Brigham and Women's Hospital
Founding Member, Mass General Brigham

# Interstitial Nephritis: Overview for the Boards

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CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

HARVARD MEDICAL SCHOOL
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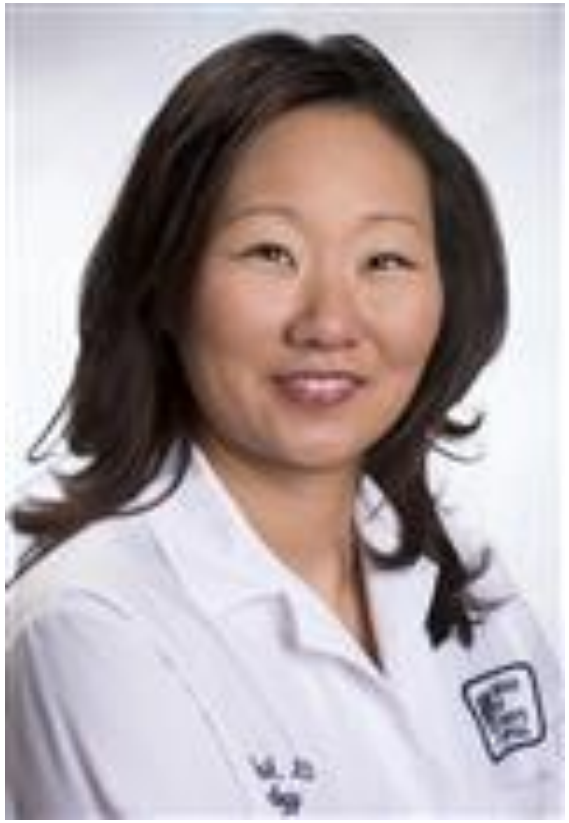

- BA from Harvard College
- MD and MPH from Mount Sinai School of Medicine
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# Disclosures

None

# Objectives

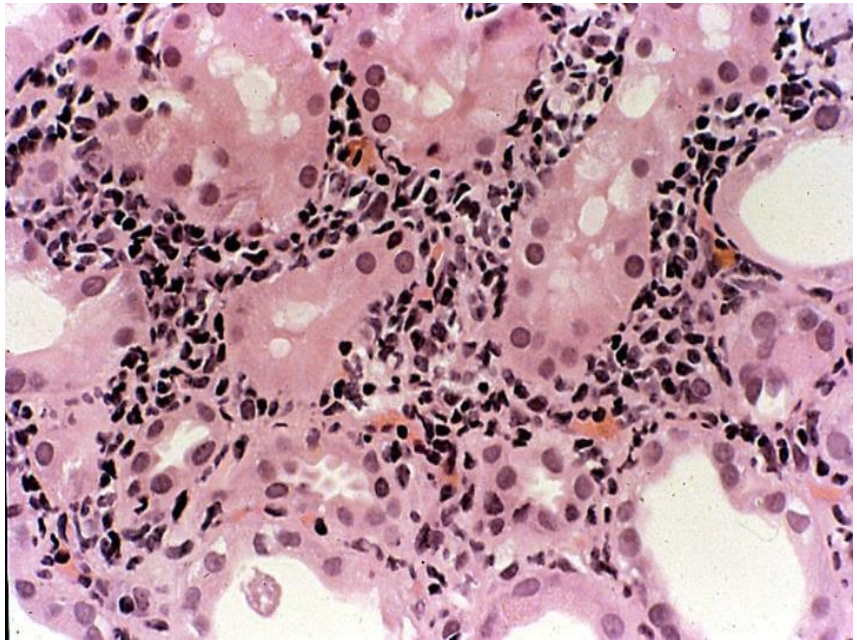
Use 3 case vignettes to:

- Highlight common causes and features of acute interstitial nephritis (AIN)
- Highlight common causes and features of chronic interstitial nephritis (CIN)

# Review Question #1

A 42-year old patient was referred by her primary care physician with new onset azotemia, her serum creatinine had increased from 0.9 mg/dL to 1.96 mg/dL over a 2-week period. One week prior to presentation, she had been seen by her PCP for a new- onset cough and yellow-tinged sputum and was empirically started on a 5-day course of levofloxacin (Levaquin). What is this pathology pattern?

a. AIN due to drug
b. AIN due to infection
c. CIN due to Myeloma
d. CIN due to Sarcoidosis



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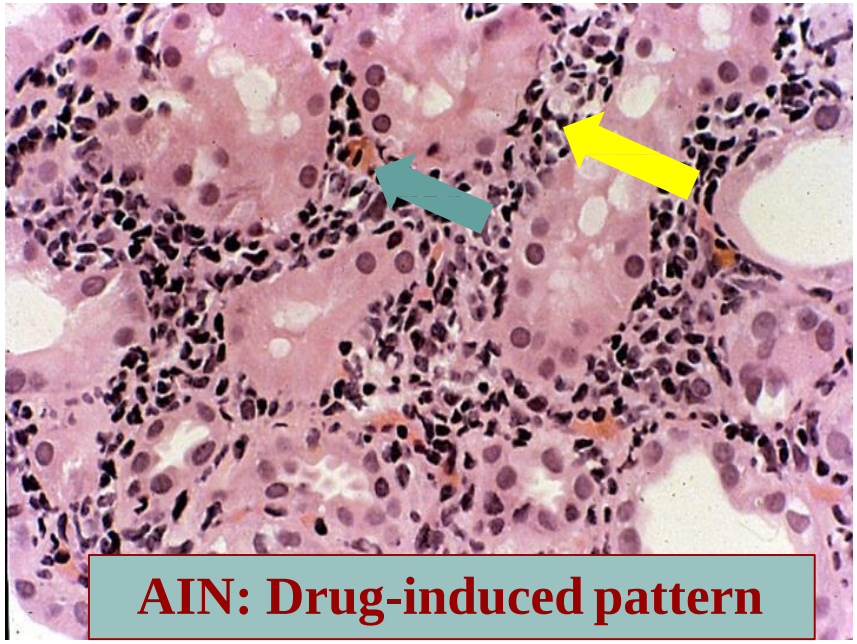


# Acute Interstitial Nephritis (AIN)

- Renal biopsy remains the definitive diagnostic modality
  - ➢ Hallmark of AIN:
    - ✓ Inflammatory interstitial infiltrate of monocytes and lymphocytes (fewer eosinophils, plasma cells, and neutrophils)
    - ✓ Interstitial edema
    - ✓ Renal tubule separation
    - ✓ Tubulitis
    - ✓ Absence of glomerular or vascular pathology
  - ➢ Fibrotic changes may be seen as early as within 7-10 days
  - ➢ Granuloma patterns can occur and are commonly drug-related

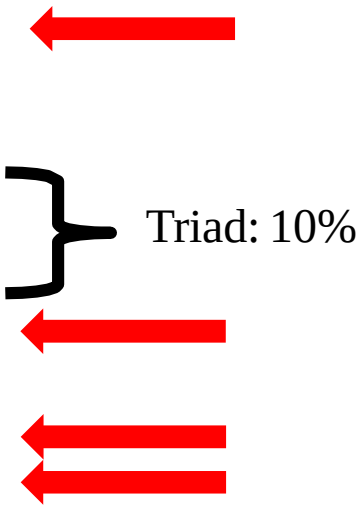
Grad et al. *NEJM* 2010; Perazella et al. *Nature reviews Nephrology* 2010; Rossert et al. Floege J JR, Feehally J, ed. *Comprehensive Clinical Nephrology* 2010; Michel et al. *JASN* 1998

# Clinical Presentation of AIN

**Table 2 | Clinical and laboratory features at presentation in patients with AIN (pooled data from González *et al.*[18] and Clarkson *et al.*[19])**

| Features | |
|---|---|
| Acute renal failure | 100% |
| Acute renal failure requiring dialysis | 40% |
| Arthralgias[a] | 45% |
| Fever | 36% |
| Skin rash | 22% |
| Eosinophilia (>500 eosinophils per $mm^3$) | 35% |
| Microhematuria[b] | 67% |
| Gross hematuria[b] | 5% |
| Leukocyturia[b] | 82% |
| Non-nephrotic proteinuria | 93% |
| Nephrotic-range proteinuria | 2.5% |
| Complete nephrotic syndrome | 0.8% |

[a]Data from Clarkson *et al.*[19]
[b]Data from González *et al.*[18]




Praga and Gonzalez, *KI(2010) 77, 956–961*

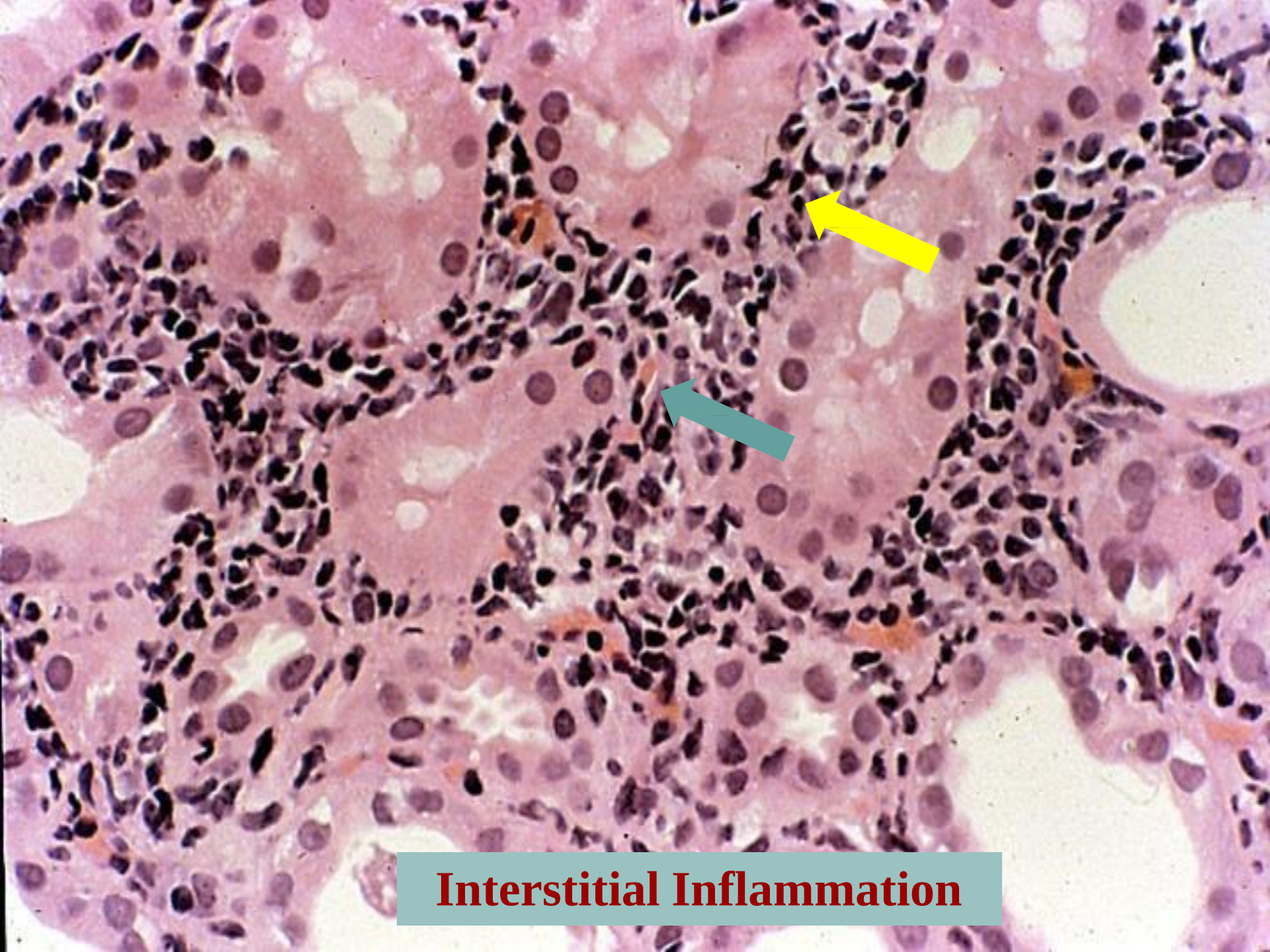
# Etiologies of AIN

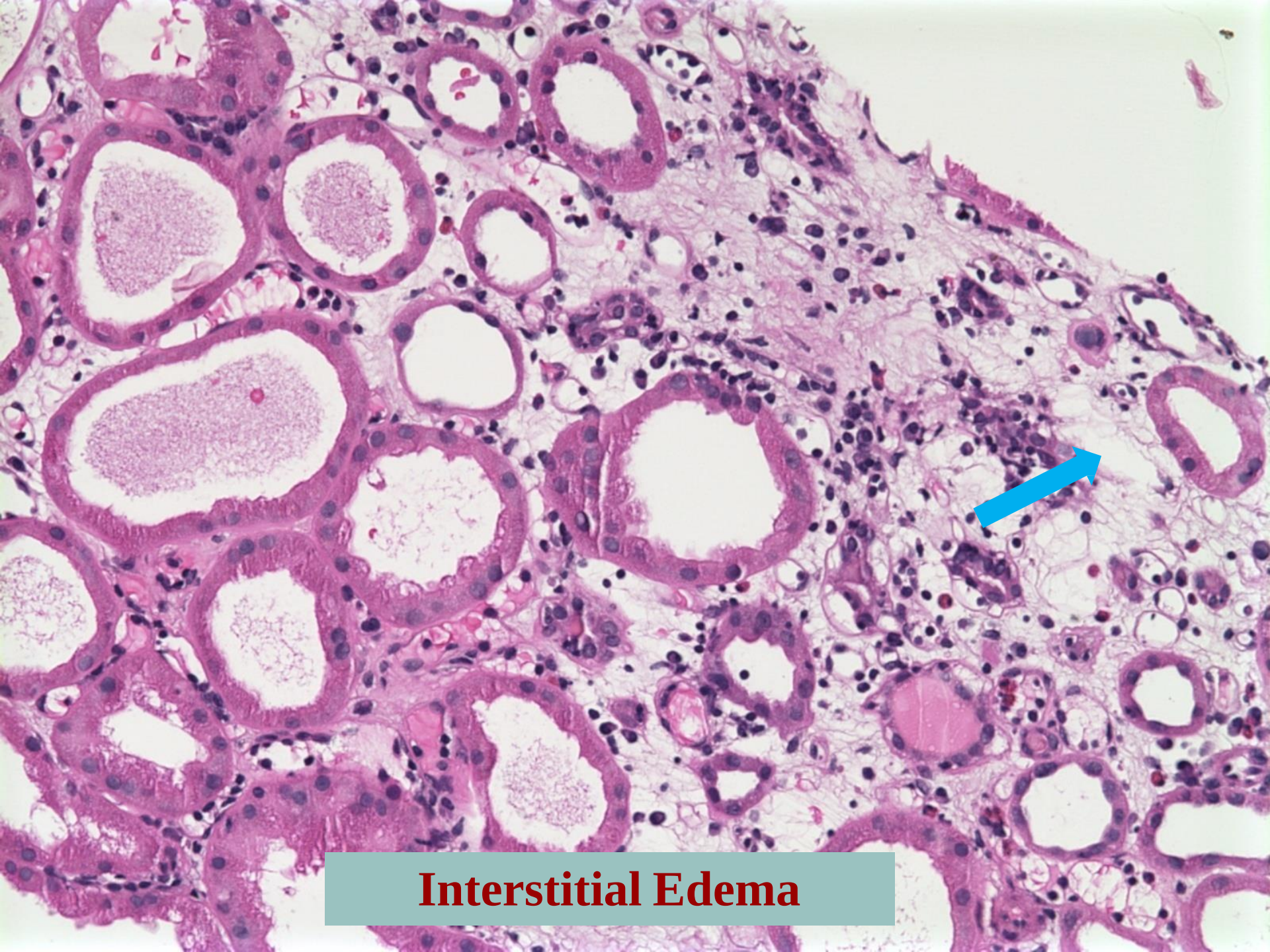
## Acute vs. Chronic

- Drugs (Allergic interstitial nephritis) (70-75%)
  - Antibiotics: 30-50%
  - Mean delay between drug start date and AKI is 10 days
  - Latent period can be as short as 1 day with some antibiotics
- Infections (bacterial, viral, parasitic) (5-10%)
- Systemic disease (10-20%)
  - Autoimmune diseases (Sarcoidosis SLE, Sjögren's, ANCA)
  - Neoplastic (leukemias, lymphomas)
  - Acute allograft rejection
- Idiopathic (5-10%)

# Pathologic Interstitial Changes (focal or diffuse)

- Inflammation (acute or chronic)
- Edema
- Fibrosis


Interstitial Inflammation


Interstitial Edema

# Pathological pattern of CIN


Interstitial Fibrosis, Tubular Atrophy, and “Benign” Hyaline casts

# Case 1

75 year old male with a history of hypertension and metastatic melanoma presents with AKI. He presented with nausea one week prior without emesis or diarrhea. No recent contrast administration. No NSAIDs or other new medications.

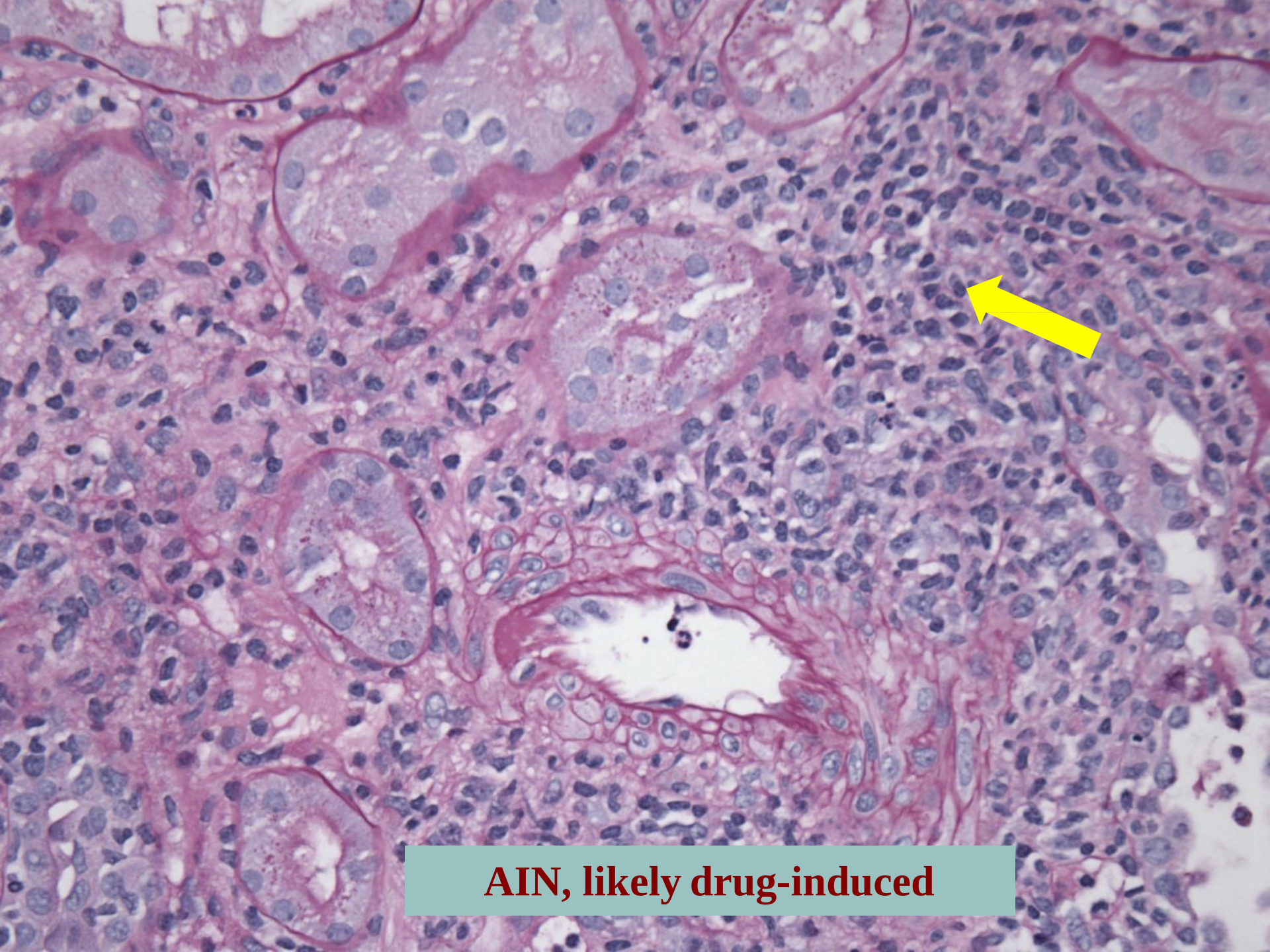
Melanoma was diagnosed one year ago. Six months later, he noted a left submandibular mass. Biopsy showed metastatic melanoma. He was enrolled in a clinical trial of combination therapy with ipilimumab/nivolumab, immune checkpoint modulator (anti-CTLA-4 or ipilimumab and anti-PD-1/PD-L1 or nivolumab).

# Case 1

- He received 2 cycles of ipilimumab/nivolumab, but his 3rd cycle was held when his Cr was noted to be 4 mg/dL on routine labs. His baseline Cr is 1 mg/dL, and the most recent Cr was 0.9 mg/dL one month ago.
- PMH: malignant melanoma, hypertension (not on medication)
- FH: No history of melanoma or renal disease
- SH: Non-smoker and drinks alcohol socially; No illicit drug use
- Medications: Ipilimumab, Nivolumab

# Case 1

- Physical Examination:
  - ✓ T: 99, HR: 93, BP:178/80, RR:16, Urine Output ~ 1 L/d
  - ✓ L submandibular mass palpated, JVP: ~ 10 cm; 1+ LE edema
- Laboratory Data:
  - ✓ HCO3 18, BUN 65, Cr 4, Glu 156, CBC WNL, No Eos Albumin: 3.7 g/dL, LFTs WNL, CK 39, LDH 189, CK 39
  - ✓ C3- 120; C4- 31; ANA: positive at 1:40; Anti-ds DNA: 1:25; anti-histone: negative, Cortisol: 21.3 ug/dL
  - ✓ Renal Ultrasound: R Kidney: 12.4 cm; L Kidney: 13.0 cm; No hydronephrosis
  - ✓ Urine Sediment: Multiple WBC cell casts; Urine No Eos


AIN, likely drug-induced

# Drug-induced AIN

- **Drugs: Allergic interstitial nephritis**
  - ✓ **Antibiotics:**
    - ✓ **Beta-lactam (**PCN, Cephalosporins): remains a frequent reported cause of AIN
    - ✓ **Quinolones:** most often seen with ciprofloxacin
    - ✓ **Sulfonamide:** Sulfamethoxazole/Trimethoprim (bactrim)
    - ✓ **Others:** rifampin, sulfa, vanco, erythromycin, acyclovir, ethambutol (EMB)
  - ✓ **Diuretics:** thiazides, furosemide, bumetanide, triamterene
  - ✓ **NSAIDS (including selective COX-2 inhibitor):** pure interstitial nephritis (ISN) ± papillary necrosis/ minimal change nephropathy (MCN) + ISN (85%)
  - ✓ **PPI** (omeprazole and lansoprazole)
  - ✓ **$H_2$ blockers** (cimetidine, ranitidine-rare)
  - ✓ **Allopurinol**
  - ✓ **Indinavir**
  - ✓ **5-aminosalicylates (5-ASA)** ( i.e. mesalamine)
  - ✓ **Others:** phenobarbital, phenytoin, nitrofurantoin, IFN, IL-2, Angiotensin converting enzyme inhibitor (ACEI: i.e.captopril)

- Drug-induced AIN is not dose-dependent, and recurrence or exacerbation can occur with repeat exposures to the same or related drug (Up-To-Date)

# Infection-induced AIN

- Infection:
  - Acute pyelonephritis: PMN infiltrate
  - Systemic infection:

➢Bacteria:

Streptococci, Staphylococcus, E. coli, Legionella, Salmonella, Campylobacter, Yersinia, Leptospirosis, Brucella, Diphtheria

➢Viruses:

CMV, HIV, HepB, Epstein-Barr, Hantavirus, Polyomavirus

➢Others:

Schistosoma,TB, Mycoplasma, Rickettsia

"Councilman's" = response to disseminated infection (mononuclear infiltrate)

Idiosyncratic response to microbial Ag

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  - Neoplastic (leukemias, lymphomas)
  - Acute allograft rejection
- Idiopathic (5-10%)

# Idiopathic AIN

- Idiopathic:
  - ❖ Uncommon, 5-10%
  - ❖ Fever common; Infrequent eosinophilia/rash
  - ❖ Mononuclear infiltrate
  - ❖ Anti-TBM Abs
  - ❖ Kawasaki
  - ❖ Tubulointerstitial nephritis and uveitis Sx (TINU)

# Rare Causes of AIN (I): IgG4-Related Disease

Pachymeningitis

Orbital pseudotumor Dacryoadenitis
Sialadenitis

Pericarditis

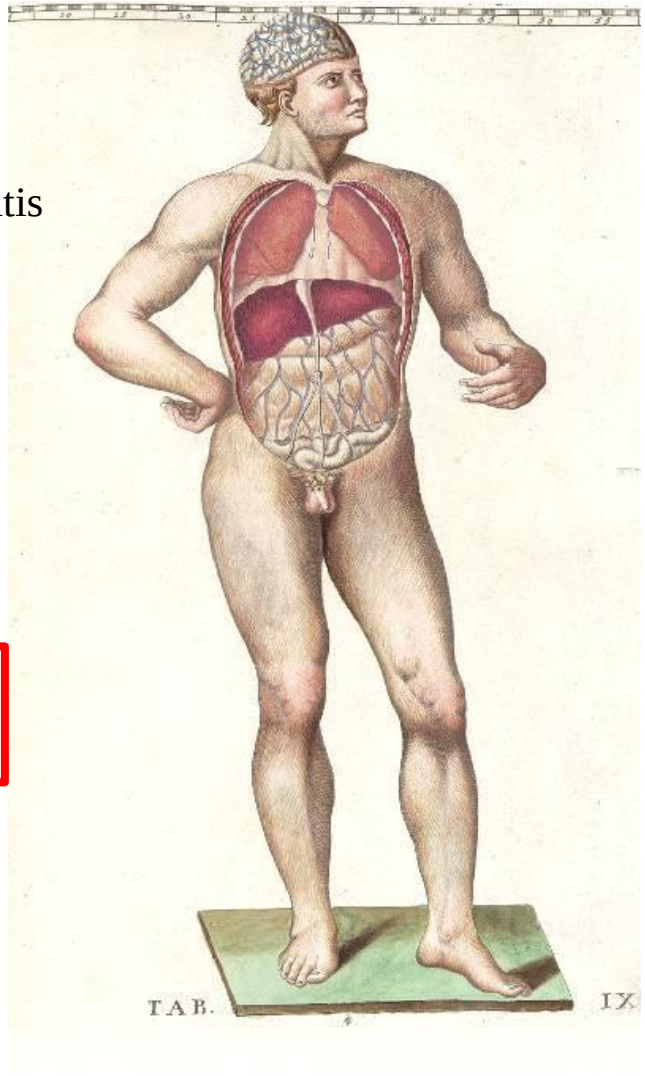
Autoimmune pancreatitis, type I

Sclerosing cholangitis

Cholecystitis

Tubulointerstitial nephritis (TIN)
Membranous glomerulonephritis

Inflammatory skin lesions




Sinusitis

Thyroiditis

Pleuritis

Interstitial pneumonitis

Breast inflammatory pseudotumor

Inflammatory aneurysm

Lymphadenopathy

Prostatitis

Retroperitoneal fibrosis
Sclerosing mesenteritis

Raissian et al, JASN 2011

Eustachi, Bartholomeo (d. 1574). Tabulae anatomicae.
Rome: P. Junchus, 1783.

# Clinical Feature of IgG4-TIN

## Laboratory features

- **88% (22/25) with ↑ serum total IgG, IgG4, or hypergammaglobulinemia**
- 33% peripheral blood eosinophilia
- **56% hypocomplementemia**
- 31% +ANA, mostly low titer

## Imaging findings

- 18/23 (78%) showed radiographic abnormalities of the kidney
- Small low-attenuation lesions, usually bilateral and multiple, or a mass
- In few patients, bilateral markedly enlarged kidneys (≥14.5 cm)

Raissian et al, *JASN* 2011 Jul;22(7):1343-52

# Course of AIN

- Most resolve with removal of offending agent/ treatment of underlying infection
  - 30-70% did not fully recovered their baseline renal function (Buysen *et.al. NDT 1990*; Rossert *KI 2001*; Galpin *et.al. Am J Med 1978*; Pusey *et.al. Q J Med 1983*; Kida *et.al. Clin Nephrol 1984 ; Laberke et.al. Clin Nephrol 1980; Bhaumik et.al. Ren Fail 1996)*
  - Up to 1/3 may need dialysis
- Likelihood of recovery inversely proportional to degree of renal failure
- Scattered infiltrates associated with better outcome (Buysen *et.al. NDT 1990; Laberke et.al. Clin Nephrol 1980)*
- 50% of idiopathic remain with some renal dysfunction

# Treatment of AIN

- NSAID-induced AIN: withdraw the offending drug
  - ➢ Addition of steroids does not change the clinical course (Porile *et.al. j Clin Pharmacol 1990*)
- Steroid: mainstay of treatment in idiopathic AIN, TINU and AIN associated with systemic diseases (Rossert *KI 2001*; Neilson *KI 1989*; Finkelberg *et.al. NEJM 2006*; Yoneda *et.al. Am J Kidney Dis 2007*)
- Cyclophosphamide, Cyclosporine: steroid-resistant idiopathic AIN (Zuliani *et.al. Clin Nephrol 2005*)
- Mycophenolate Mofetil (MMF): steroid-dependent, resistant AIN; or unable to tolerate steroid therapy (Preddie *et.al. Clin J Am Soc nephrol 2006*)
- ? Plasmapheresis or cytotoxics: if strong anti-TBM Ab

# Current Recommendations for Steroids

- Treat patients who do not have significant improvement in the Cr within 3-7 days after discontinuation of the offending agent
  - ✓ Renal biopsy is preferred
    - to confirm AIN
    - to exclude other possible diseases
    - Assess the presence of interstitial nephritis with significant chronic damage (interstitial fibrosis, tubular atrophy, and minimal or no acute inflammation), in which case immunosuppressive therapy might not be indicated
- An empiric trial for patients with a history strongly suggestive of drug-induced AIN when kidney biopsy is not feasible
- The optimal dose and duration of therapy are unclear
  - ✓ Administer prednisone at a dose of 1 mg/kg per day (max 40 to 60 mg) for 1-2 weeks with gradual taper for a total therapy duration of 2-3 months.
  - ✓ In more severe AKI, may use IV methylprednisolone (0.5 to 1 g/day for three days)
  - ✓ The duration of steroids varies widely among the many (cohort) studies in the literature, from days to 12 weeks (Rossert J. *KI 2001*; Galpin *et al. Am J Med* 1978; Handa SP *CMAJ 1986;* Buysen *et al NDT 1990*)

# Take Home Message

- The "triad" of AIN: fever, rash and eosinophilia
  - ✓ Only seen in ~ 10% of patients with AIN
  - ✓ Negative of "triad" does not r/o AIN
- Drugs are a common cause of AIN
  - ✓ Most of the drug-induced AIN improve spontaneously after stopping the offending agent.
  - ✓ Clinical suspicion for drug-induced nephrotoxicity should be high
  - ✓ Delayed intervention results in poor renal outcomes
- Steroids remains the mainstay treatment option for AIN
  - ✓ The optimal dose and duration are currently unclear

# Chronic Interstitial Nephritis (CIN)

- Diverse spectrum of etiologies
- Maintains fairly homogenous pathologic pattern
  - Interstitial fibrosis--> causing tubule separation
  - Areas of mononuclear cell infiltration: less pronounced
  - Tubule cell atrophy and/or dilation
  - Thickened TBM
  - “Tubulitis” and luminal cellular casts
  - Occasional C3/Ig along TBM
  - Normal glomeruli → periglomerular fibrosis → segmental sclerosis → global sclerosis
  - Small vessels → fibrointimal thickening

# Pathological pattern of CIN


Interstitial Fibrosis, Tubular Atrophy, and “Benign” Hyaline casts

# Clinical Presentation of CIN

- Often asymptomatic or symptoms of CRI
- Incidental ↑creatinine, abnormal urinalysis
- Anemia occurs early
- HTN in 50% (unrelated to GFR)
- Acidifying and concentrating defects
- UA lower than expected
- Biopsy series:
  - GFR < 50 in 75%, < 15 in 33%
  - Non-nephrotic proteinuria
  - Microscopic haematuria, pyuria, glycosuria (25%)
  - + urine culture in 28%

# Etiology of CIN

- **Hereditary diseases:**
  - ADPKD
  - Medullary cystic disease
- **Metabolic:**
  - Hypercalcaemia
  - nephrocalcinosis
  - Hyperoxaluria
  - Hypokalaemia
  - Hyperuricaemia
  - Cystinosis
  - Methylmalonic acidaemia
- **Drugs and toxins:**
  - Analgesics
  - Cd, Pb
  - Nitrosureas
  - Lithium
  - Cyclosporine
  - Cisplatin
  - Chinese herbs: AA
- **Immune-mediated:**
  - Allograft rejection
  - Wegener's granulomatosis
  - Sjogrens
  - SLE
  - Vasculitis
  - Sarcoidosis
- **Hematologic:**
  - Multiple myeloma
  - Light chain deposition disease
  - Sickle cell disease
  - Paroxysmal nocturnal haemoglobinuria
  - Lymphoma
- **Infection:**
  - Direct infection
  - Xanthogranulomatous pyelonephritis

# Case 2

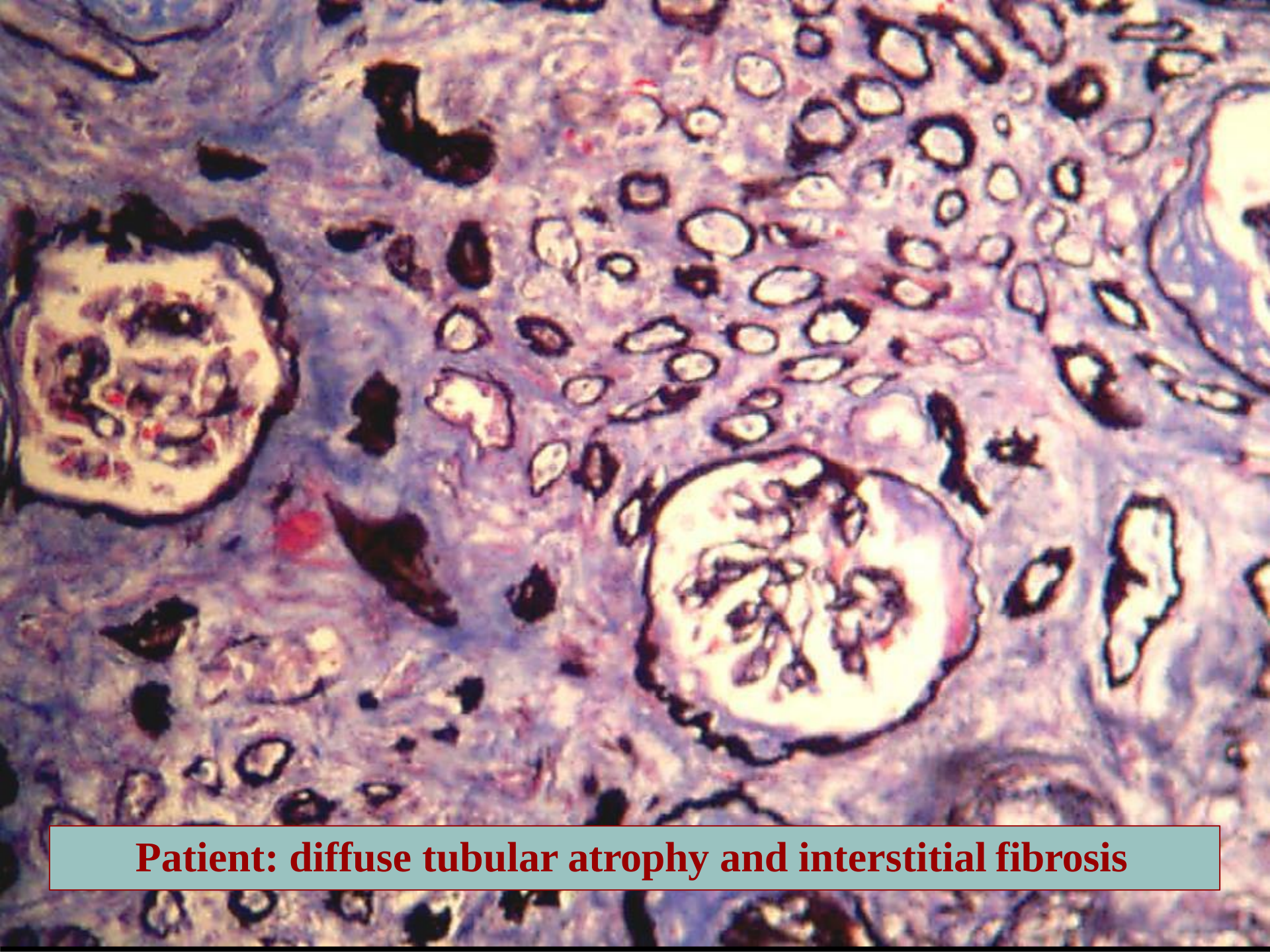
- 49 yo female presents with 4 months history of nausea, fatigue, nocturia and 11 pound weight loss
- PMH is significant for Herpes ~2 years ago. She self-medicated with the Chinese herb "Longdanxiegan " 6g/d for 3 months. She has been taking this medication intermittently in the past 18 months and her last use was 5 months ago.
- She denies taking NSAIDs.

PE: BP 145/84 mmHg, no edema.

# Case 2

Labs:

- ✓ Na 136, K 2.9, Cl 106, $HCO_3^-$ 18, Cr 1.5, BUN 54, Glucose 96, $PO4^{2+}$ 1.8. CrCl: 43 ml/min
- ✓ Hb 10.3, Hct 31
- ✓ Urine: 3+ protein, Glucose 100mg/dl, 3-4 RBC/HPF, No WBC, No casts. + phosphorus, NAG and $\alpha$1-MG↑
- ✓ Renal Ultrasound: LK 10.0 cm, RK 9.8 cm
- ✓ Analysis of Chinese herb showed that it contained Aristolochic acid



**Patient: diffuse tubular atrophy and interstitial fibrosis**

# Aristolochic Acid Nephropathy (AAN)

- Rapidly progressive IN leading to ESRD
- The first case was reported in Belgium after an outbreak of renal failure in 100 young women
- Balkan Nephropathy

Slimming pill and cross-section of a root of *aristolochia*

Aristolochic acid containing *Aristolochia clematitis* growing in a field of wheat (Croatia)

*Asarum* species

*Aristolochia* Species

Debelle, et al. *Kidney I* (2008) 74, 158–169

# Aristolochic Acid Nephropathy (AAN)

**Morphological findings:**

- Extensive interstitial fibrosis
- Tubular atrophy
- Striking complete tubular disappearance
- ***Gradient of intensity ranging from most severe in the outer cortex to less involvement in the inner cortex and medulla***
- Remarkable interstitial hypocellularity:
  - few lymphocytic infiltrates
  - essentially, no granulocytes
- ***Glomeruli are relatively spared***
- Immunofluorescent staining is essentially negative
- Interlobular and afferent arterioles wall thickening: most likely the result of endothelial cell swelling

Reginster *etal kidney Int* 1995

# AAN: Clinical Presentation

- AAN can develop as early as 2 months after exposure, as late as 3 years after discontinuation of drug (Meyer *et al. Proc Bayl Univ Med Cent* 2000*;* Vanherweghem *etal Lancet* 1993; Cosyns *etal Drug Saf.* 2003;26:33-48)
- The condition is more commonly seen in young females
- Patients are typically asymptomatic
- The Dx is usually made through abnormal laboratory findings indicating renal insufficiency
- Proteinuria: mild
- Anemia: more severe than the degree of renal failure
- Hypertension (80%)
- Glycosuria, Leukocytouria (40%)
- sCr doubling time: significantly shorten
- Course to ESRD is subacute and faster than in other tubular interstitial nephropathy
- Asymmetrical kidney (54%)

# AAN: Clinical Presentation

## Proteinuria:

- Consisting of 5 low molecular weight proteins:
  - β-Microglobulin, Cystatin C, Clara cell protein (CC16), Retinal binding protein: increasing levels in urine
  - Neutral endopeptidase (NEP): decreasing levels in urine
- Low molecular weight proteinuria can be detected before there is a demonstratable decline GFR (Kabanda *etal KI* 1995; Nortier *etal* 1997)

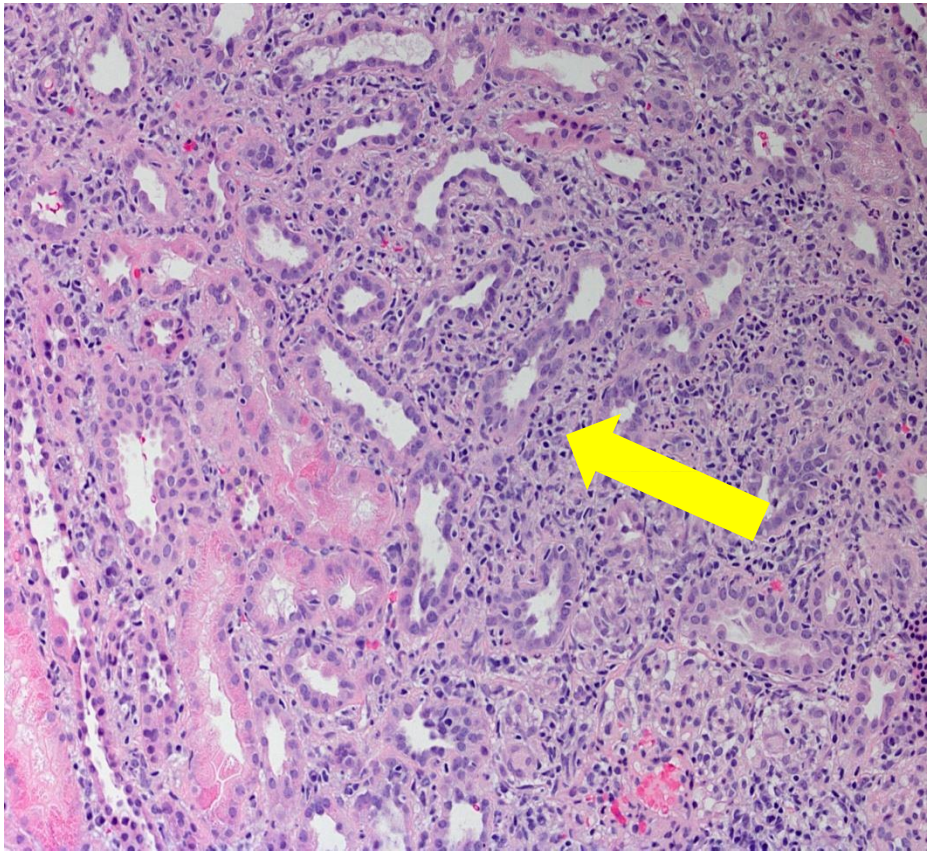
# Case 3

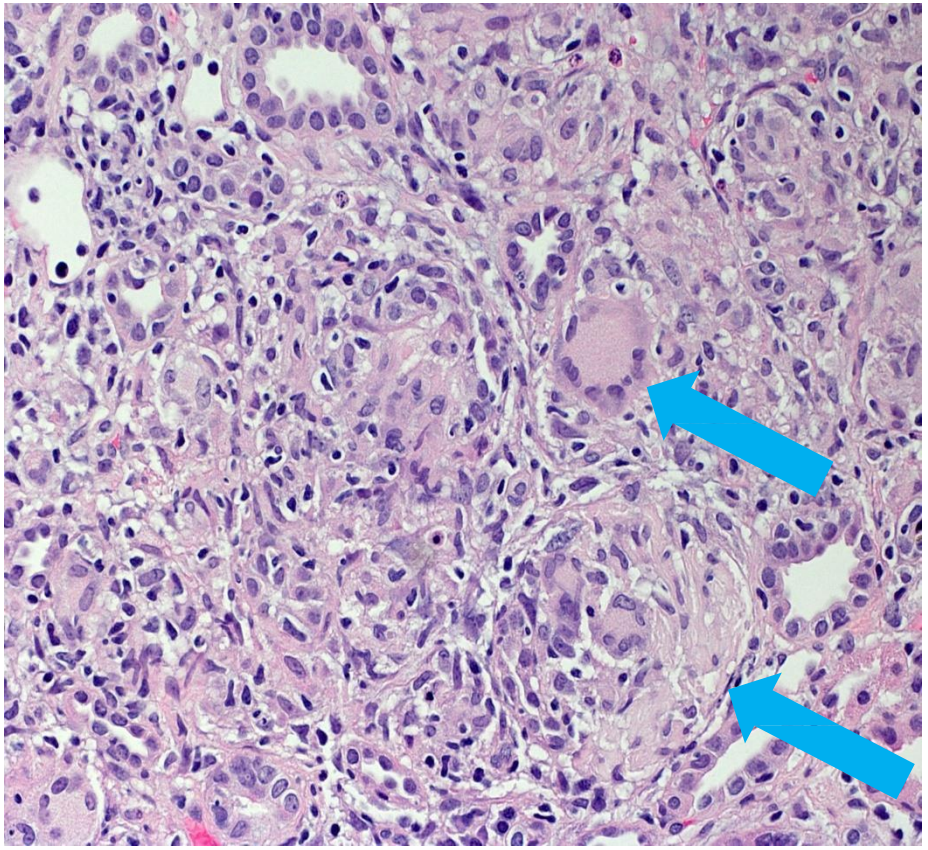
- 66 yo female with recently diagnosed hypersensitivity pneumonitis
- Waxing and waning dry cough along with fatigue and weight loss for 9 months
- Cr 0.8 at onset of illness, 1.4 four months prior to clinic visit and 2.5 during hospitalization for CAP one month prior
- Two days prior to visit, outside labs showed Cr 3.5 with Ca 13.3 (from 10.7 two weeks prior)
- Taking fish oil and vitamin D supplements since last hospital discharge, denied use of NSAIDs and other new medications

# Case 3

- Physical Examination:
  - ✓ Vitals: T 36.7, BP 142/65, HR 87, RR 18, JVP not elevated, Crackles at left lung base, 2/6 SEM, No edema, No rashes

- Labs and Studies:
  - ✓ WBC 4.8, Hb 11.1, Plt 313
  - ✓ Na 132, K 3.9, Cl 96, CO2 20, BUN 57, Cr 3.2, glucose 93
  - ✓ Ca 13.5, P 5.3, Vit D 35 (from 7, one month prior), Alb 4.5
  - ✓ UA: 1+ blood, 1+ protein, 1+ glucose
  - ✓ Urine Protein/Cr ratio (PCR): 750 mg
  - ✓ Renal US: Kidneys normal in size, no hydronephrosis, irregular 1.6 cm septated cystic lesion in left kidney
  - ✓ CT chest: Improving ground-glass opacification in left base, no hilar/mediastinal LAD or nodules





Diffuse Granulomatous Interstitial Nephritis
due to Hypercalcemia in Sarcoidosis

# Sarcoidosis

- Affects kidney through ↑ Ca
- 10-15% patients have hypercalcemia
- More have hypercalciuria
- → concentrating defects, ↓ GFR, nephrocalcinosis, nephrolithiasis
- 15-30% noncaseating granulomas at autopsy → unusual c/o dysfunction
- May be atypical, lacking skin, eye, pulmonary involvement,
- > men
- Responds well to steroids

# Review Question #2

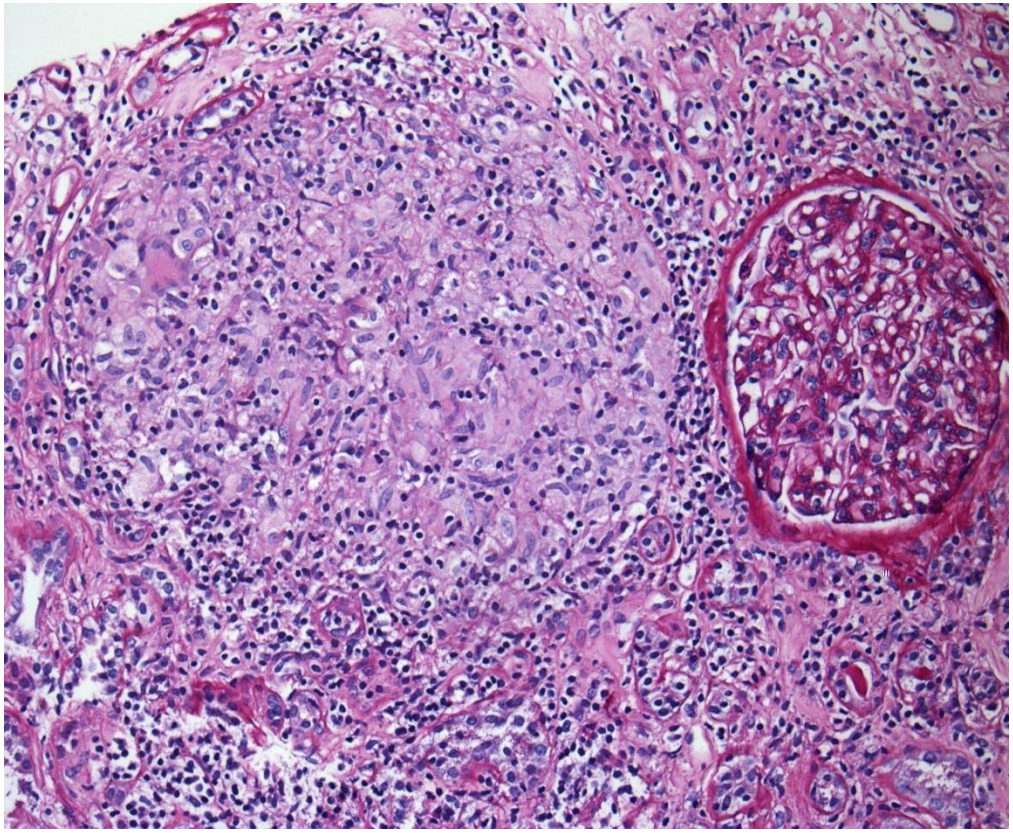
55 yo male presents with renal insufficiency, kidney stone hypercalcemia, hypercalcuria, renal biopsy is done. What is the diagnosis?

a. Myeloma

b. TB

c. Sarcoidosis

d. Obstructive Uropathy



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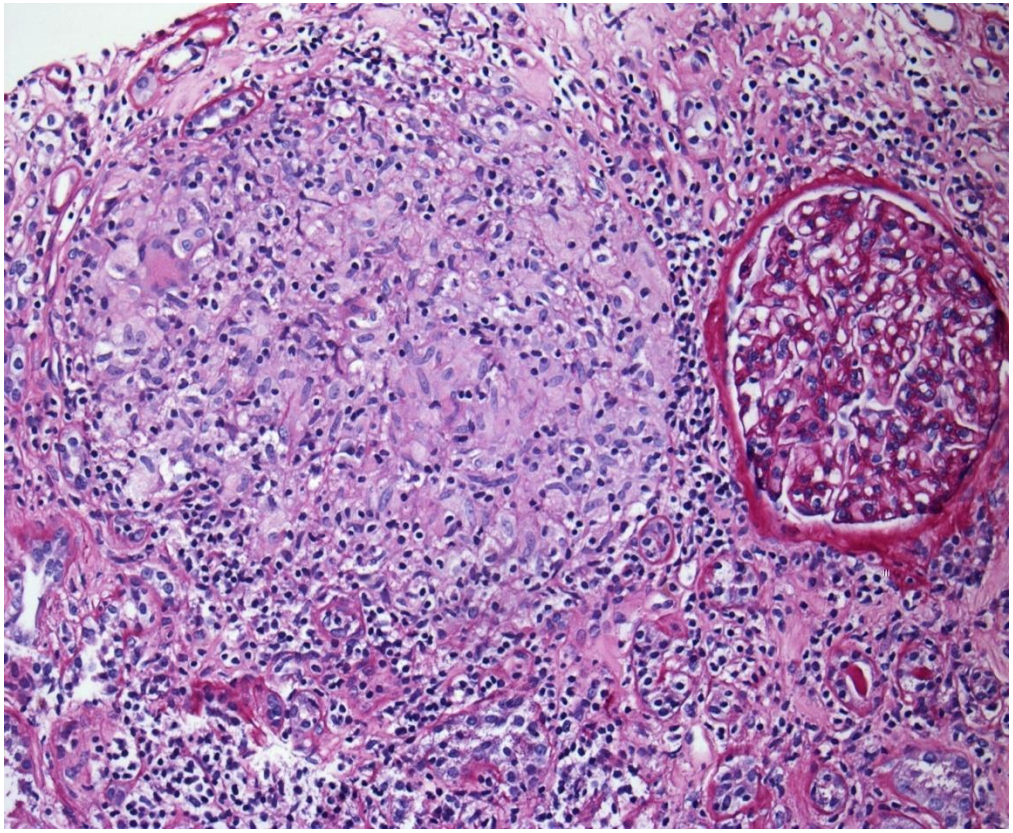
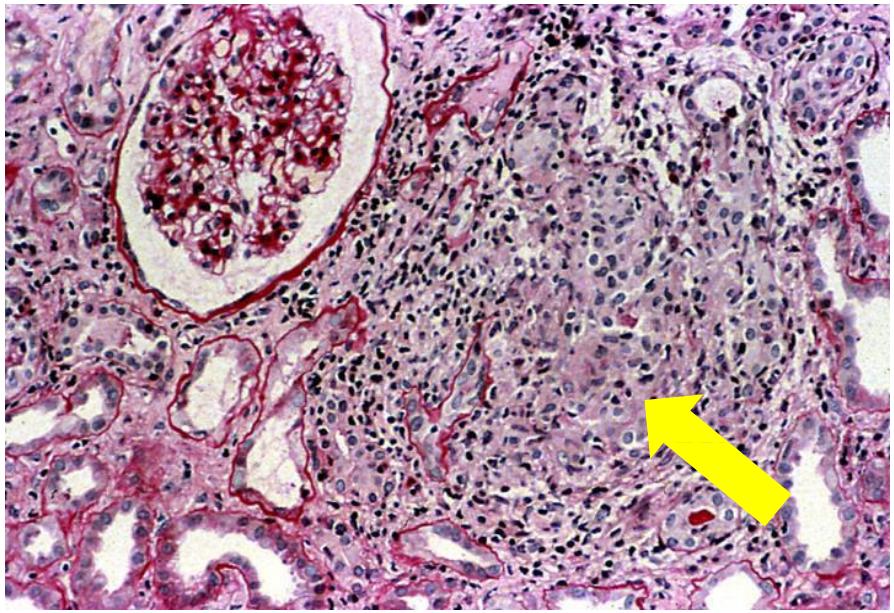
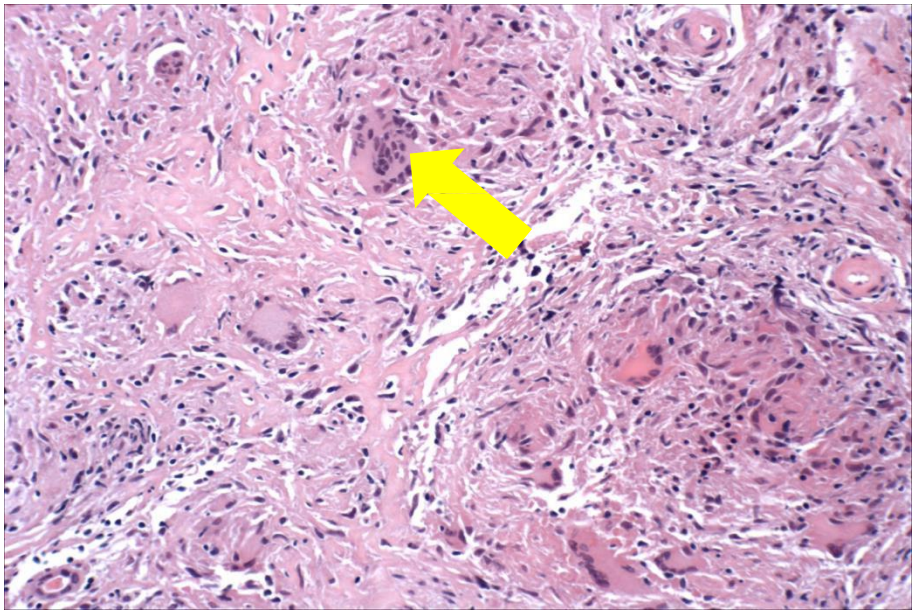


**Granuloma without multinuclear giant cells**



**Granuloma with multinuclear giant cells**



# CIN pattern due to Sarcoidosis

# CIN: Course and Treatment

- Most are slowly progressive
- Treat underlying disease/ eliminate offending agents
- BP control, treat electrolyte disturbances
- Chelation of Pb
- Steroids in sarcoid
- Biopsy not often indicated because of lack of specific therapy

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- Acknowledgements:
  - Dr. Li-Li Hsiao (Brigham & Women’s Hospital)
  - Dr. Helmut Rennke (Brigham & Women’s Hospital)
  - Dr. Vanesa Bijol
  - Dr. Ragnar Palsson