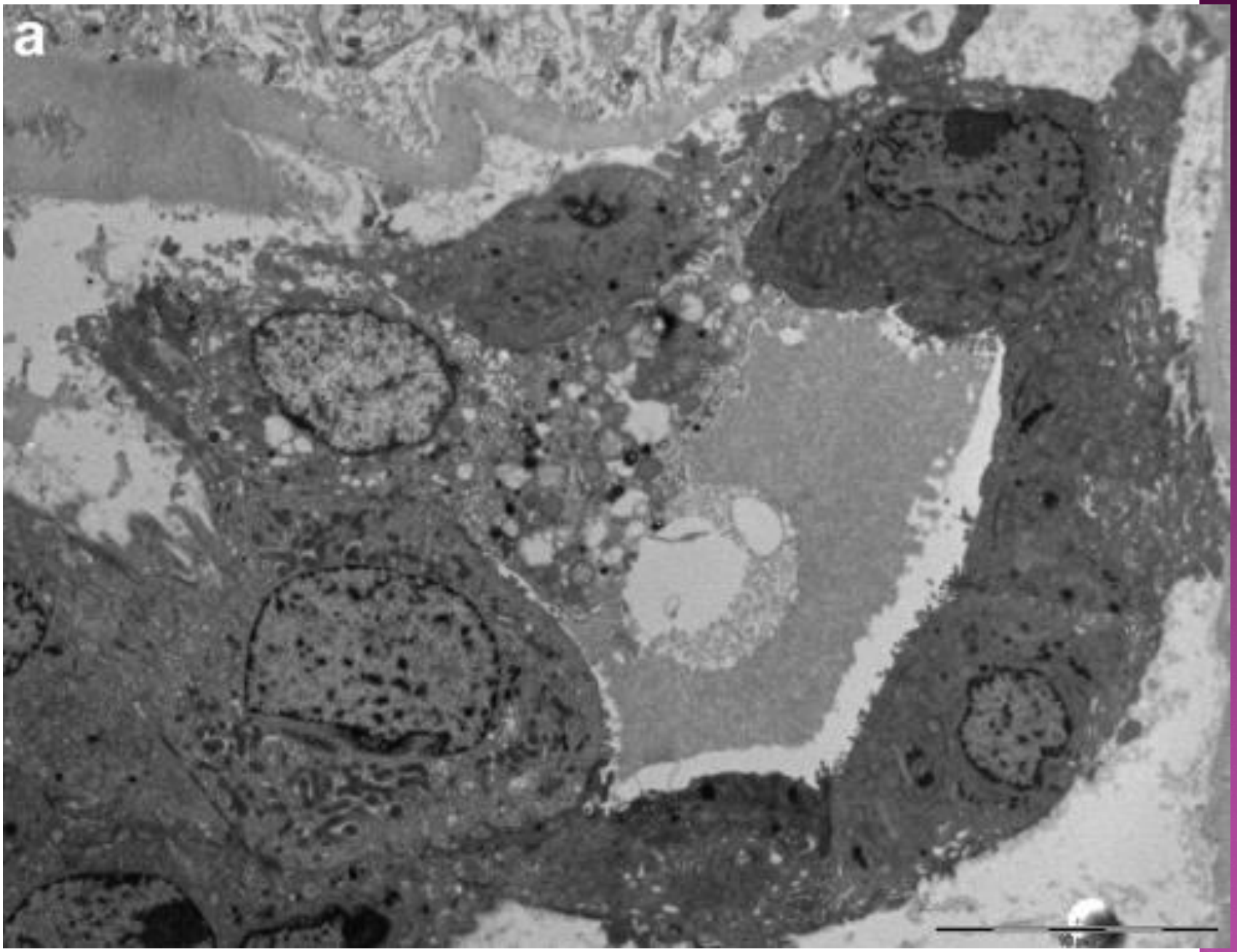
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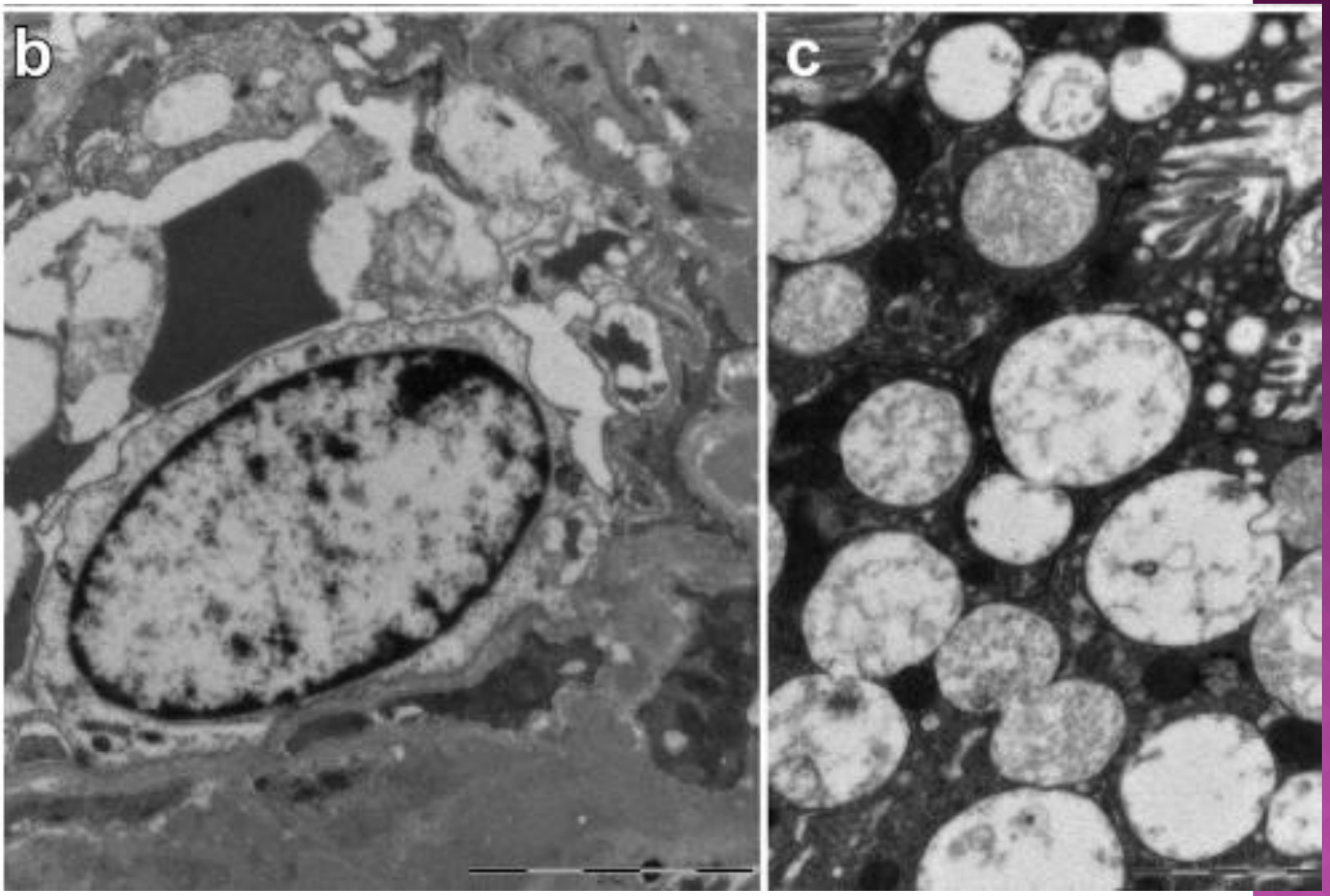
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AKI IN THE SETTING OF COVID-19

- Relative hypoperfusion of the kidney developing through alteration in microcirculation.
- Molecules released in the cytokine storm.
- Medications can have direct or indirect kidney toxicity.

AKI IN CASES

- In both cases, the kidney biopsy specimen showed ATI with mild reactive interstitial inflammation and no glomerular involvement; interestingly, tubular damage was often associated with the presence of calcium oxalate crystals in the tubular lumen, a picture that is suggestive of oxalate nephropathy.

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AKI IN CASES

- Oxalate nephropathy (also named secondary oxalosis) is characterized by tubular crystalline deposits of calcium oxalate leading to acute and chronic tubular injury.
- Primary hyperoxaluria was unlikely and our patients had no history of kidney stones, and therefore we hypothesized that secondary hyperoxaluria somehow connected to the critical illness phase of COVID-19.

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AKI IN CASES

- Secondary hyperoxaluria is usually the result of increased dietary oxalate intake, increased intestinal oxalate availability, decreased intestinal oxalate degradation, or increased colonic permeability to oxalate.

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AKI IN CASES

- The most likely cause of high blood levels of oxalate causing hyperoxaluria and secondary oxalosis was vitamin C administration during the intensive care unit stay.

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VITAMIN C AND HYPEROXALURIA

- vitamin C causes hyperoxaluria through the endogenous conversion of ascorbic acid to oxalate
- In the setting of hyperoxaluria, calcium oxalate super saturation can occur and form crystal nuclei in urine.

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VITAMIN C AND HYPEROXALURIA

- while crystals are quickly passed in healthy individuals, intratubular retention is believed to occur in areas of damaged and regenerating tubular epithelium, where molecules with potential crystalbinding capacity are expressed.

VITAMIN C AND HYPEROXALURIA

- There is no clear toxic dose for vitamin C, but a dose of 1000 mg/d can increase oxalate excretion by 6–13 mg/d and may induce calcium oxalate calculi and oxalate nephropathy has been reported after as few as 2 i.v. doses of vitamin C in a patient with preexisting kidney dysfunction.

VITAMIN C YES OR NO

- Considering the potentially beneficial effects of high-dose vitamin C in patients with sepsis, we believe that a cautious risk/benefit balance of its prolonged administration should be assessed on a case-by-case basis in patients with COVID-19 and kidney dysfunction.

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VITAMIN C YES OR NO

- In addition to vitamin C–induced hyperoxaluria, antibiotic administration and possible COVID-19–related enteritis could have contributed to the picture of secondary oxalosis, favoring intestinal microbiota alterations and oxalate hyperabsorption.

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VITAMIN C YES OR NO

- Some antibiotics (in particular ceftriaxone) can precipitate in the urine and cause the formation of Crystals.
- Protease inhibitors, especially darunavir, have been reported to possibly form intratubular and cellular crystals.

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TREATMENT STRATEGIES

1) Discontinuation of vitamin C
2) Maintaining high urine output if possible
3) Oxalate removal via (citrate-based) hemodialysis.