# Acute Interstitial Nephritis

## Diagnostic Difficulties Related to Bacterial Infections

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# Acute Interstitial Nephritis (AIN)

- **Infectious**
  - Bacterial, rarely fungal (pyelonephritis), dominated by neutrophilic granulocytes
  - Viruses (EBV, CMV, adenovirus, hantavirus, polyomavirus), rickettsia, parasites (usually dominated by mononuclear cells)
- **Noninfectious** (dominated by mononuclear cells)
  - Drugs (allergic/hypersensitivity AIN) (usually many eosinophil granulocytes)
    - Antibiotics – most common
    - Proton pump inhibitors – 2nd most common
    - NSAID – 3rd most common
    - Many other drugs
  - Autoimmune diseases
    - SLE
    - Sjögren syndrome
    - IgG4-related
    - TINU syndrome
    - Mixed connective tissue disease
    - Anti-TBM antibodies
- Sarcoidosis
- Reactive AIN (glomerulonephritis, vasculitis)
- Metabolic disease (e.g. oxalate nephropathy, gout)
- Rare familial forms
- Monoclonal gammopathy-associated
- Idiopathic

# Acute Nonbacterial Interstitial Nephritis Clinical Symptoms

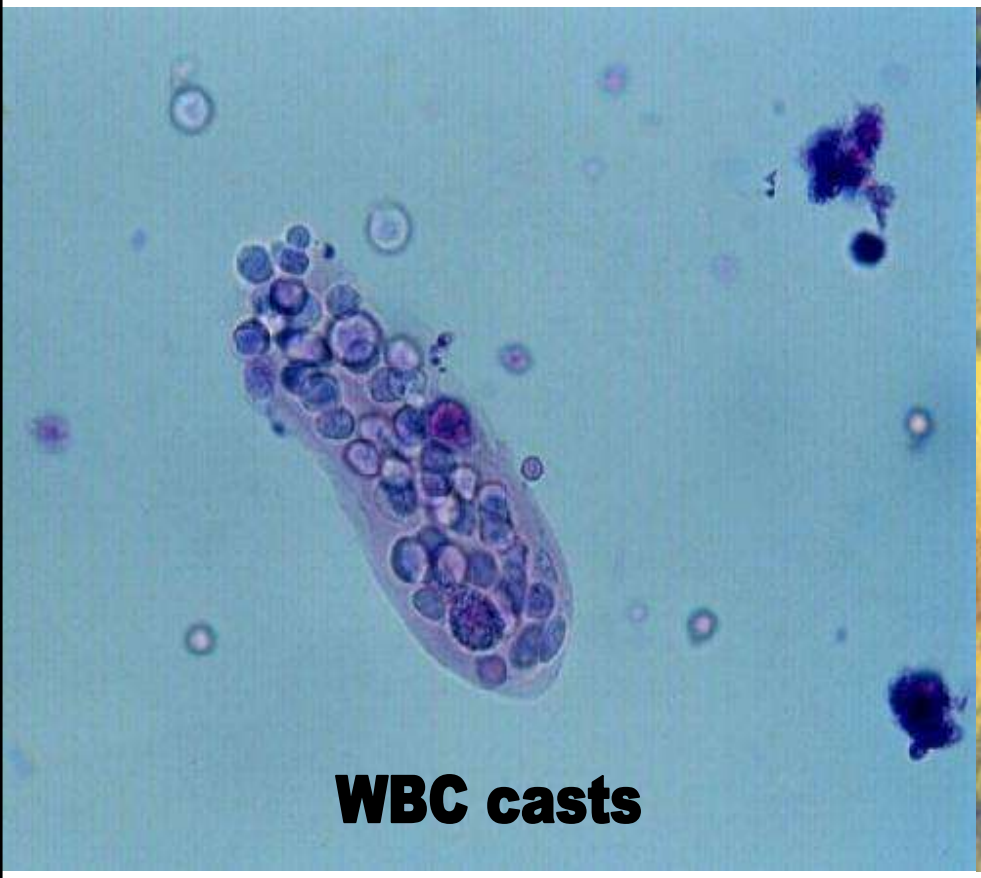
- Mostly nonspecific
- Acute Kidney Injury
- Sterile pyuria (sometimes WBC casts)
- Mild proteinuria
- Microscopic hematuria

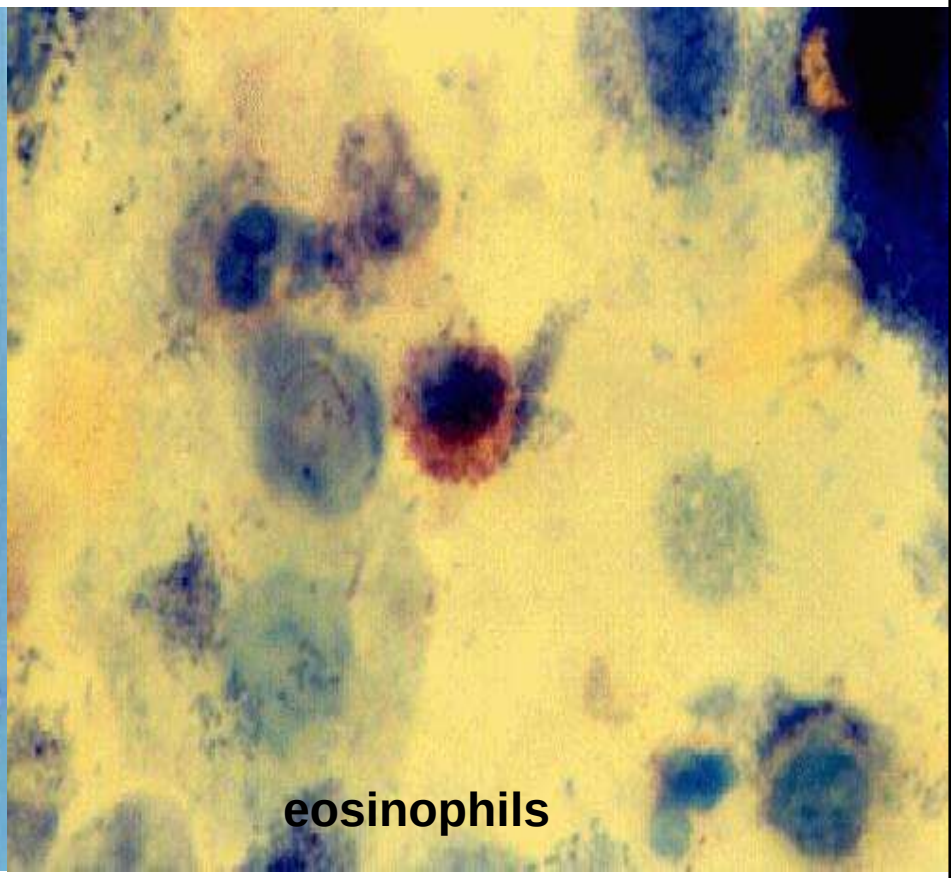
# DRUG-INDUCED (HYPERSENSITIVITY) INTERSTITIAL NEPHRITIS
## Clinical Symptoms

**Symptoms follow drug exposure (days, weeks, sometimes months)**

- **Symptoms similar to other forms of interstitial nephritis (see previous slide)**
- **There are certain symptoms that are more common, such as**
  - **eosinophiluria**
  - **skin rash**
  - **Fever**
  - **peripheral eosinophilia**

# Acute Interstitial Nephritis
# Urine Sediment

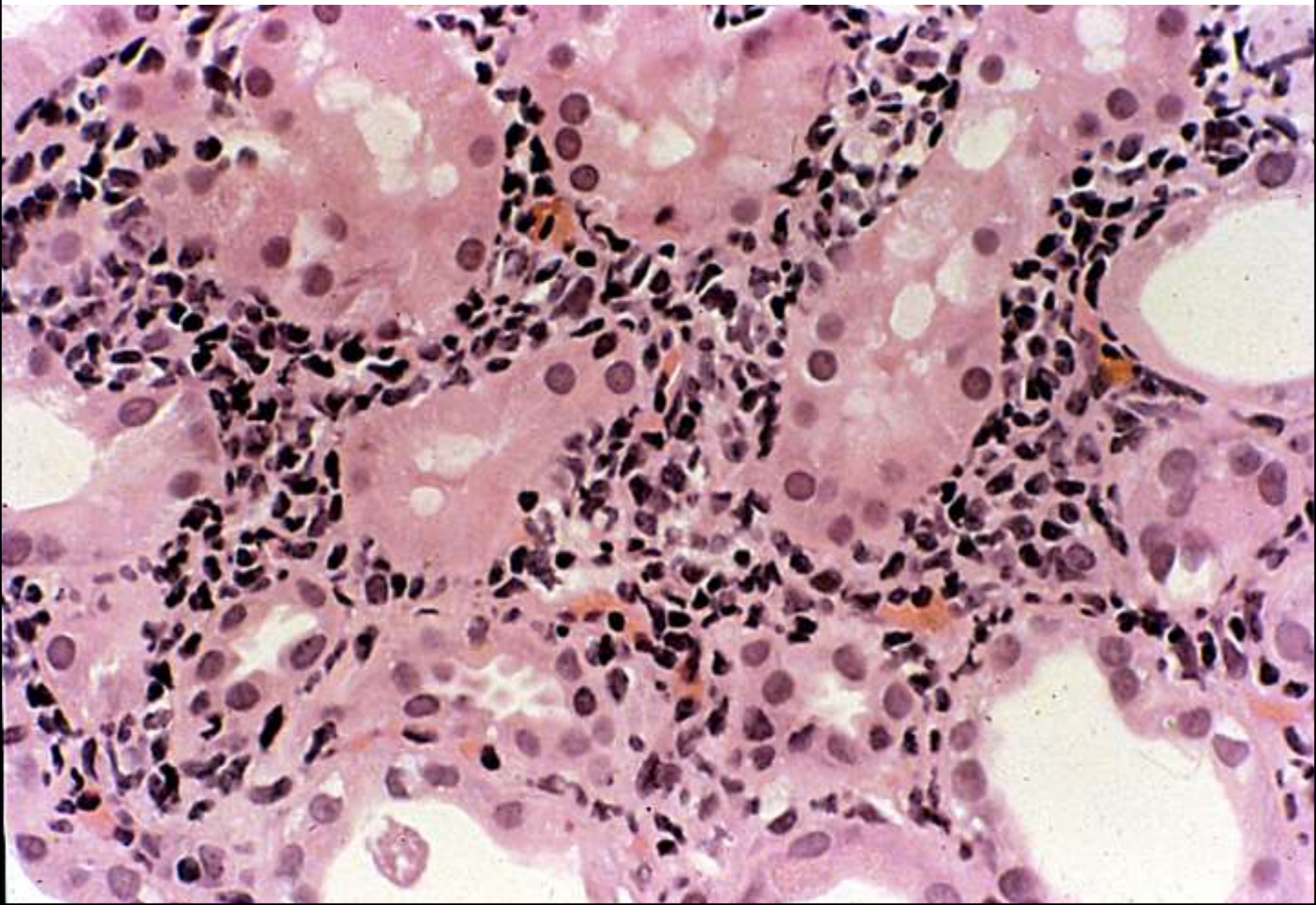


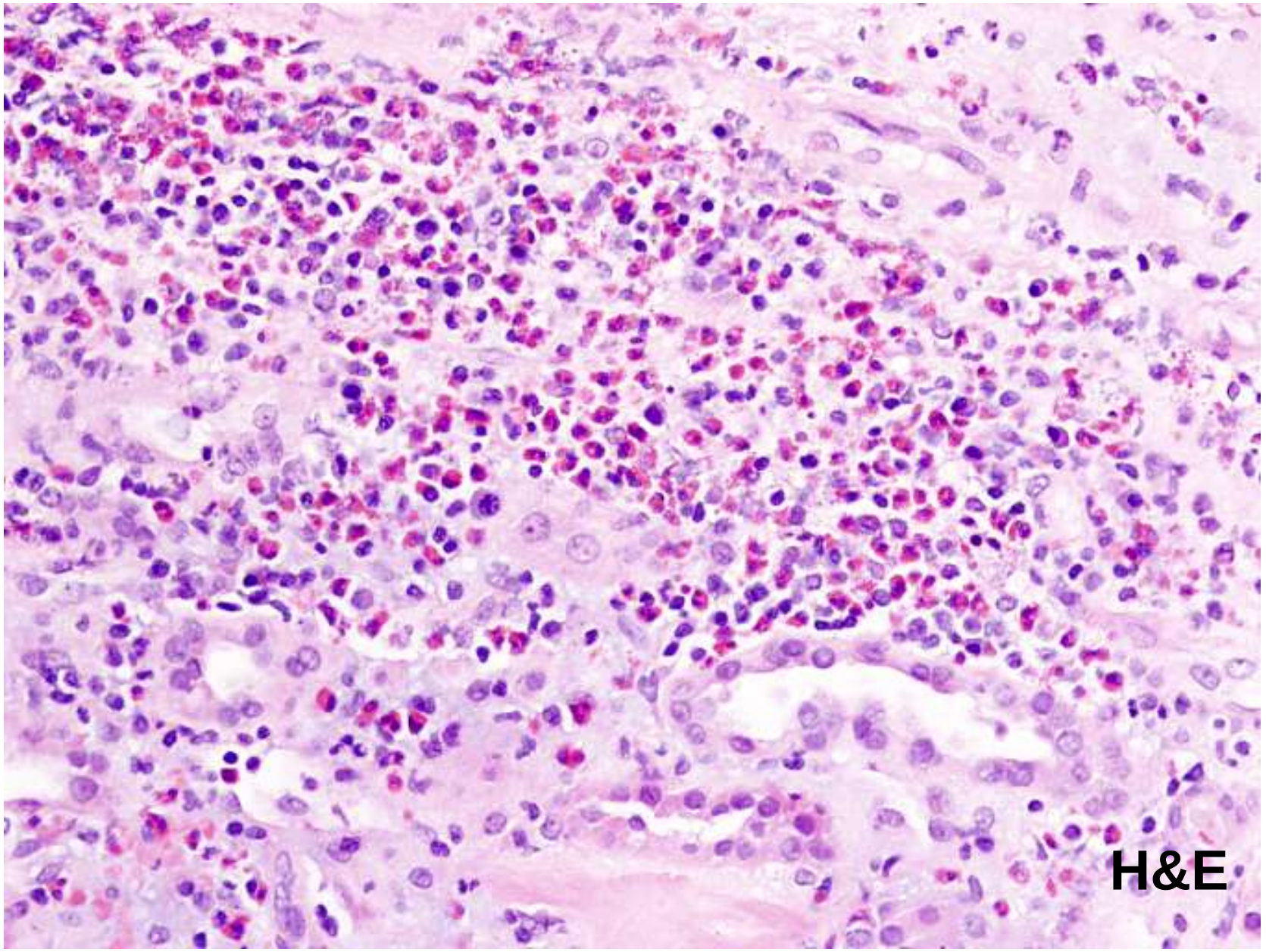
# Acute (nonbacterial) Interstitial Nephritis Microscopic Findings

- Interstitial inflammatory cell infiltrate
  - Mainly mononuclear cells
  - Eosinophils common in hypersensitivity interstitial nephritis (drugs)
  - Plasma cells, polymorphonuclear leukocytes may occur
- Interstitial edema
- Tubular epithelial injury with infiltration of the tubular epithelium by inflammatory cells (tubulitis)
- Granuloma formation may occur
  - Common in sarcoidosis but granulomas may occur in other forms of interstitial nephritis (such as in drug-induced forms)

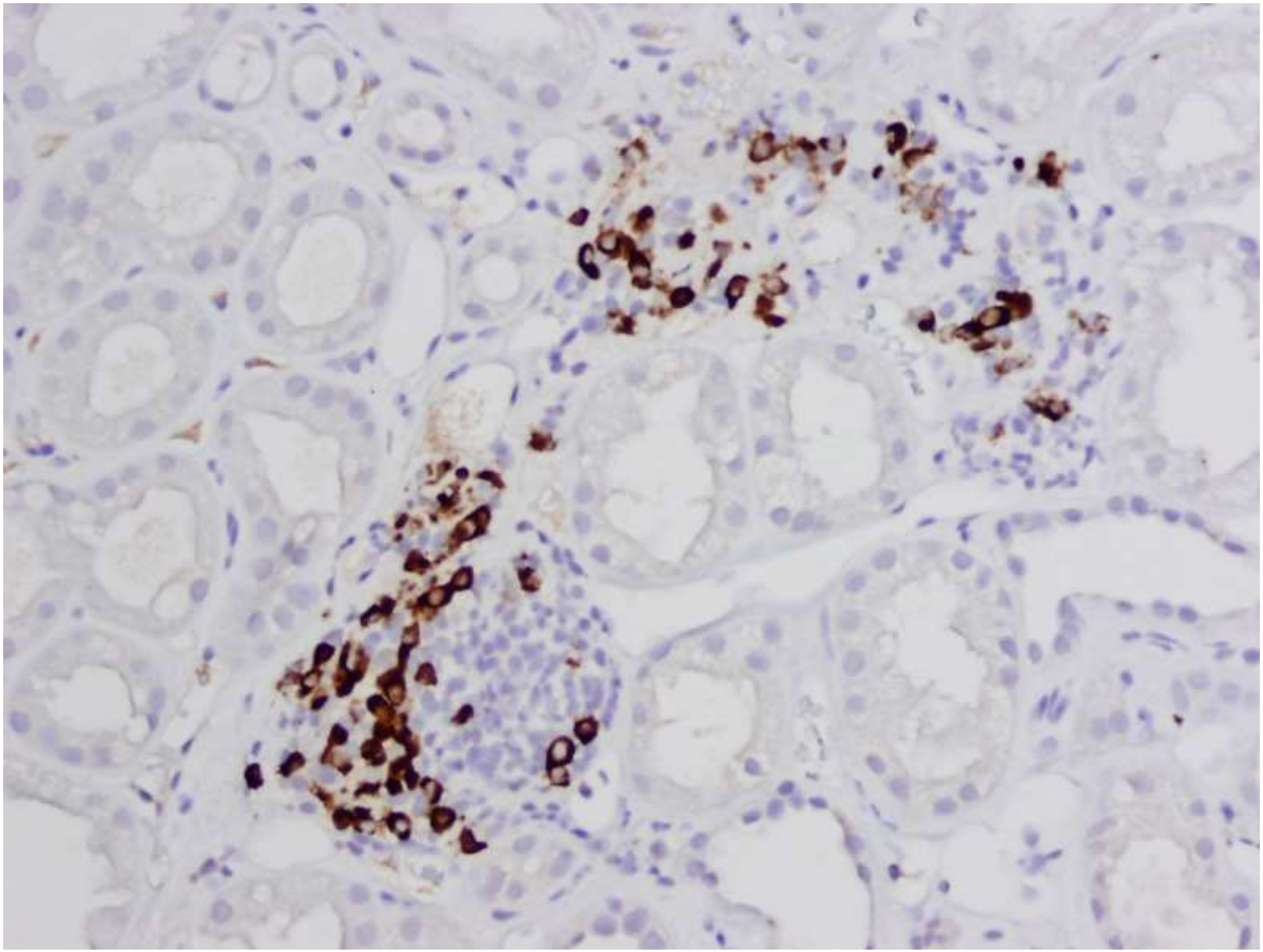
Interstitial inflammation



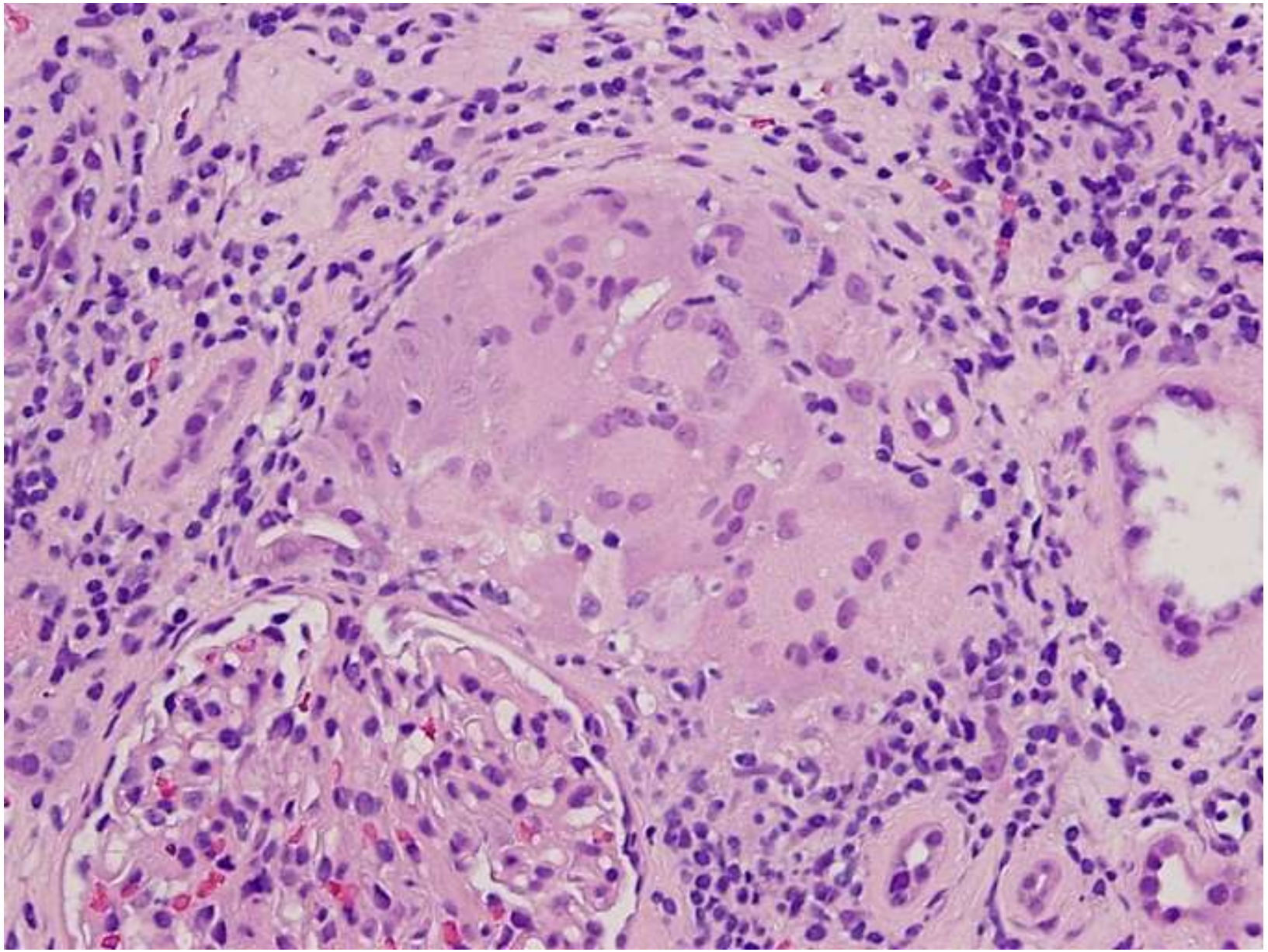
Interstitial eosinophils in drug-induced interstitial nephritis.



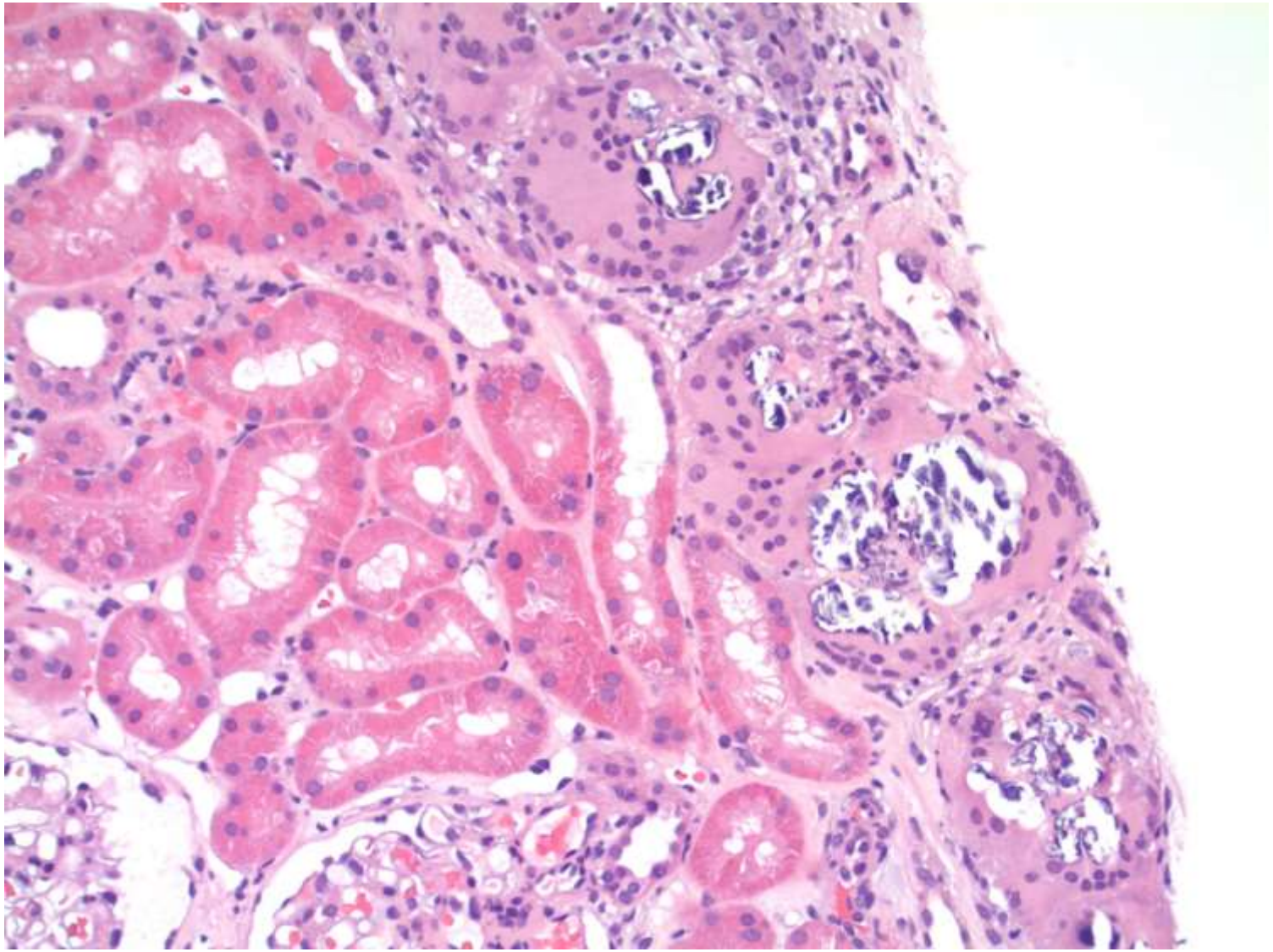
IgG4 positive plasma cells in IgG4 disease-associated interstitial nephritis



# Granulomatous interstitial nephritis



Giant cells with calcium deposits – Patient with sarcoidosis



| **CAUSES OF GRANULOMATOUS INTERSTITIAL NEPHRITIS** |
| --- |
| Infection<br>Tuberculosis<br>Fungal Infections<br>Brucellosis<br>Parasites<br>Drugs (e.g. penicillins, fluoroquinolones, nitrofurantoin, allopurinol, proton pump inhibitors, nonsteroidal anti-inflammatory drugs [NSAIDs], diphenylhydantoin, 5-amlinosalicylic acid,<br>Sarcoidosis<br>Tubulointerstitial nephritis and uveitis syndrome (TINU)<br>Granulomatous vasculitis (Wegener's)<br>Oxalosis<br>Gout<br>Cholesterol granuloma<br>Idiopathic |

# Sample Case: Clinical History

58-year-old Caucasian female with history of ulcerative colitis but normal renal function previously.

On presentation she had fever and serum creatinine (S. Cr.) of 3.7 mg/dl.

S. cr. rapidly increased to 5 mg/dl.

No eosinophilia, edema or rash.

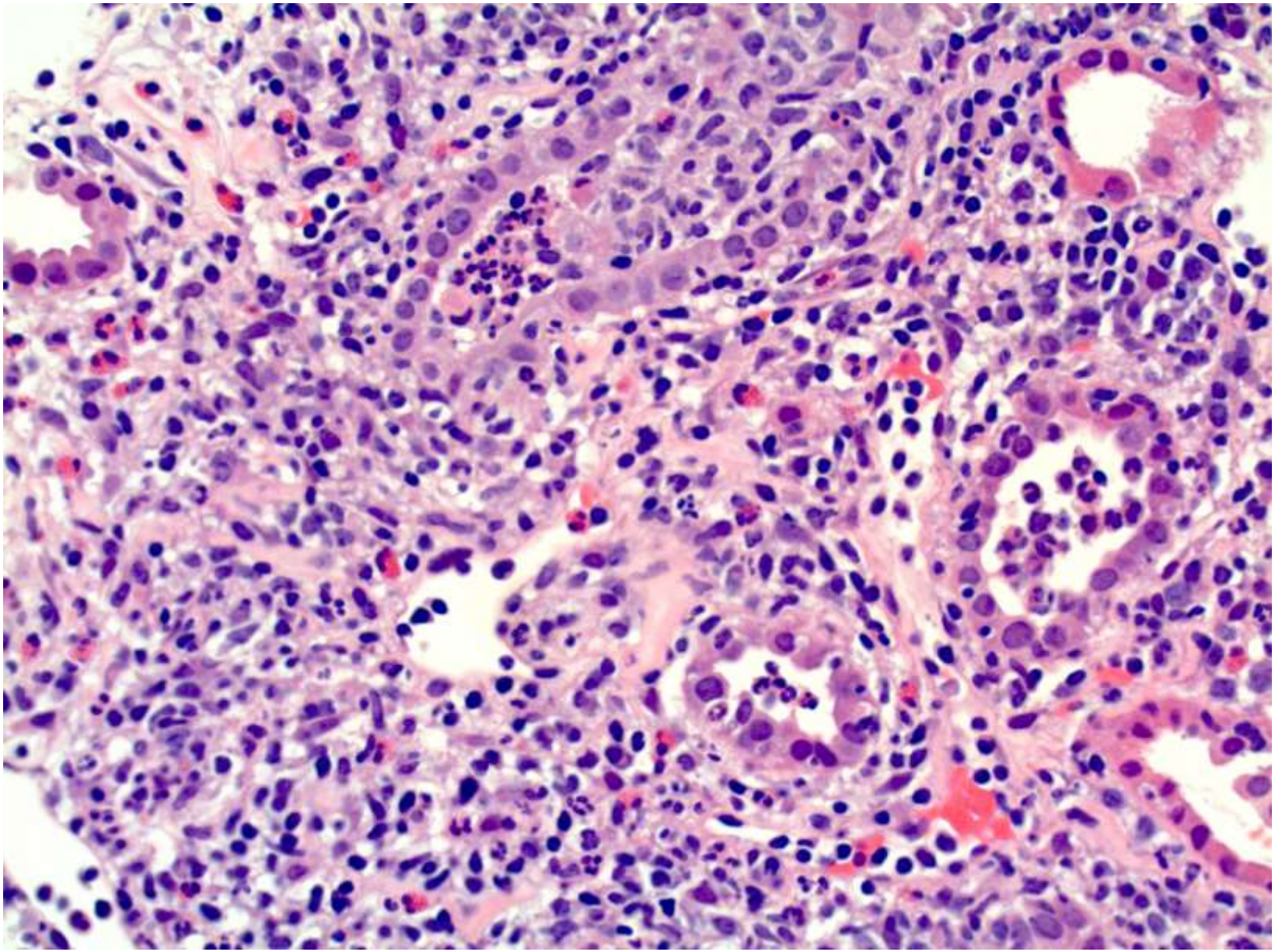
Urinalysis showed numerous WBCs.

Urine cultures – low numbers of Enterobacter, Candida.

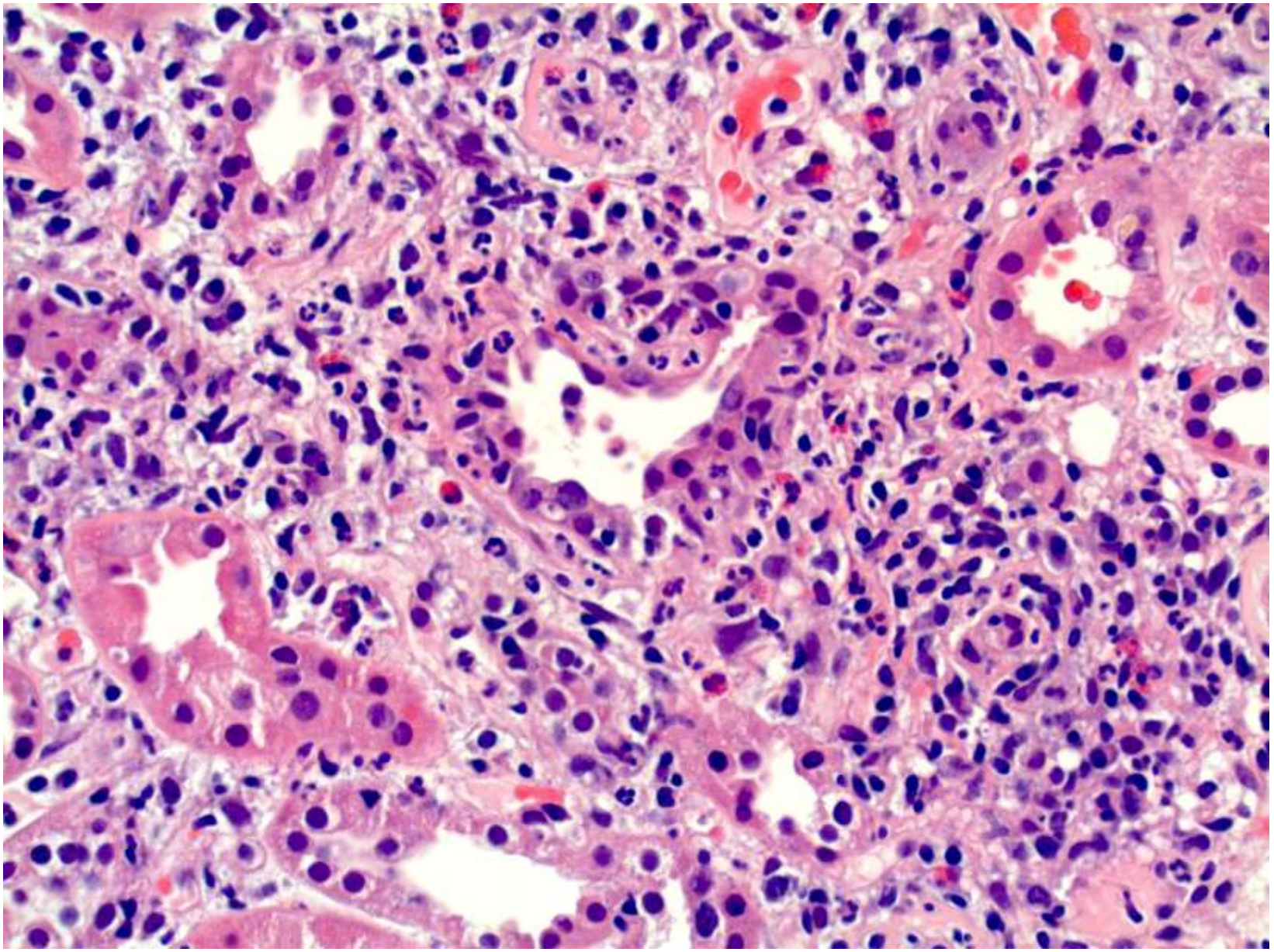
Urine leukocyte esterase test positive.

Negative serologies (ANCA, ANA anti-GBM hepatitis panel, serum complements).

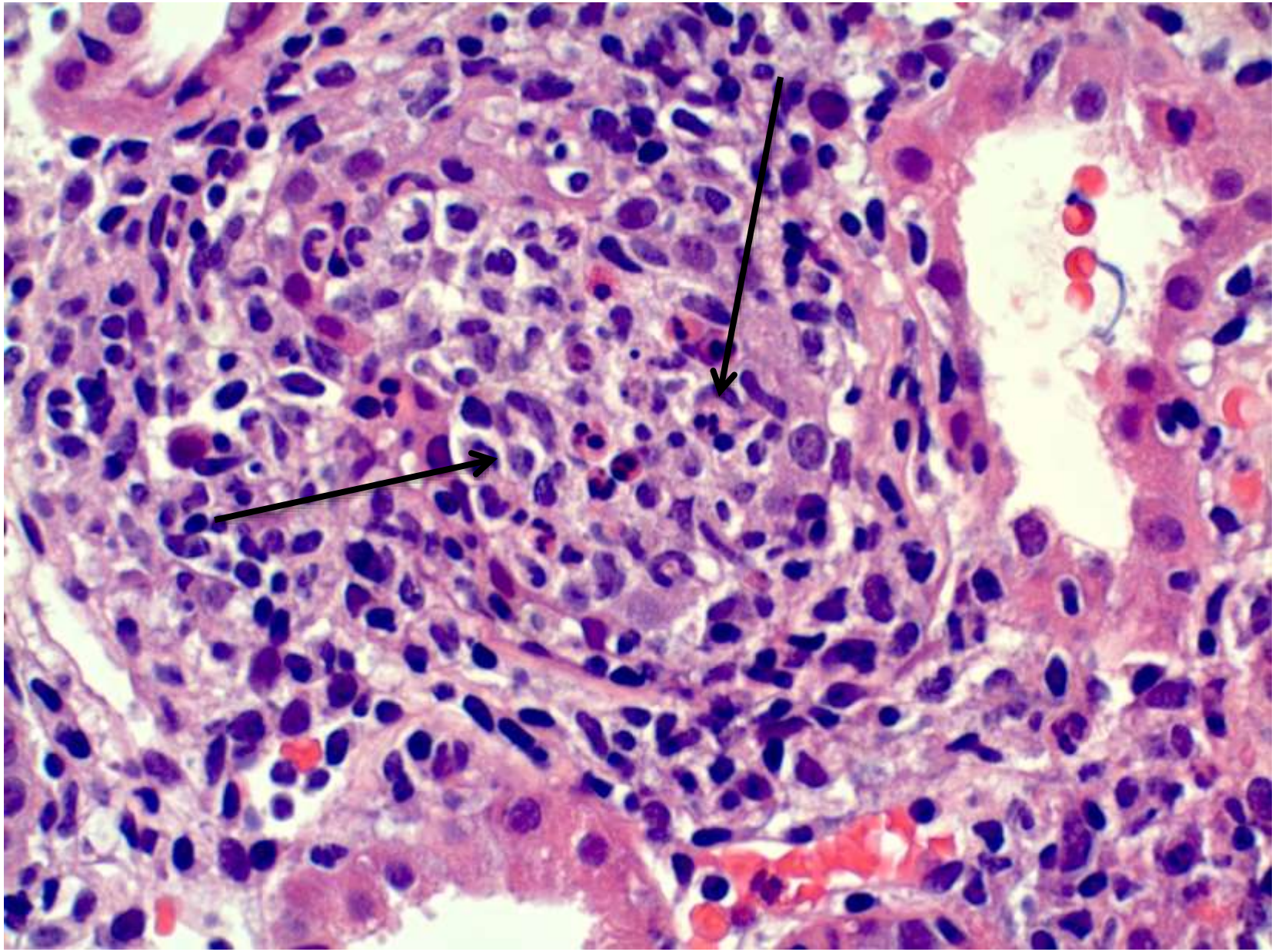
Mixed inflammatory cell infiltrates with some interstitial eosinophils and numerous neutrophil granulocytes in tubules



# PMNs infiltrating tubules



# Tubular microabscess



# Diagnosis

- Acute interstitial nephritis with features suggestive of acute pyelonephritis.

  Note: Considering the history of fever, pyuria, urine culture results and histologic findings, acute pyelonephritis should be considered.

- Clinical Management:

  - Treatment with antibiotics, but she did not show any improvement after 2 weeks

  - Case was again reviewed

Patient had history of inflammatory bowel disease. She was receiving Asacol (Mesalamine/5-aminosalicylic acid) for a few months.

The possibility of severe drug-induced interstitial nephritis was raised

Patient recovered normal renal function after stopping the drug and administration of steroids.

# Teaching points

## Careful and detailed clinical history is very important!!!

The kidney has limited ways of responding to injurious stimuli.

Therefore overlapping morphologic patterns are commonly seen in many renal diseases, including interstitial nephritis.

Neutrophil leukocytes forming microabscesses in pyelonephritis may be missed in a needle biopsy but, more importantly, severe acute nonbacterial interstitial nephritis biopsies may contain focally numerous neutrophil granulocytes

**Therapy is very different**:

Acute pyelonephritis – antibiotics

Allergic drug-induced tubulointerstitial nephritis – steroids

# Teaching points

**Acute pyelonephritis in native kidneys rarely causes acute renal failure**,

- unless it is severe and bilateral (e.g., secondary to bilateral urinary tract obstruction, neurogenic bladder, severe reflux)
- or is associated with urosepsis
- Clinical symptoms of acute pyelonephritis in such cases are usually obvious and kidney biopsy is not performed

# Acute pyelonephritis in native kidney

- Classic clinical tetrad – Fever, costovertebral angle tenderness, positive urine culture, leukocytosis.
- Females commonly affected.
- Young children, newborns – nonspecific symptoms Poor feeding, vomiting, irritability, fever alone.
- May be unilateral depending on the anatomic situation and pathogenesis (acute suppurative nephritis secondary to sepsis is always bilateral)
- For acute kidney injury to develop, the disease must be severe and usually bilateral.
- Renal biopsy is contraindicated if the clinical picture is classic.

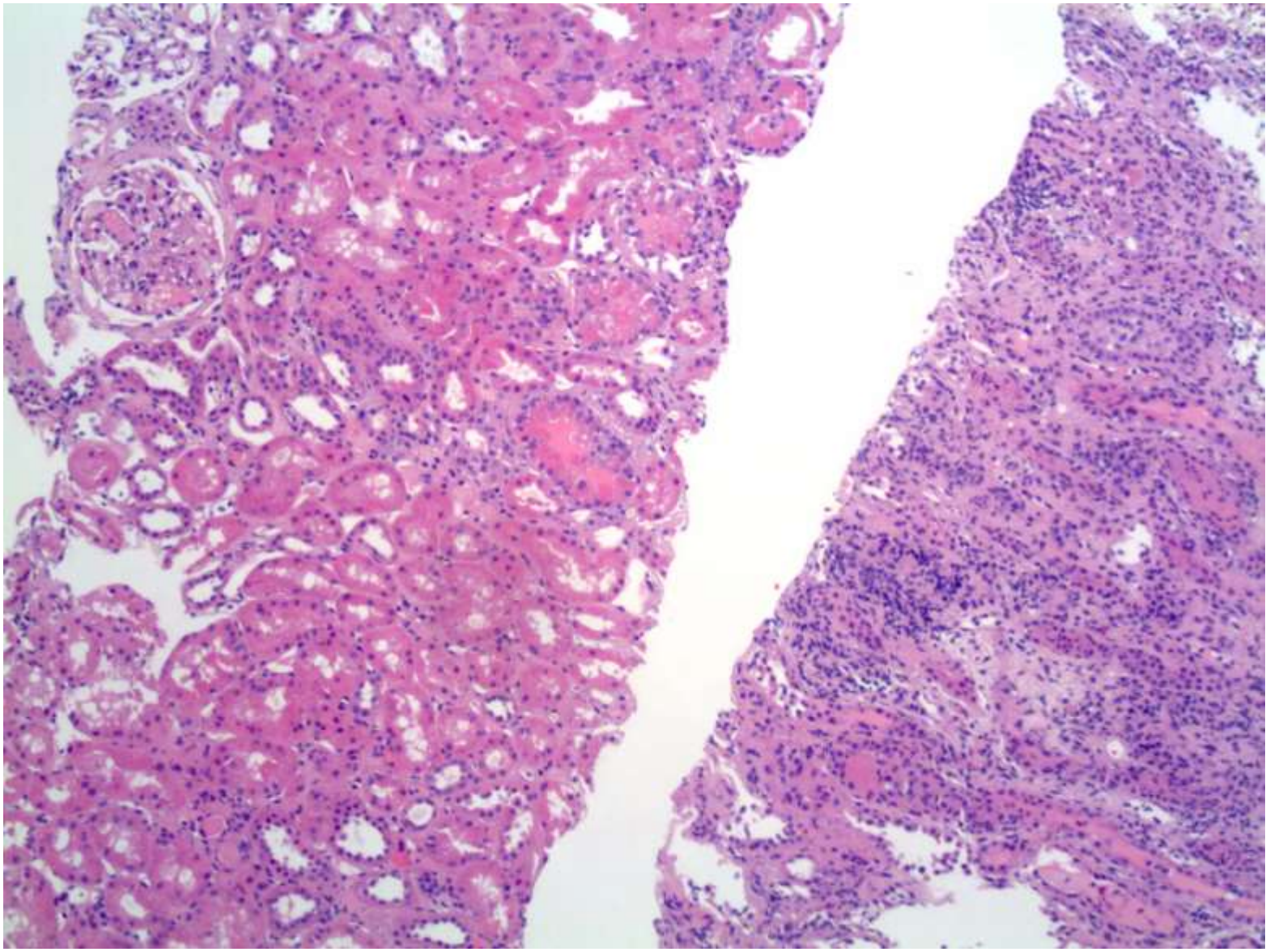
# Biopsy may be performed with atypical clinical presentation

- The typical tetrad of symptoms may not always be present.
  - Fevers, costovertebral angle tenderness, positive urine cultures.
- Elderly patients with septicemia may present with non-specific symptoms.
  - Altered mental status and acute renal failure.
- Renal dysfunction does not improve despite antibiotic treatment.
- Absence of positive urine cultures and/or significant bacteriuria
- Multiple co-morbidities such as diabetes mellitus, history of recurrent lower UTIs, now has renal dysfunction.

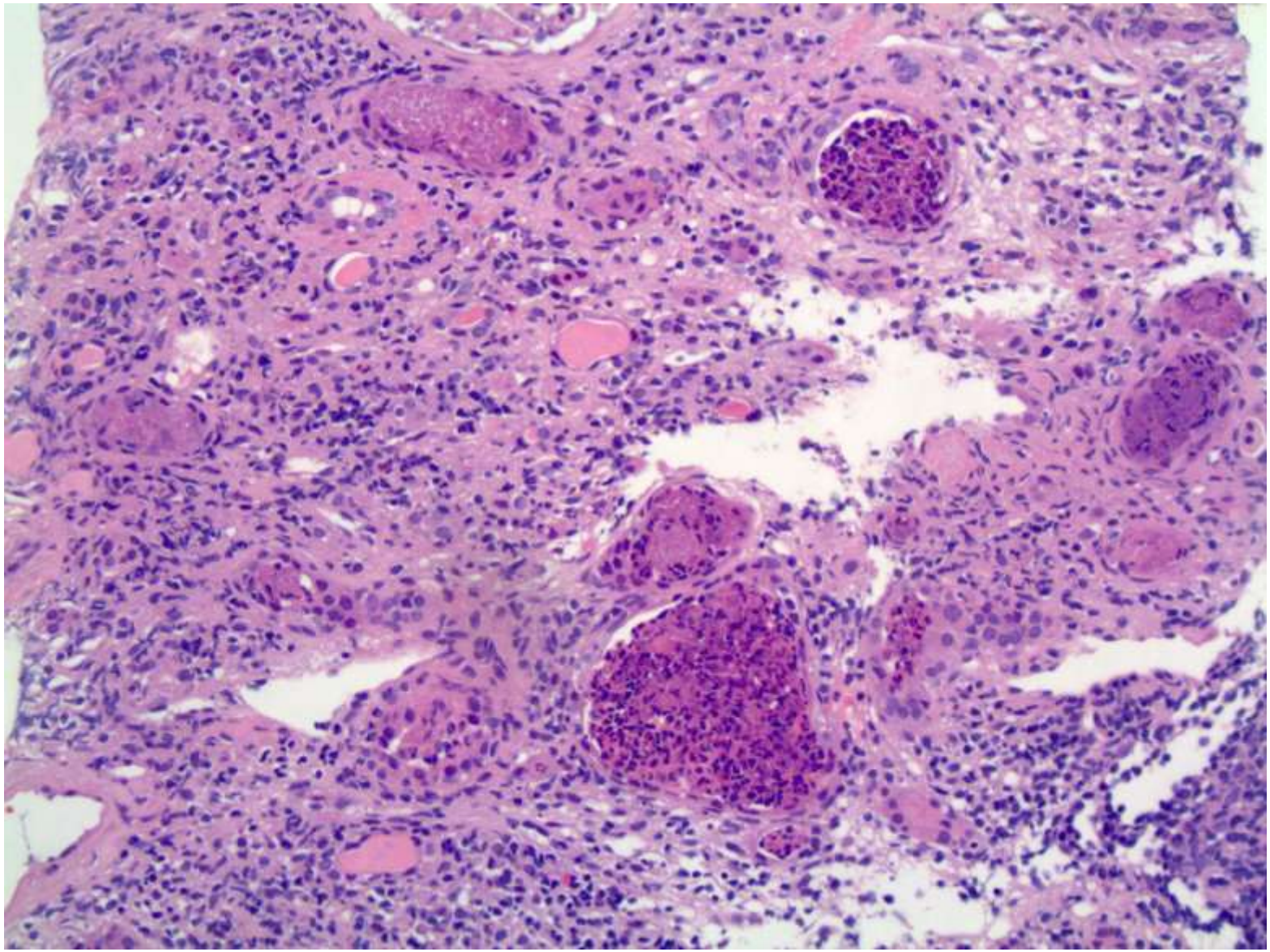
# Morphologic features in biopsy with acute pyelonephritis

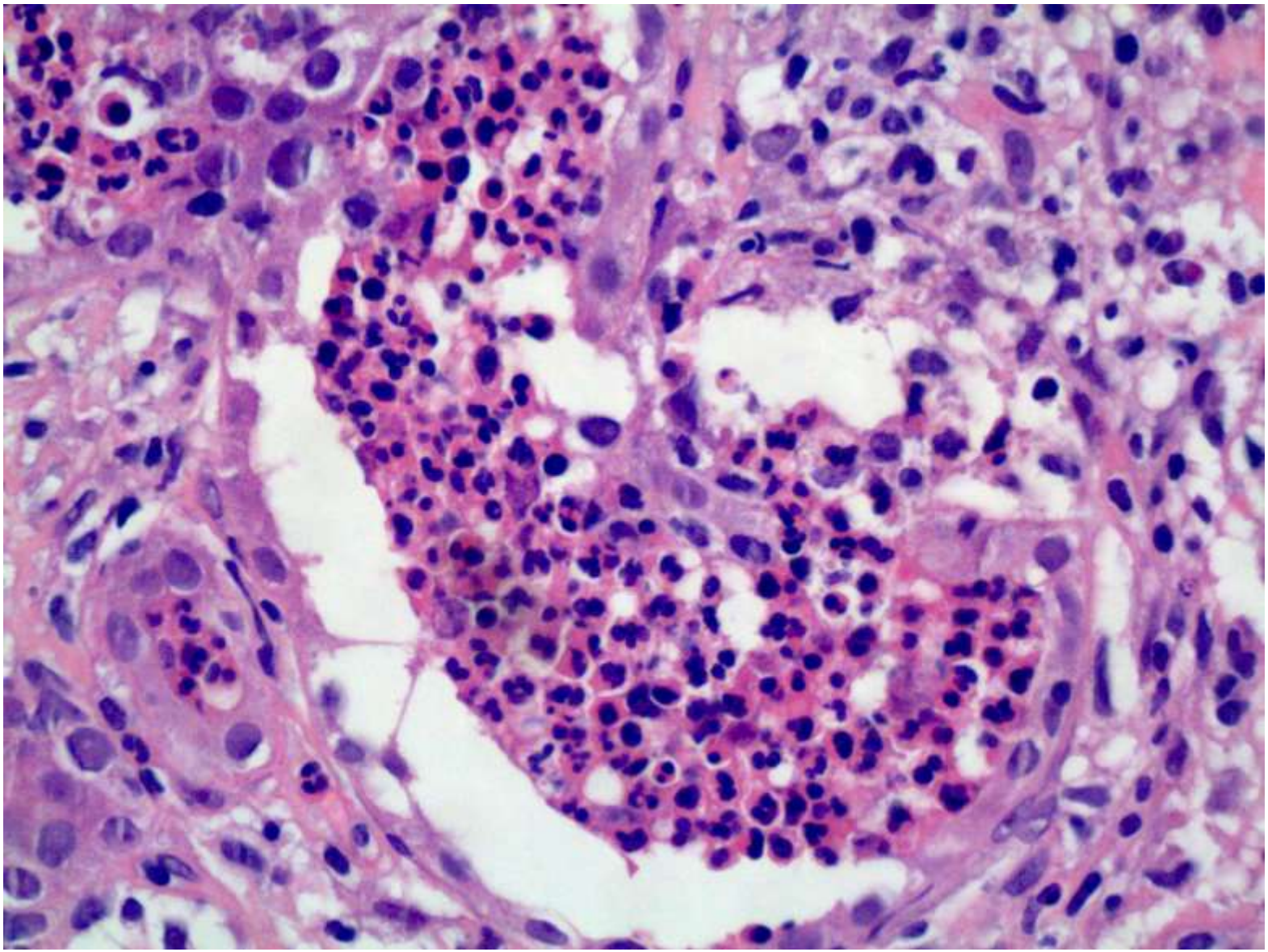
- Suppurative inflammation with abundant PMNs in the interstitium, neutrophilic tubulitis, and clusters of PMNs and apoptotic cell debris in tubules, forming “microabscesses”.
- Ascending infection - Inflammation in the renal pelvis, calyces, may extend into the cortex.
- Blood stream infection or after infectious emboli (e.g., in bacterial endocarditis) - Mainly cortical abscesses (may be glomerulocentric) .
- The renal involvement/inflammation is usually *focal/zonal.*

# Zonal pattern of inflammation

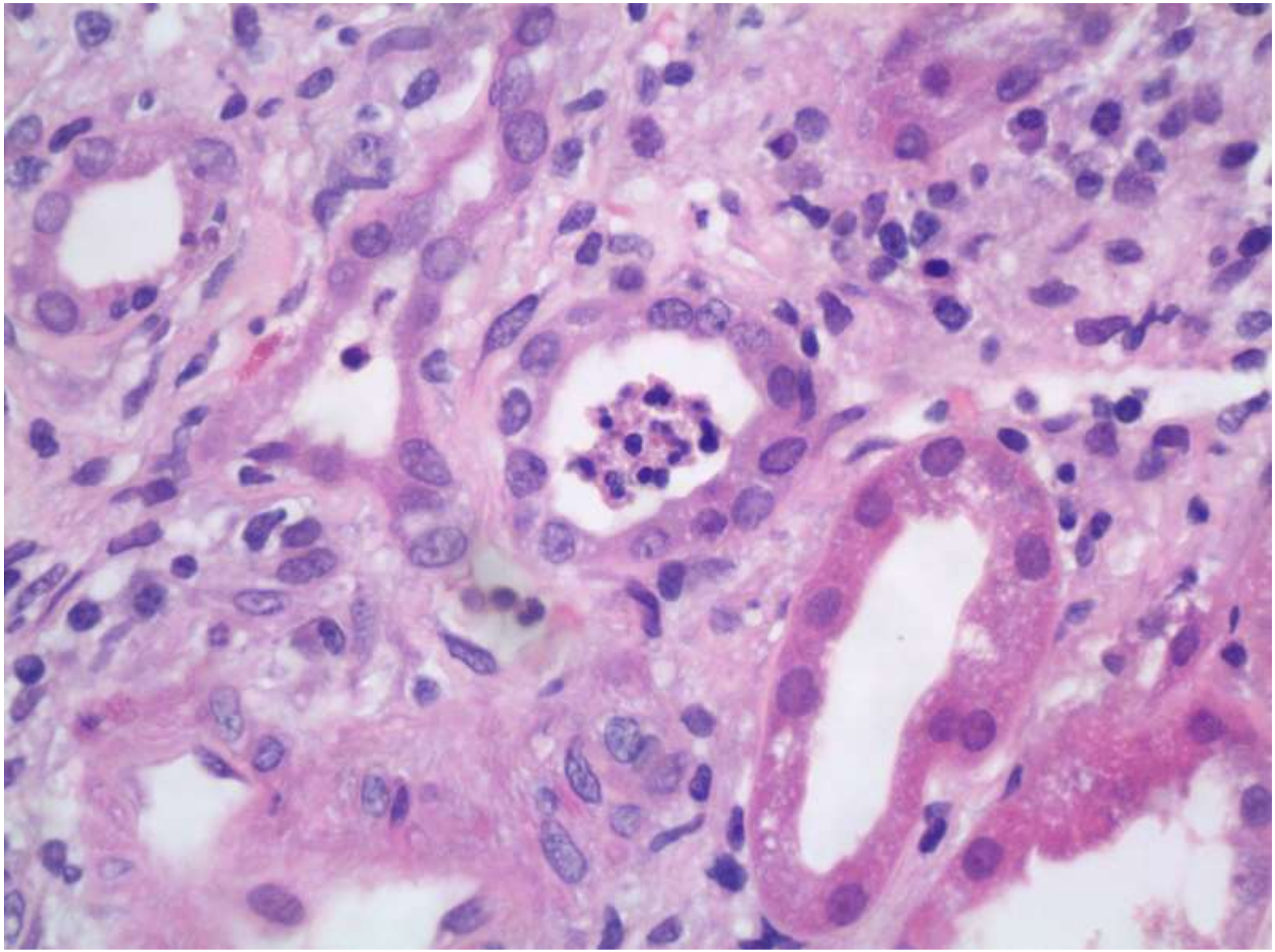


# Tubular microabscesses





A diagnostic pitfall: ATN with apoptotic debris, resembling microabscesses



# Acute Pyelonephritis in Kidney Transplants

- High risk population for infection – immunosuppressed.
- UTIs are the most common infections in renal transplant recipients, despite prophylactic antibiotics.
- Potential risk factor for poor graft outcome.
- Diagnosis is often difficult, because of many other concurrent problems such as rejection, non-compliance with medications, dehydration, cardiac problems, drug toxicity (calcineurin-inhibitors, mTOR inhibitors).
- Most common during the first year post transplant. Strictures at the vesicoureteral junction, female gender, history of CMV infection are risk factors.

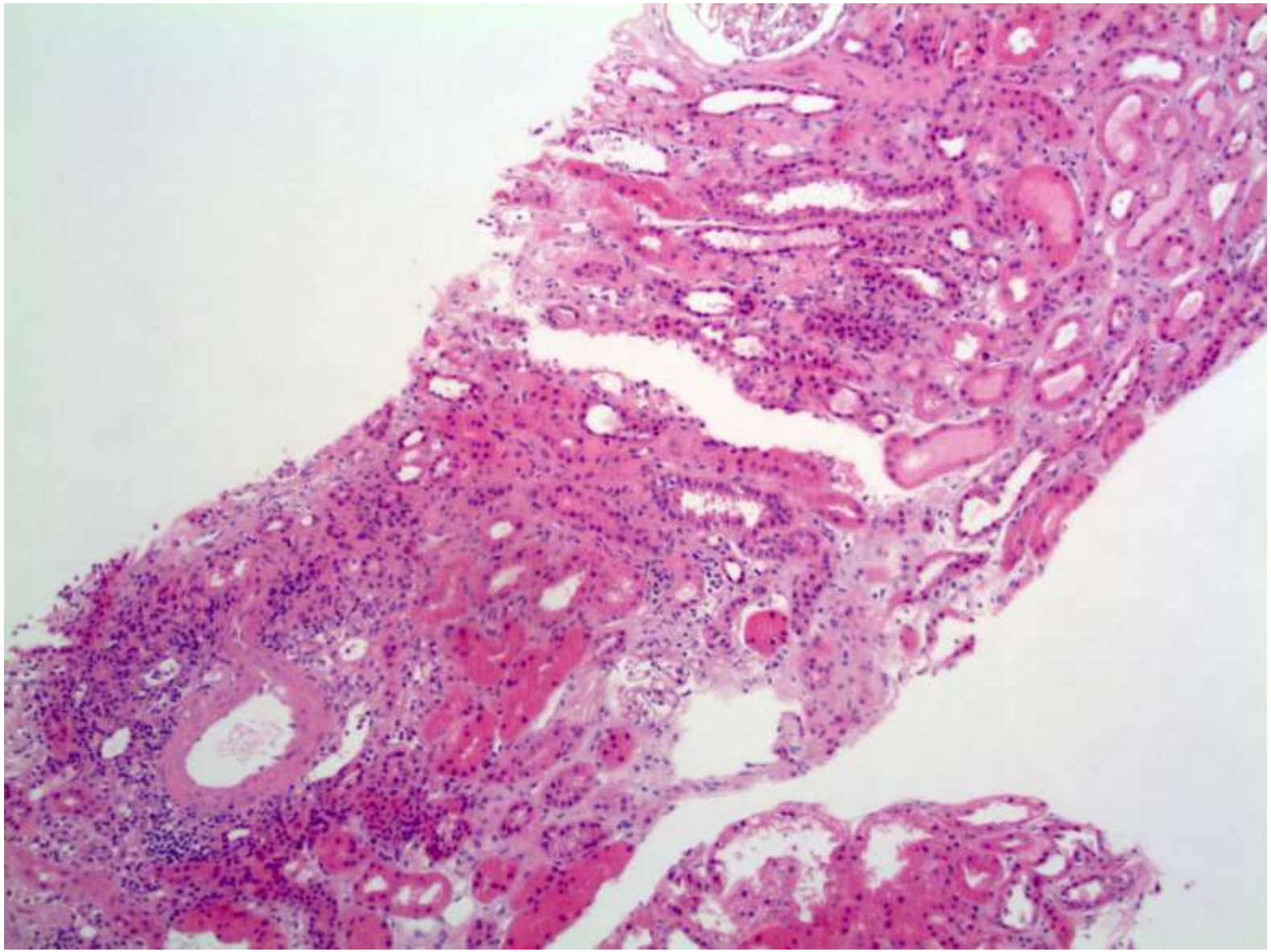
# Acute pyelonephritis in kidney transplants – Need for biopsy

- Absence of the classic clinical tetrad – Fever, costovertebral angle tenderness, positive urine culture, leukocytosis.
- Symptoms of fever, graft tenderness may be less prominent because of immunosuppression and denervated graft, but these sypmtoms may also occur in acute rejection.
- Leukocytosis may not manifest in immunosuppressed patients.
- Acute graft dysfunction is the presenting feature, similar to acute rejection.
- Urine cultures may not be consistently positive, since patients are on antibiotic and antifungal prophylaxis.
- Colony counts on urine culture, may be low ($<10^5$ CFU/ml).
- *Therefore unlike in the native kidney where diagnosis of acute pyelonephritis is usually based on clinical examination, in transplant patients renal allograft biopsy is commonly required.*

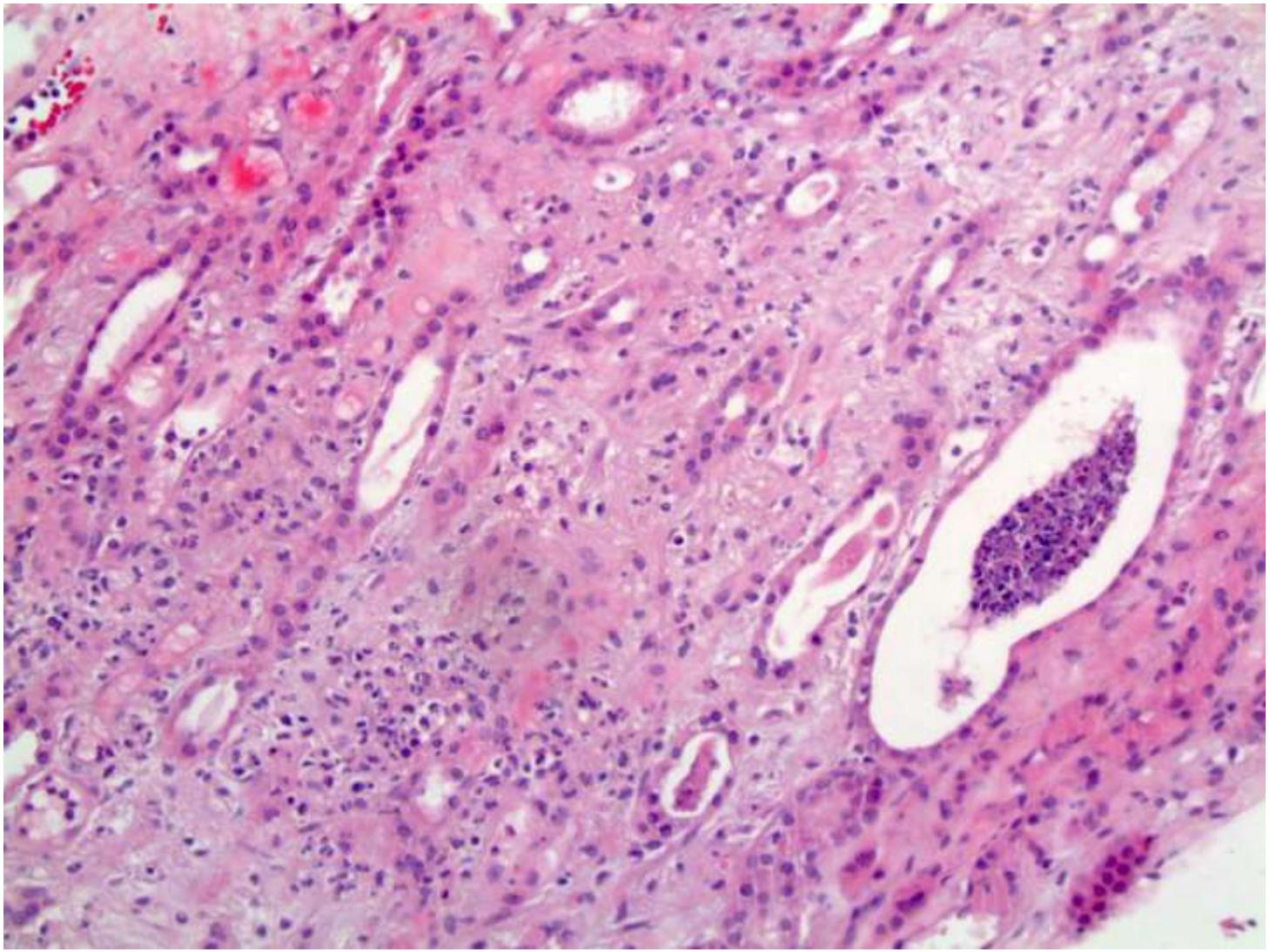
# Transplant Case - Clinical History

- 71 year old Caucasian female with deceased donor kidney transplant
- Native kidney disease: diabetic nephropathy.
- Thymoglobulin induction, Neoral, Rapamycin maintenance immunosuppressive regimen.
- Delayed graft function with serum creatinine between 5 to 7 mg/dl.
- Panel reactive antibodies (PRA) Class I: 0 and Class II: 50 at the time of transplant but negative flow cross-matches.
- Baseline biopsy showed mild subcapsular scarring.
- Urine cultures grew Klebsiella pneumoniae >100,000 CFU/ml.
- Biopsy performed 12 days post-transplant.

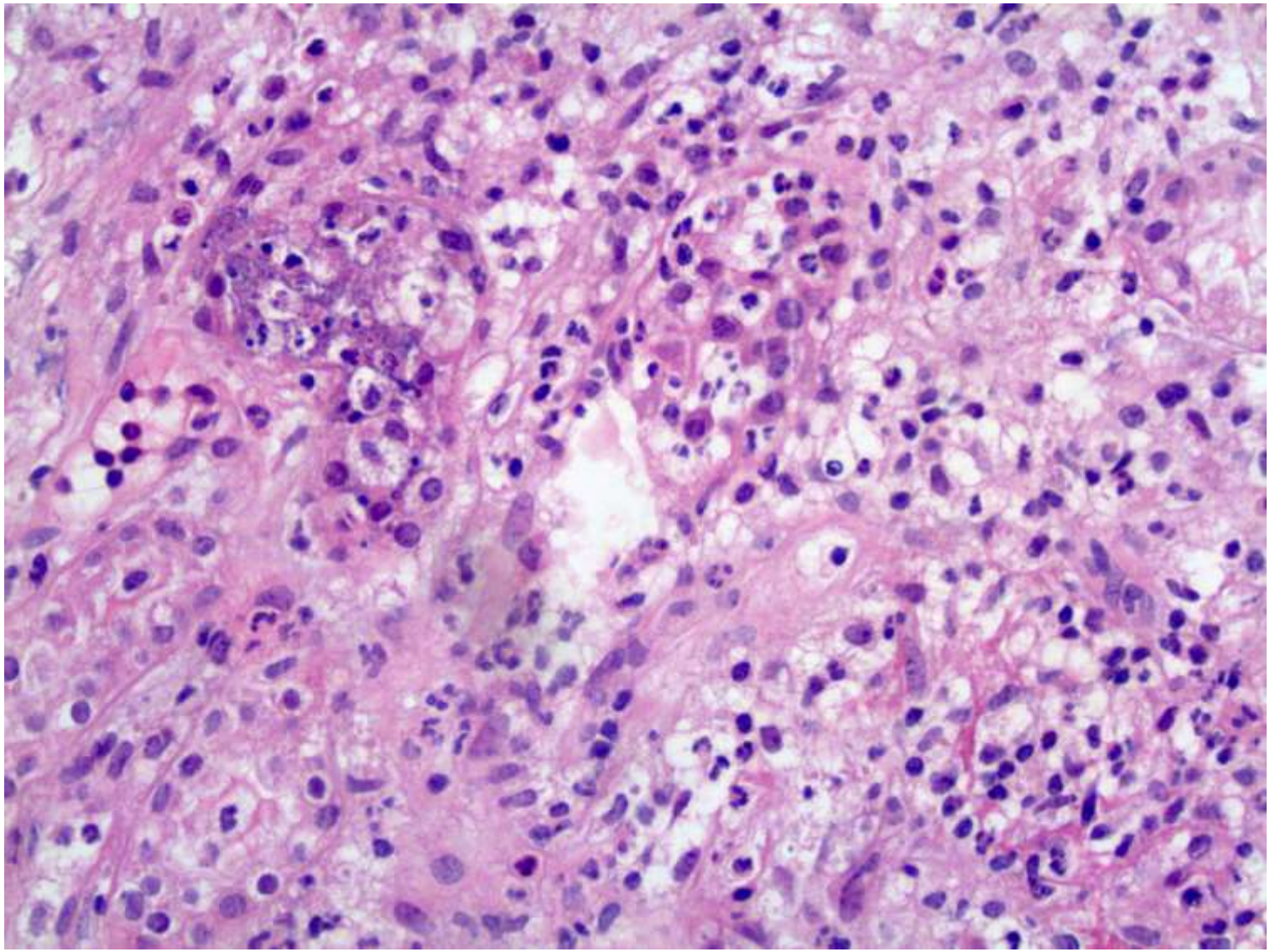
Zonal distribution of inflammation



Tubular microabscess



Neutrophilic tubulitis, interstitial neutrophils



# Treatment and Follow-up

- Treated with Ciprofloxacin course, followed by Amoxicillin.
- Serum creatinine values after biopsy:
  - At biopsy: 5.9 mg/dl
  - 1 month later: 3.5 mg/dl
  - 2 months later: 1.1 to 1.2 mg/dl
- Urine culture 1 week after starting antibiotics: No growth.

- Typical case of graft pyelonephritis, which resolved with antibiotic treatment.

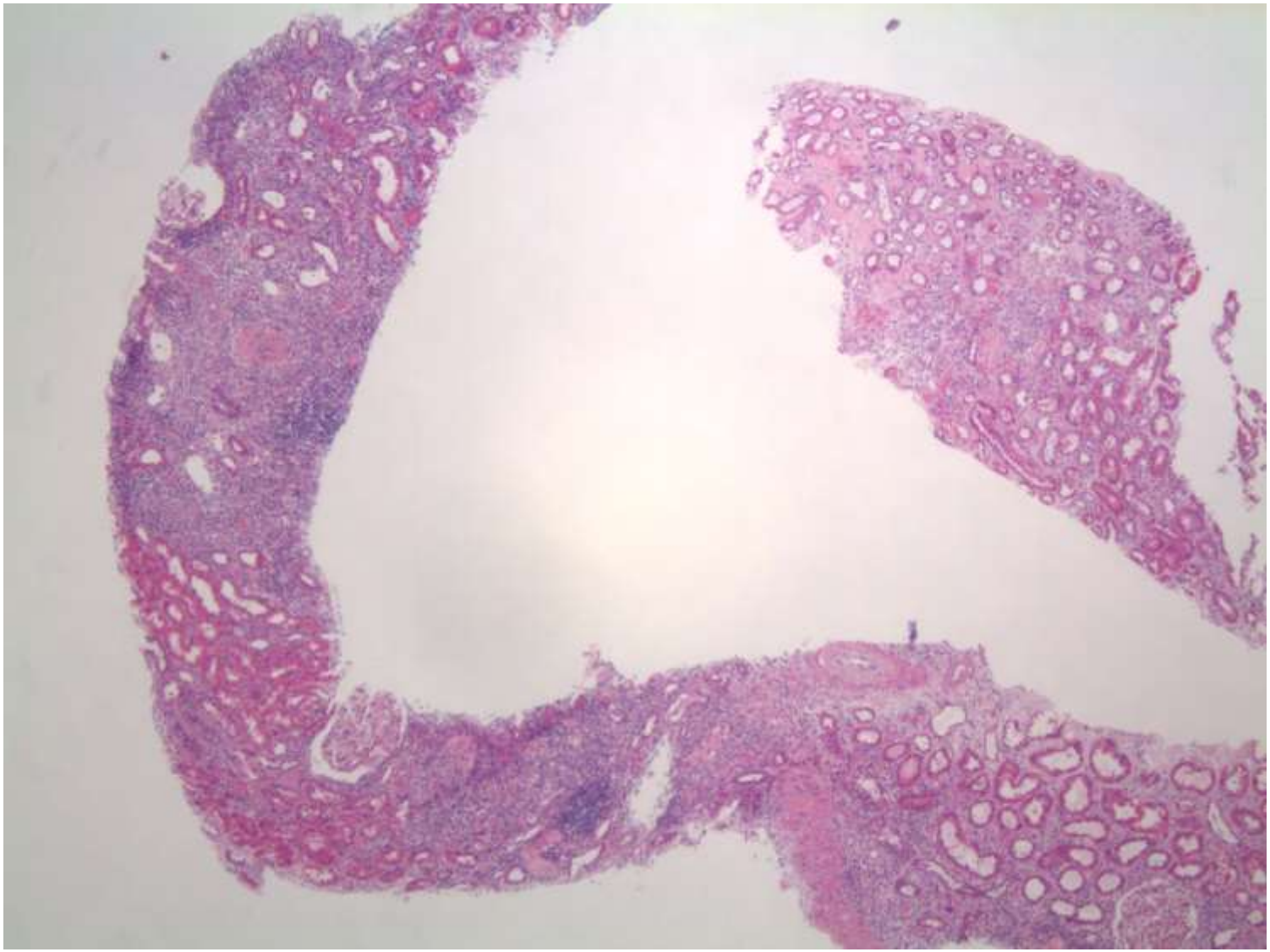
# 2nd Transplant Case: Clinical History

- 66-year-old Caucasian male with deceased donor renal transplant.
- Native kidney disease: diabetic nephropathy (type II diabetes) with hypertension.
- Baseline allograft biopsy: mild nephrosclerotic changes.
- Thymoglobulin induction, Myfortic and Rapamune immunosuppressive therapy.
- BP 150/92 mmHg, weight 198 pounds, BMI 29.
- Increased urination frequency and dysuria.

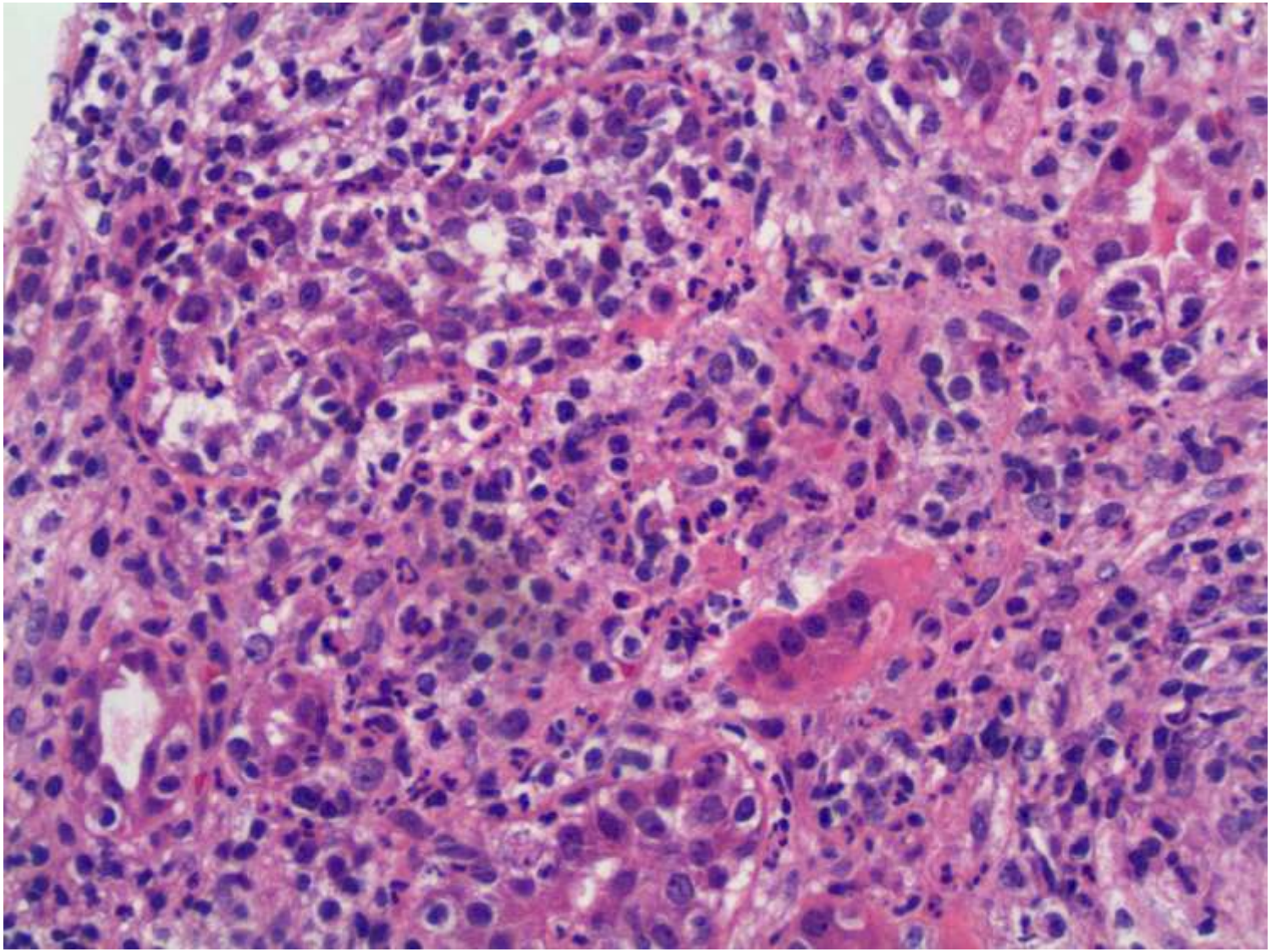
# Laboratory findings

- Lowest serum creatinine was measured 8-day post-transplant: 2.8 mg/dl,.
- Over the next 5-day period, serum creatinine increased to 3.9 mg/dl.
- PRA Class I: 0; Class II: 0.
- Platelet count 382,000/µl.
- WBC count 14,700/ µl.
- Urine Pr/Cr ratio 1.1
- Urine culture <10,000 CFU/ml (negative).
- Urinalysis: 10-14 WBCS, 15-19 RBCs, bacteria absent, urine leukocyte esterase and nitrites: negative.
- An allograft biopsy was performed 13 days post-transplant.

# Zonal inflammation



Neutrophilic tubulitis, tubular microabscess



# What is the diagnosis??

- Pathology diagnosis:

  Somewhat zonal, neutrophil-rich inflammatory cell infiltrates with tubular  microabscesses, favor acute pyelonephritis.

- Clinical Diagnosis and treatment:

  Acute rejection (urine culture negative, no fevers, patient on Bactrim prophylaxis)

  Treatment: Steroid taper.

# Followup

- Serum creatinine values (mg/dl):

  Baseline (8 days post-transplant): 2.8

  At the time of biopsy: 3.9

  10 days post-biopsy: 2.4

  1 month post-biopsy: 2.1

  2 months post-biopsy: 1.8

Table 1. Clinical and laboratory data on the 49 patients transplanted between 2003 to 2011, with biopsy features of acute pyelonephritis. The biopsy was performed during the first 2 years post-transplant.

| Patient characteristics | Group I - Positive urine culture within 10 days before or after biopsy | Group II - Positive urine culture beyond 10 days before or after biopsy | Group III - Urine culture negative |
|---|---|---|---|
| Number of patients (n) | 16 | 14 | 19 |
| Gender Male; Female | 6; 10 | 5; 9 | 9; 10 |
| Mean age (years) | 45 +/- 13 | 46 +/-19 | 42 +/- 15 |
| Patients with biopsy within one month post-transplant | 7 (43%) | 4 (28%) | 12 (63%) |
| Patients with colony count below 100,000 CFU/ml | 8 (50%) | 4 (28%) | N/A |
| Graft loss within 1 year post-biopsy (death censored) | 5 (31%) | 5 (35%) | 0 |
| Baseline serum creatinine before biopsy (mg/dl) | 1.8 +/- 1.4 | 1.8 +/- 1.0 | 2.3 +/- 1.4 |
| Serum creatinine 1 month post-biopsy (mg/dl) | 2.9 +/- 1.8 | 3.3 +/- 1.8 | 2.13 +/-1.1 |
| Serum creatinine 1 year post-biopsy (mg/dl) | 2.1 +/- 0.8 | 2.1 +/- 0.4 | 1.9 +/- 1.1 |
| Δserum creatinine (at 1 year versus baseline) mg/dl | 0.3 | 0.3 | -0.3 |
| Patients who received antibiotic treatment in addition to routine prophylaxis for pyelonephritis | 14 | 12 | 11 |

CFU/ml = colony forming units/millilter, AR=acute rejection, ATN=acute tubular necrosis.

*Oghumu S, et al. Transplantation 2014, 15;97(5):559-568*

# Diagnosis of allograft pyelonephritis can be difficult

- The typical clinical symptoms and signs (tetrad) are commonly absent (probably because of immunosuppression, kidney denervation).
- Urine cultures can be negative or show low colony counts.
- Biopsy findings of pyelonephritis and acute rejection frequently overlap. Possible explanations:
  - Combination of infection and alloimmunity may play a role in the inflammatory process related to allograft pyelonephritis.
  - Even a mild infection may predispose to rejection do to upregulation of donor antigens
  - Severe persistent ATN, particularly early post-transplant (delayed graft function) may recruit neutrophil-rich inflammatory infiltrates and develop apoptotic cell debris in the lumens, resembling tubular microabscesses.

# Treatment and Outcome

- It appears that acute rejection is easier to treat and eliminate than pyelonephritis.
- In our experience, one year survival in culture negative cases (in spite of histologic features of pyelonephritis) is much better then in culture positive pyelonephritis cases.
- Although the diagnosis of pyelonephritis should be raised if the renal biopsy findings suggest it, correlation with urine culture results are important and a low threshold for treating the patients as acute rejection (with prophylactic antibiotics) is recommended

# Take Home Message

- Defining the etiology of AIN is frequently difficult, morphologic signs are nonspecific; careful clinical history is the most important.
- If a native kidney biopsy report indicates acute pyelonephritis, think critically: if the clinical picture is not that of acute pyelonephritis, the diagnosis is probably wrong
- Acute pyelonephritis and acute rejection in renal allografts have many overlapping features. Urine culture negative cases (repeated), even with morphologic findings of neutrophil rich infiltrates, should probably treated as acute rejection with antibiotic prophylaxis

# Suggested Reading


- Brodsky SV, Nadasdy T: Acute and Chronic Tubulointerstitial Nephritis. In: Jennette JC, Olson JL, Silva FG, D'Agati VD (eds.): Heptinstall's Pathology of the Kidney, Seventh Edition. Wolters Kluwer, Philadelphia, 2015, pp. 1111-1165.
- Muriithi AK, Leung N, Valeri AM, et al. Clinical characteristics, causes and outcomes of acute interstitial nephritis in the elderly. Kidney Int. 2015; 87(2):458-64.
- Muriithi AK, Leung N, Valeri AM, et al. Biopsy-proven acute interstitial nephritis, 1993-2011: a case series. Am J Kidney Dis. 2014; 64(4):558-66.
- Praga M, Sevillano A, Aunon P, Gonzalez E. Changes in the aetiology, clinical presentation and management of acute interstitial nephritis, an increasingly common cause of acute kidney injury. Nephrol Dial Transplant. 2014 Oct 16. pii: gfu326. [Epub ahead of print]
- Lee YJ, Cho S, Kim SR. Unilateral and bilateral acute pyelonephritis: differences in clinical presentation, progress and outcome. Postgrad Med J. 2014; 90(1060):80-5.
- Oghumu S, Bracewell A, Nori U, et al. Acute pyelonephritis in renal allografts: a new role for microRNAs? Transplantation. 2014; 97(5):559-68.