

Differential Diagnosis of Acute Interstitial Nephritis

KEY FACTS

TERMINOLOGY

- Acute interstitial inflammation, commonly also involving tubules, due to variety of causes

ETIOLOGY/PATHOGENESIS

- Drugs
 - May account for 60-70% of AIN cases
- Autoimmune
- Infection
- Hereditary/toxic/metabolic

CLINICAL ISSUES

- ~ 15-27% of renal biopsies for acute renal failure show AIN
- Treatment: Discontinuation of causative drug in drug-related AIN; corticosteroids (controversial)

MICROSCOPIC

- Interstitial inflammation with lymphocytes, monocytes/macrophages, eosinophils, plasma cells

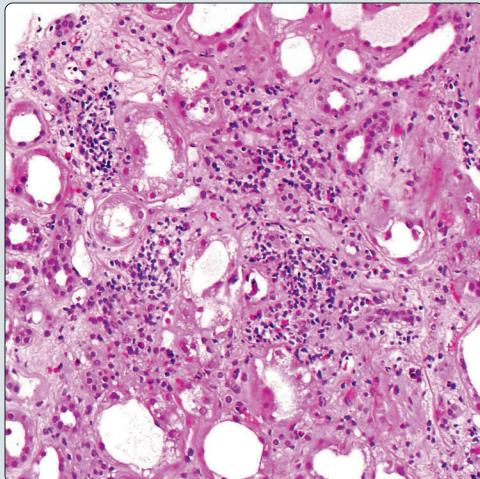
- High number of eosinophils suggestive of allergic AIN but not specific
- Tubulitis
- Interstitial fibrosis may be present

TOP DIFFERENTIAL DIAGNOSES

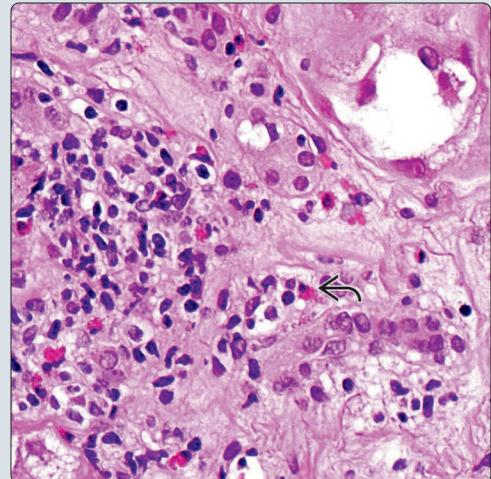
- Drug-induced interstitial nephritis
- Sarcoidosis
- IgG4-related systemic disease
- Light chain deposition disease
- Infection
- Acute cellular rejection in renal allograft
- Interstitial inflammation associated with glomerular disease
- Hematopoietic neoplasm

(Left) Acute interstitial nephritis is a heterogeneous group of diseases. This case in a 78-year-old man with acute renal failure was due to a recent exposure to antibiotics. **(Right)** Eosinophilic tubulitis is seen in a case of acute allergic interstitial nephritis due to antibiotics, regarded as a useful sign of drug-induced AIN, although the specificity has not been proven.

Acute Allergic Interstitial Nephritis

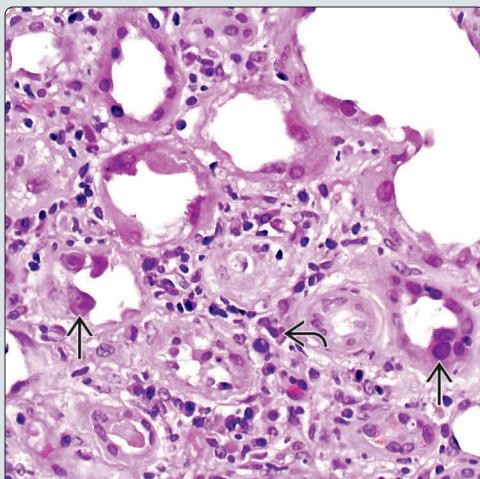


Acute Allergic Interstitial Nephritis

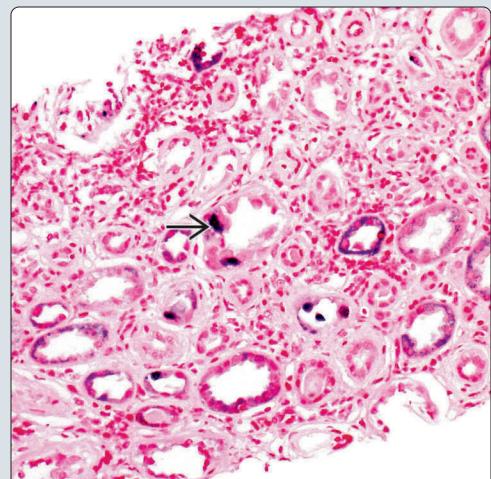


(Left) BK polyomavirus tubulointerstitial nephritis shows interstitial inflammation with increased plasma cells in an allograft. Some tubular epithelial cells show viral cytopathic effect . **(Right)** In situ hybridization for BK polyomavirus reveals several tubules with positive epithelial cell nuclei . Polyoma can also be readily detected by immunohistochemistry, using an antibody to the large T antigen.

BK Polyomavirus



BK Polyomavirus



Differential Diagnosis of Acute Interstitial Nephritis

ETIOLOGY/PATHOGENESIS

Drugs

- May account for 60-70% of acute interstitial nephritis (AIN)
- Allergic (e.g., antibiotics, proton pump inhibitors, nonsteroidal anti-inflammatory drugs [NSAIDs])
- Toxic (e.g., cisplatin, lithium, NSAIDs)

Autoimmune

- Primary in kidney
 - e.g., anti-tubular basement membrane (TBM) disease
- Associated with systemic disease
 - e.g., Sjögren syndrome, tubulointerstitial nephritis with uveitis (TINU) syndrome, IgG4-related systemic disease

Infection

- Direct infection
 - Bacteria (e.g., pyelonephritis), mycobacteria
 - Virus (e.g., BK polyomavirus tubulointerstitial nephritis)
 - Other, including parasites
- Reaction to distant infection (e.g., poststreptococcal GN)

Hereditary/Toxic/Metabolic

- e.g., hyperoxaluria, gout, heavy metal toxicity
- Typically chronic injury, less inflammation

Idiopathic

- Accounts for ~ 25% of cases

CLINICAL ISSUES

Epidemiology

- Incidence
 - ~ 15-27% of biopsies for acute renal failure show AIN

Presentation

- Acute or subacute renal failure
- Proteinuria, subnephrotic
- Microhematuria
- Pyuria
- Eosinophiluria
- In drug-related AIN, renal failure may be accompanied by rash, fever, arthralgias, and eosinophilia
- Clinical history important to determine cause of AIN
 - Recent (a week to months) exposure to new drug may suggest allergic AIN
 - Longer period of exposure prior to AIN associated with NSAID use

Treatment

- Drugs
 - Corticosteroids
 - May be of benefit in some cases with more acute onset of AIN
 - Cytotoxic drugs (e.g., cyclophosphamide) and plasmapheresis may be used in anti-TBM disease
- Discontinuation of causative drug in drug-related AIN

MICROSCOPIC

Histologic Features

- Interstitial inflammation with lymphocytes, macrophages, plasma cells, and eosinophils

- High number of eosinophils suggest allergic AIN but not specific
- Increased plasma cells suggest autoimmune AIN but not specific
- Interstitial edema
- Tubulitis
- Acute tubular injury
- Granulomatous AIN
 - Nonnecrotizing granulomas in sarcoidosis and drug-related AIN
 - Poorer prognosis in drug-related AIN
- Interstitial fibrosis / tubular atrophy when chronic

Immunofluorescence

- Granular TBM deposits in some cases of autoimmune interstitial nephritis
- Linear TBM deposits in anti-TBM disease

Electron Microscopy

- Amorphous, electron-dense deposits in TBMs in some cases of autoimmune interstitial nephritis

DIFFERENTIAL DIAGNOSIS

Diverse Causes of AIN Pattern on Biopsy

- AIN may be due to drugs, autoimmune disease, infection, hereditary/toxic/metabolic, idiopathic

Granulomatous AIN

- Type of AIN; most commonly allergic drug reactions or sarcoidosis
- Rarely direct infection (e.g., tuberculosis)

Interstitial Inflammation Associated With Glomerular Disease

- Glomerulonephritis (GN)
 - Pauci-immune necrotizing and crescentic GN
 - IgA nephropathy
 - Acute postinfectious GN
 - Other
- Focal segmental glomerulosclerosis, collapsing variant

Neoplasm

- Infiltrating lymphoid neoplasm or plasma cell myeloma

Light Chain Deposition Disease (Monoclonal Immunoglobulin Deposition Disease)

- Interstitial inflammation and acute tubular injury
- Linear glomerular and tubular basement membrane immunofluorescence staining by monoclonal protein
- Finely granular, electron-dense deposits in basement membranes seen by electron microscopy

Acute Cellular Rejection in Renal Allograft

- May be indistinguishable from AIN

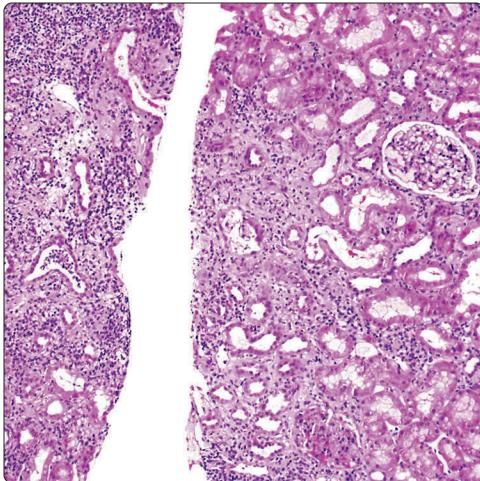
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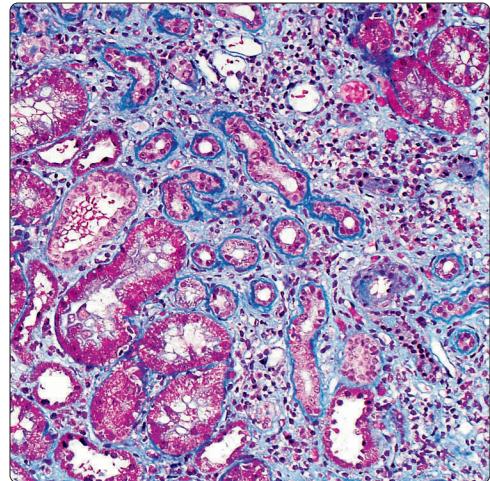
Differential Diagnosis of Acute Interstitial Nephritis

Acute and Chronic Allergic Interstitial Nephritis

(Left) H&E shows acute and chronic allergic tubulointerstitial nephritis with diffuse interstitial inflammation. This patient had been taking a number of herbal preparations for many months, after which she was found to have an elevated serum creatinine. Immunofluorescence staining was negative. (Right) This case of AIN also showed areas of interstitial fibrosis with inflammation. The fibrosis is indicative of a chronic component of the interstitial nephritis (trichome stain).

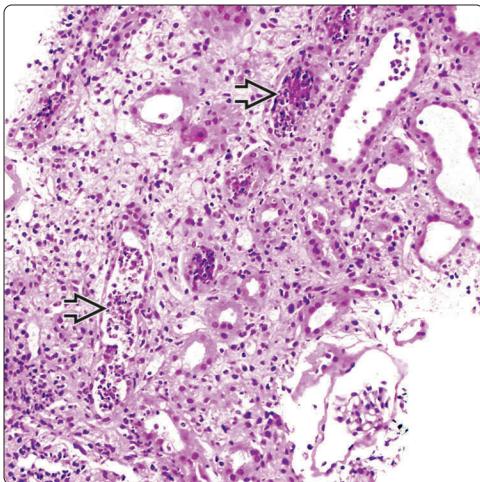


Acute and Chronic Interstitial Nephritis

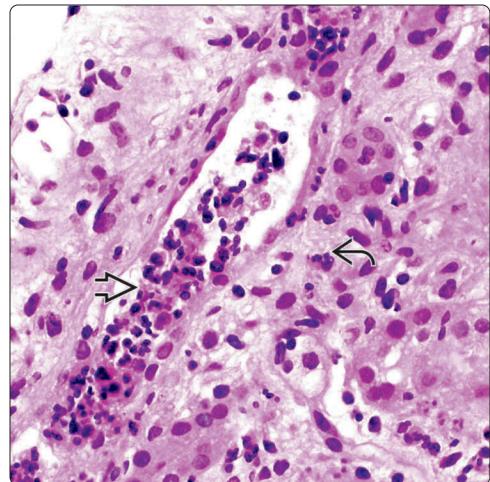


Acute Pyelonephritis

(Left) Acute interstitial inflammation with mononuclear cells and neutrophils is seen in a case of acute pyelonephritis. Neutrophilic casts are present (→). This biopsy is from a renal transplant patient who had laboratory evidence of a urinary tract infection. (Right) A neutrophilic cast (→) within a tubule is seen in acute pyelonephritis. Neutrophils are also present within the interstitium (→). Occasional neutrophil casts can be seen for no apparent reason in end-stage kidneys.

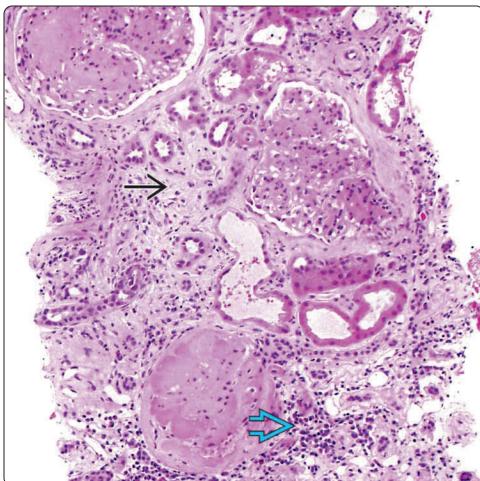


Acute Pyelonephritis

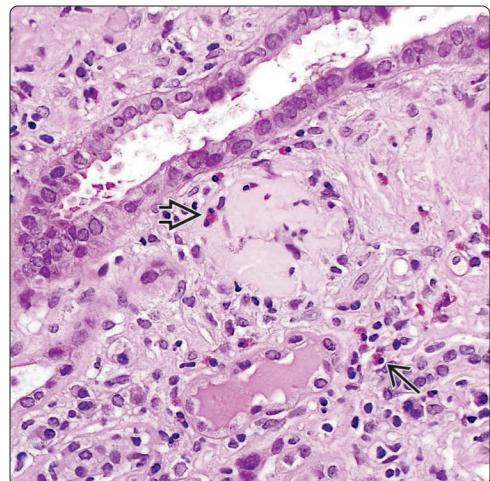


Diabetic Glomerulosclerosis and Allergic AIN

(Left) This biopsy shows nodular diabetic glomerulosclerosis as well as interstitial edema (→) and increased inflammation (→). (Right) This example of diabetic glomerulosclerosis and AIN shows eosinophils in the interstitium (→) and embedded within proteinaceous cast material (→). This patient had acute renal failure and recent exposure to antibiotics. Increased eosinophils have been observed in patients with diabetes, but patients with diabetes may also develop allergic AIN.

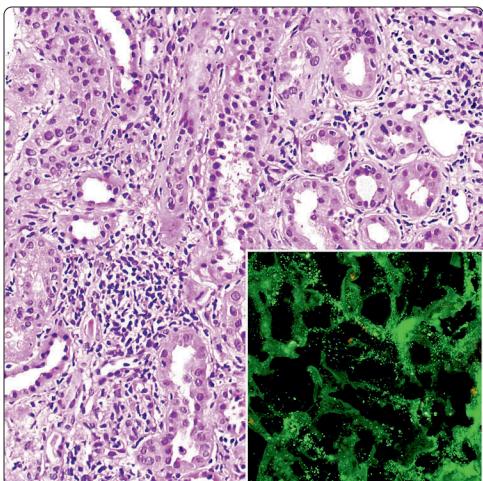


Diabetic Glomerulosclerosis and Allergic AIN

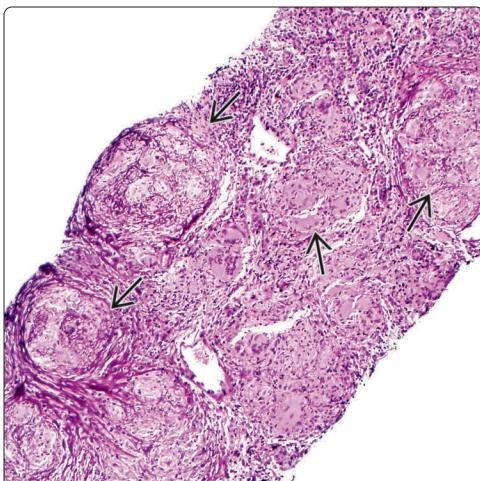


Differential Diagnosis of Acute Interstitial Nephritis

Sjögren Syndrome

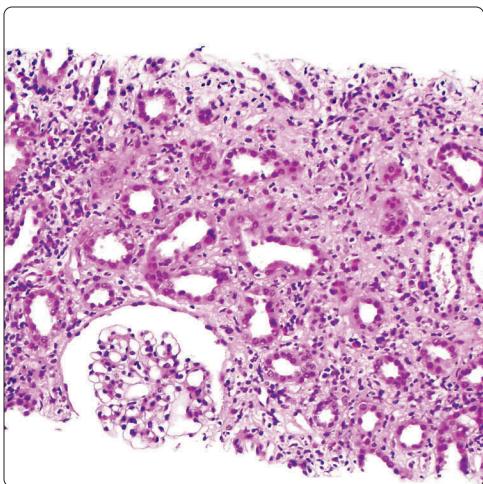


Sarcoidosis

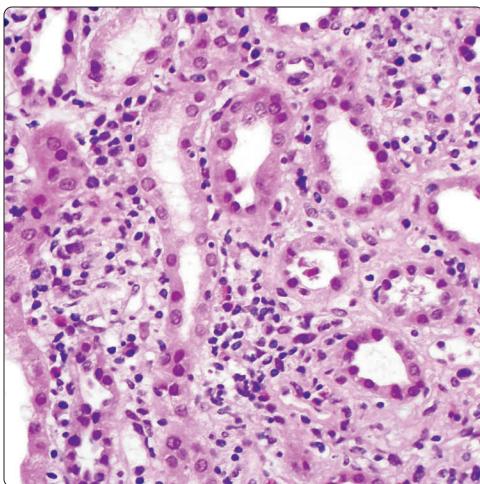


(Left) Tubulointerstitial nephritis with mononuclear cells and plasma cells is seen in Sjögren syndrome. Tubular basement membrane immune complex deposits (inset, immunofluorescence staining for IgG) aid in the diagnosis of an autoimmune interstitial nephritis. (Right) Renal biopsy is shown from a 50-year-old man with a history of sarcoidosis and progressive renal failure over several months. This case shows extensive involvement by nonnecrotizing granulomatous inflammation □.

TINU Syndrome

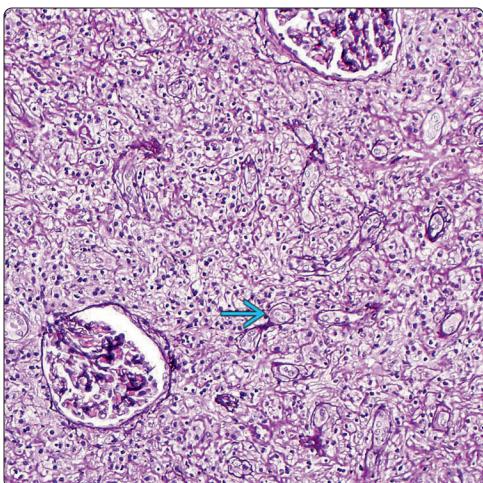


TINU Syndrome

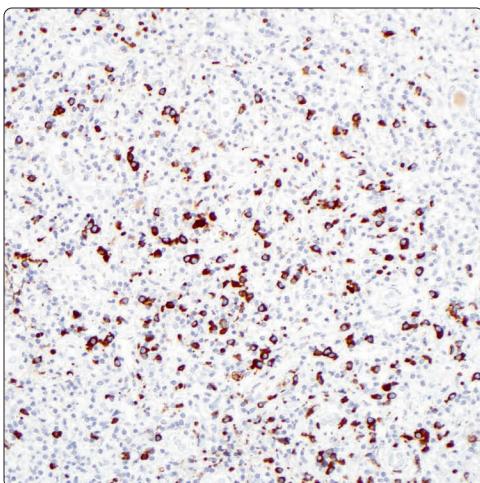


(Left) AIN is seen in a 10-year-old girl who presented with acute renal failure. Several weeks prior, she had a cough and fever; no antibiotics were given. Four months later, the patient developed uveitis and was diagnosed with tubulointerstitial nephritis-uveitis (TINU) syndrome. (Right) The infiltrate in this case of TINU syndrome is composed of mononuclear cells, plasma cells, and eosinophils, mimicking drug-induced AIN, but this patient was on no medications.

IgG4-Related Tubulointerstitial Nephritis



IgG4(+) Plasma Cells

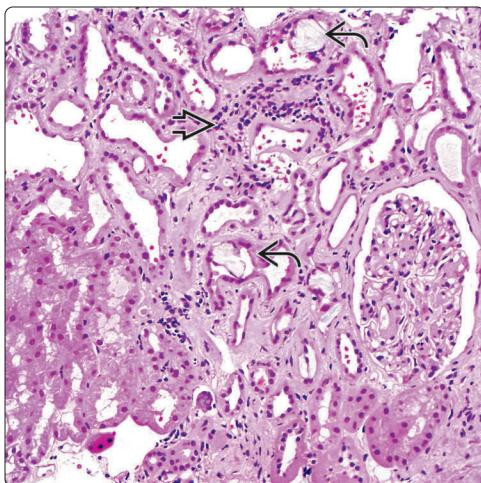


(Left) This example of IgG4-related tubulointerstitial nephritis shows interstitial plasma cell-rich inflammation with "storiform" fibrosis. Residual tubular basement membranes □ are seen on this silver stain. (Right) In IgG4-related tubulointerstitial nephritis, there is a marked increase (> 30 cells/HPF) in IgG4(+) plasma cells.

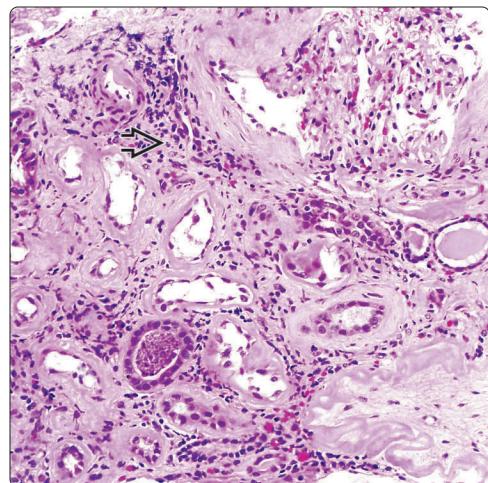
Differential Diagnosis of Acute Interstitial Nephritis

(Left) Hyperoxaluria related to gastric bypass shows interstitial fibrosis and tubular atrophy with interstitial mononuclear cell inflammation. Focal tubules contain calcium oxalate crystals. Usually this condition does not have a florid inflammatory component, in contrast to the usual AIN. (Right) A form of hereditary interstitial nephritis/nephropathy is shown with chronic tubulointerstitial nephritis in a patient with a mutation in the gene for renin.

Secondary Hyperoxaluria

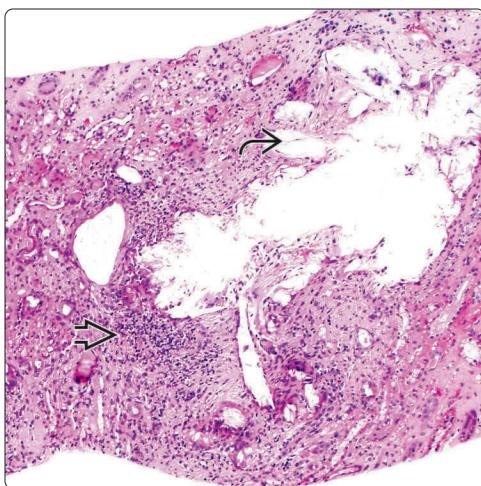


Hereditary Interstitial Nephritis/Nephropathy

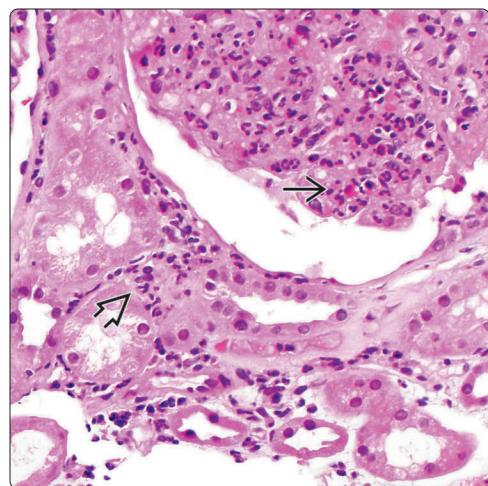


(Left) Urate nephropathy shows interstitial inflammation surrounding dissolved urate crystals in a patient with a history of gout and chronic renal failure. (Right) Acute postinfectious glomerulonephritis often shows focal interstitial inflammation, including several neutrophils as shown here. A glomerulus shows an acute exudative glomerulonephritis.

Urate Nephropathy

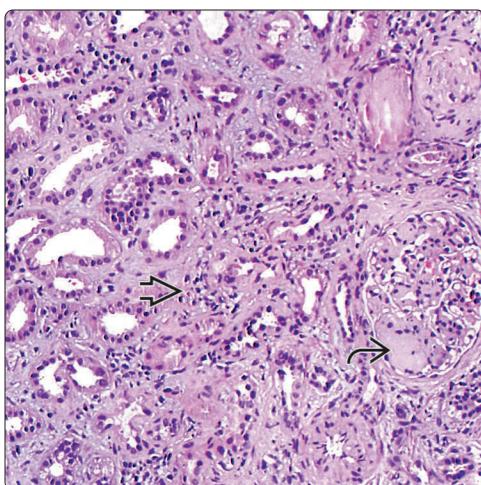


Interstitial Inflammation Secondary to Glomerulonephritis

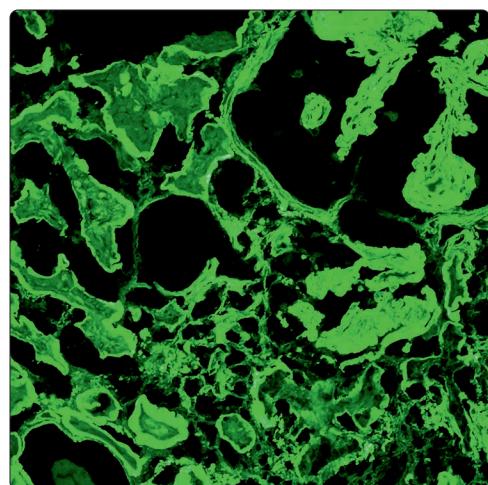


(Left) Interstitial inflammation is seen in a case of light chain deposition disease (LCDD). A glomerulus shows a nodular glomerulosclerosis. (Right) This case showed bright linear glomerular and tubular basement membrane staining for lambda light chain but not kappa light chain by IF, although most cases of LCDD show kappa light chain. Electron microscopy showed finely granular glomerular and tubular basement membrane deposits.

Light Chain Deposition Disease

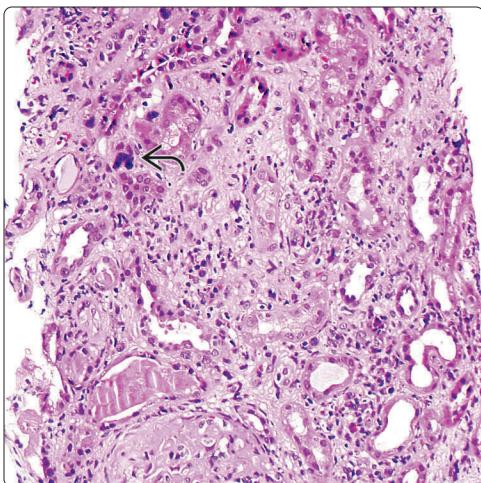


Light Chain Deposition Disease

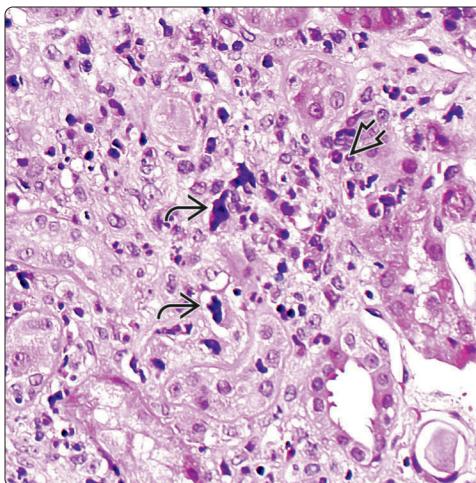


Differential Diagnosis of Acute Interstitial Nephritis

Extramedullary Hematopoiesis

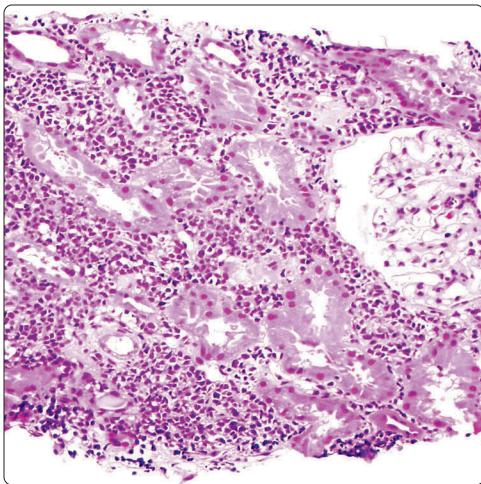


Extramedullary Hematopoiesis

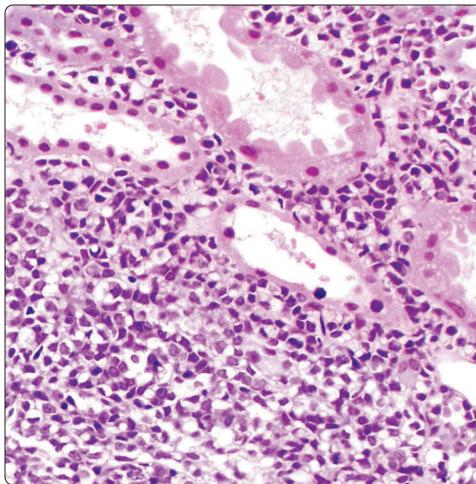


(Left) Extramedullary hematopoiesis shows an interstitial infiltrate at medium magnification. A few cells with large, irregular nuclei stand out □. The biopsy is from a 77-year-old man with renal failure and a history of myelofibrosis. (Right) Extramedullary hematopoiesis can be confused with AIN. The larger cells can be recognized as megakaryocytes □, confirming the diagnosis. Eosinophil and neutrophil precursors are also present □.

Acute Myeloid Leukemia

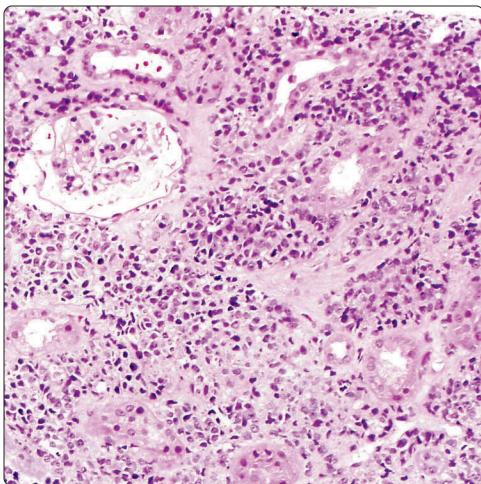


Acute Myeloid Leukemia

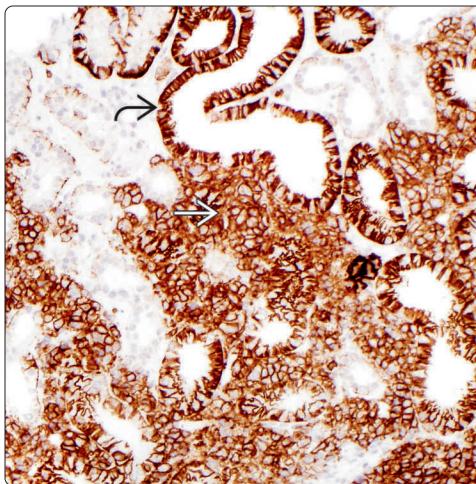


(Left) Acute myeloid leukemia (AML) involving the kidney can resemble AIN. This case has extensive interstitial infiltration by leukocytes. This patient had a history of treated AML and then developed acute renal failure and markedly enlarged kidneys. (Right) On higher magnification in this case of AML, atypical cells are seen to be large and monomorphic. Immunohistochemistry revealed blasts positive for CD33 and CD34 and negative for CD3 and CD20.

Plasma Cell Myeloma



Plasma Cell Myeloma



(Left) Plasma cell myeloma in an allograft is shown. Atypical cells are infiltrating the interstitium. No mass lesion was detected; the biopsy was performed for renal dysfunction. (Right) Infiltrating cells □ are positive for the plasma cell marker CD138, as are some tubular epithelial cells □ (a normal finding).