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Tubulointerstitial Nephritis Uncovered: From Cause to Cure

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Abstract: *Tubulointerstitial nephritis (TIN) represents a significant cause of acute kidney injury (AKI) and may progress to chronic kidney disease (CKD) if not recognized and managed. It is characterized by immune-mediated inflammation of the renal interstitium, often resulting in fibrosis over time. Clinical manifestations are usually non-specific, mostly leading to diagnostic delays and suboptimal treatment outcomes.The etiology of TIN is diverse, including drug-induced, infectious, idiopathic, and genetic causes, as well as associated with systemic inflammatory disorders such as tubulointerstitial nephritis and inflammatory bowel disease, and IgG4-related multiorgan autoimmune disease (MAD)uveitis (TINU) syndrome,. A high index of clinical suspicion is therefore essential to identify and remove potential causative agents and to manage any underlying systemic condition effectively.Management strategies for TIN are primarily guided by the underlying etiology. Although randomized controlled trials are lacking, corticosteroids remain the cornerstone of therapy, with emerging evidence supporting the use of mycophenolate mofetil in certain cases. Urinary biomarkers, including alpha-1 microglobulin and beta-2 microglobulin, show promise for both diagnosis and monitoring of disease activity. Routine screening for TIN should be considered in pediatric patients with inflammatory bowel disease, uveitis, or IgG4-related systemic autoimmune disorders.[1].*

Keywords: Tubulointerstitial Nephritis, Acute Kidney Injury, Chronic Kidney Disease, TINU Syndrome, Inflammatory Bowel Disease, Treatment

I. INTRODUCTION

Tubulointerstitial nephritis (TIN) is a recognized kidney disorder, but it is often diagnosed late because its symptoms are usually vague and non-specific. The disease can be classified by underlying cause, histological findings, or duration, distinguishing acute from chronic forms. Early identification of the cause is critical, as it directly influences treatment decisions and long-term outcomes. In addition to well-known triggers such as drugs, infections, and systemic inflammatory conditions, recent research has uncovered genetic factors that may predispose individuals to TIN. Advances in novel urinary and serum biomarkers are also improving our ability to diagnose the condition earlier, monitor disease activity, and guide therapy more effectively. This review discusses the common causes of TIN and highlights recent developments that may enhance patient care and prognosis.

Definition

Tubulointerstitial nephritis (TIN) is defined by immune-mediated infiltration of the renal interstitium with inflammatory cells, which can result in acute kidney injury (AKI), either non-oliguric or oliguric. In some cases, persistent interstitial inflammation may cause chronic changes, eventually leading to chronic kidney disease (CKD). [6] Both genetic predispositions and environmental exposures can contribute to the development of TIN. Certain histological features, such as granulomas, or the presence of associated systemic diseases, can help identify the underlying cause. [3,8]TIN is observed in approximately 2% of native kidney biopsies and is responsible for up to 27% of unexplained kidney disease in adults. In children, both acute and chronic TIN account for 1–7% of diagnoses in renal biopsy series.[7]

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Etiology

Tubulointerstitial nephritis (TIN) has multiple causes, including drug-related, infectious, systemic, autoimmune, genetic, and idiopathic origins (Table 1). Drug-induced TIN is the most common, with beta-lactam antibiotics and NSAIDs frequently implicated, typically presenting with classic features (Table 2) [2-4, 9]. Rifampin-associated TIN may present abruptly, with biopsy findings ranging from acute TIN to acute tubular necrosis [10-12]. Overall, drug-induced TIN accounts for 7–27% of unexplained AKI in adults [13].

Infections causing TIN include viral, bacterial, fungal, or parasitic agents [14-16]. It is a notable cause of graft dysfunction in renal transplant recipients, often due to pylomovirus or cytomegalovirus, and may increase rejection risk [17-20]. Adenovirus-related necrotizing TIN can occur in bone marrow transplant patients [22-24], while HIV and Epstein-Barr virus have also been linked to TIN, including TINU syndrome [25-27]. Other infections include Mycoplasma pneumoniae, Yersinia pseudotuberculosis, and Leptospira [28-31].

TIN is also associated with systemic inflammatory and autoimmune conditions such as inflammatory bowel disease, TINU syndrome, sarcoidosis, SLE, Sjögren's syndrome, and IgG4-related disease [32-35]. IgG4-related TIN shows IgG4-positive plasma cell infiltration, C3 deposition, and often hypocomplementemia, whereas hypocomplementemic immune-complex TIN presents with plasma cell infiltrates without extrarenal involvement [36]. TIN can also occur with anti-tubular basement membrane antibodies [37]. In many cases, TIN is under-recognized, leading to delayed diagnosis.

Table 1: Medications implicated in tubulointerstitial nephritis (TIN) [1, 3, 44, 46]

Antimicrobials	NSAIDs	Diuretics	Neuropsychiatric	Other
Beta-lactams	Ibuprofen	Furosemide	Carbamezepine	Allopurinol
Cephalosporins	Ketorolac	Thiazide diuretics	Lamotrigine	Azathioprine
Sulfonamides			Levetiracetam	Antiepileptics
Macrolides		Triamterene	Phenytoin	Proton-pump inhibitors
Gentamicin		Amiloride	Lithium	
Nitrofurantoin		Tienlinic acid		Alendronate
Clotrimazole				Chlorpropamide
Doxycycline				Captopril
Rifampin				Sulfasalazine
Ethambutol				
Isoniazid				
Vancomycin				
Ciprofloxacin				
Acyclovir				
Indinavir				

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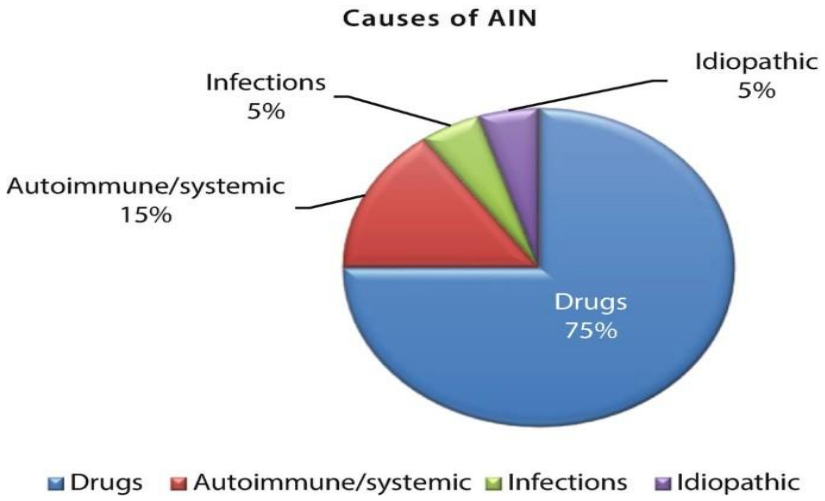
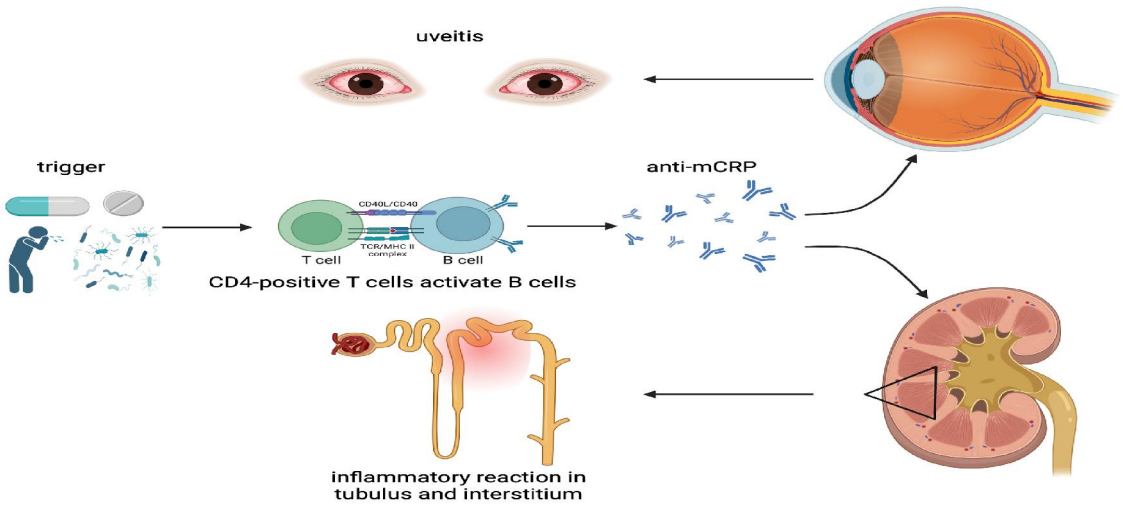


Pathophysiology

Acute interstitial inflammatory reactions are associated with damage to the tubulointerstitium, leading to AKI associated with TIN [4]. The high metabolic demand of the tubulointerstitium makes it particularly susceptible to injury because the inflammation and associated edema compromise renal blood flow, causing a decrease in glomerular filtration rate (GFR) [5]. In some situations, damage may lead to fibrosis (see below).

Interstitial edema and infiltration of lymphocytes and plasma cells, as well as poor tubular function in acute TIN, causes a decrease in GFR. In chronic TIN, fibrosis of the interstitium (as opposed to edema) causes the decrease in GFR [5, 41]. If prolonged, acute interstitial inflammatory reactions can lead to accumulation of extracellular matrix that causes irreversible impairment of renal function with interstitial fibrosis and tubular atrophy [4, 13]. Initially macrophages may help repair acute injury, but eventually can contribute to inflammation and production of fibrogenic cytokines [5]. Studies have shown that the cytokine transforming growth factor-beta (TGF-β) may mediate profibrotic responses in the tubulointerstitium [5, 42]. Tubular damage can decrease the number of functional nephrons, eventually resulting in hyperfiltration and burnout of the remaining nephrons leading to CKD [5].



The pathophysiology of drug-induced TIN is thought to be immune-mediated and related to an allergic reaction. There are five concepts that support this view: (1) TIN only occurs in a small proportion of individuals taking a certain medication; (2) There is no dose-dependence; (3) Patients develop systemic manifestations of a hypersensitivity

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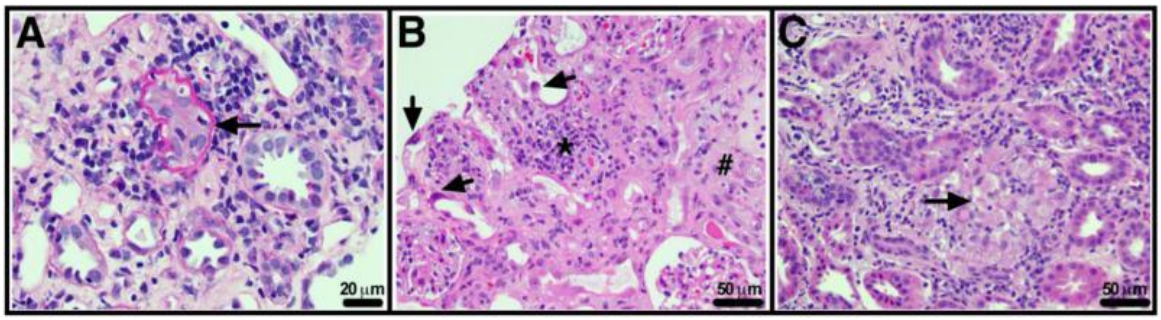
reaction; (4) TIN can recur after re-exposure to the drug; and (5) Eosinophils are often present on renal biopsy [4, 9]. This process likely involves cellular immunity, as there are seldom immune deposits noted by immunofluorescence on renal biopsies in patients with TIN [4]

Figure 1. Renal Histopathology in tubulointerstitial nephritis (TIN).



A. TIN with predominantly lymphocytic infiltrate associated with tubular damage and tubulitis (arrow). Periodic acid Schiff stain, original magnification × 400. B. Acute drug-induced tubular injury, in this case secondary to cidofovir. There is interstitial infiltrate (*), edema (#) and marked tubular regenerative changes (arrows). Glomeruli show little change. Hematoxylin and eosin stain, original magnification × 200. C. Granulomatous tubulointerstitial nephritis (arrow), in this case likely secondary to lamotrigine. Hematoxylin and eosin stain, original magnification × 200.

Granulomatous TIN

Inflammatory cells infiltrating the tubulointerstitium can form granulomas, which are usually scarce, and non-necrotic with few multinucleate giant cells [4, 43] (Fig. 1c). By contrast, necrotic granulomas are commonly seen in TIN associated with bacterial (tuberculosis) or fungal infections [44]. The presence of granulomas on renal biopsy defines granulomatous TIN, which is relatively rare, with renal biopsy incidence of 0.5 % [9]. With time, the granulomas are often replaced by fibrosis, but despite varying histopathology, a diagnosis of granulomatous TIN does not necessarily correlate with poor prognosis [43, 45]. The underlying etiology for granulomatous TIN is similar to TIN, although sarcoidosis, TINU syndrome, and certain drug-related cases are more common (Table 1). Systemic diseases such as Crohn's disease have also been implicated, though rare [46]. One study reported that the underlying etiology of granulomatous TIN is not found in 50 % of patients [45]. Interestingly, granulomatous TIN has been described in renal transplant recipients and was hypothesized to result from infections, which are more common in this patient population because of the use of immunosuppressive agents [44, 47].

Epidemiological Trend

Acute Tubulointerstitial Nephritis (ATIN)

Prevalence: ATIN accounts for approximately 1% to 3% of all renal biopsies. However, in patients with acute kidney injury (AKI), the prevalence increases to 15% to 27% ([NCBI][1]).

Etiology: The primary cause of ATIN is drug-induced hypersensitivity reactions, responsible for about 67% of cases. Other causes include infections and autoimmune diseases ([sciencedirect.com][2]).

Age and Gender Distribution: The prevalence of ATIN has increased in recent years, particularly among patients aged over 65 years. This rise is attributed to increased drug use and polypharmacy in the elderly ([PubMed][3]).

Chronic Tubulointerstitial Nephritis (CTIN)

Prevalence: CTIN is less common and often underdiagnosed due to its gradual progression and nonspecific symptoms. It can result from prolonged exposure to nephrotoxic agents, chronic infections, or systemic diseases.

Prognosis: CTIN can lead to progressive renal dysfunction and may require dialysis or kidney transplantation in advanced stages.

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Mortality Trends and Demographic Disparities

From 1999 to 2020, a total of 37,611 deaths were reported due to tubulointerstitial nephritis in the United States. The age-adjusted mortality rate (AAMR) showed a gradual decline from 1999 to 2012, followed by a progressively increasing trend from 2012 to 2020. Significant disparities in mortality rates were observed among different demographic groups and geographical regions. Notably, mortality rates were higher in female patients, Latino/Hispanic patients, and residents of metropolitan areas ([Lippincott Journals][4]).

Tubulointerstitial Nephritis and Uveitis (TINU) Syndrome

TINU syndrome is a rare condition characterized by the simultaneous occurrence of tubulointerstitial nephritis and uveitis. Estimates suggest that TINU is diagnosed in 0.2% to 2% of patients attending specialist uveitis services. The prevalence of TINU is higher in younger age groups, with a slight female preponderance. Drugs and infections have been proposed as leading acquired risk factors for the development of TINU ([BioMed Central][5]).

Regional Variation

Developed Countries: In developed nations, drug-induced ATIN is the predominant cause, reflecting higher medication usage and healthcare access.

Developing Countries: In developing regions, infectious causes are more prevalent, possibly due to limited healthcare infrastructure and higher exposure to infectious agents.

Sri Lanka : A study from Sri Lanka reported that TIN was the most common diagnosis in adults aged 15 years and above, accounting for 25% of renal biopsies. Notably, TIN was more prevalent in men (34%) than in women (17%) ([BioMed Central][6]).

Tubulointerstitial nephritis, encompassing both acute and chronic forms, presents with diverse etiologies and clinical manifestations. While ATIN is often drug-induced and more prevalent in older populations, CTIN progresses insidiously and can lead to significant renal impairment. Regional disparities in prevalence and outcomes underscore the need for tailored diagnostic and therapeutic approaches. Further research is essential to elucidate the underlying mechanisms and improve management strategies for TIN.

Implementation of these Data

After seeing all the trends we know that drugs are one of the major sourcs of for ATIN and it should be induced carefully in elderly people.

We need further research to understand the demographic and geographic disparities and to make some chances and planning accordingly

The lack of data in chronic varieties shows that we need more research on this topic for better understandings.

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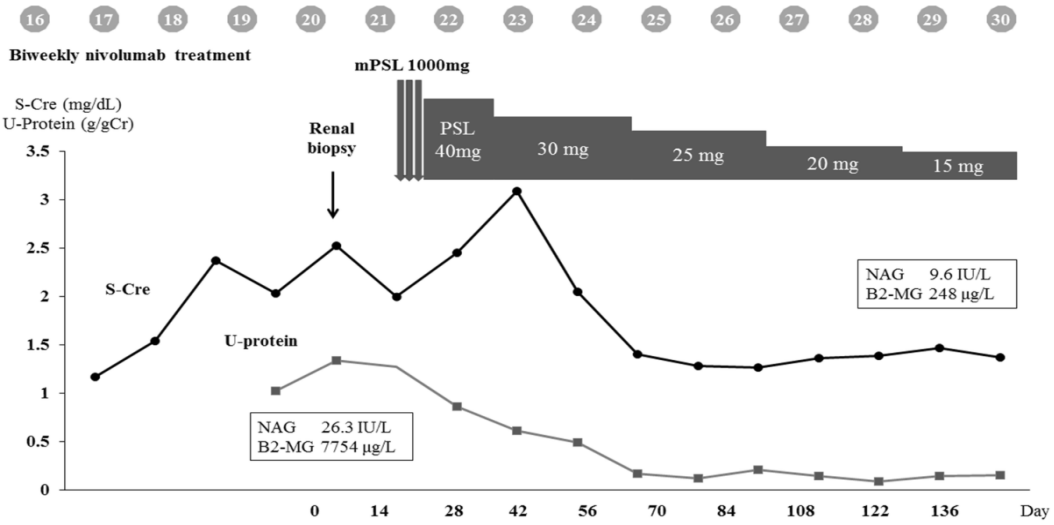

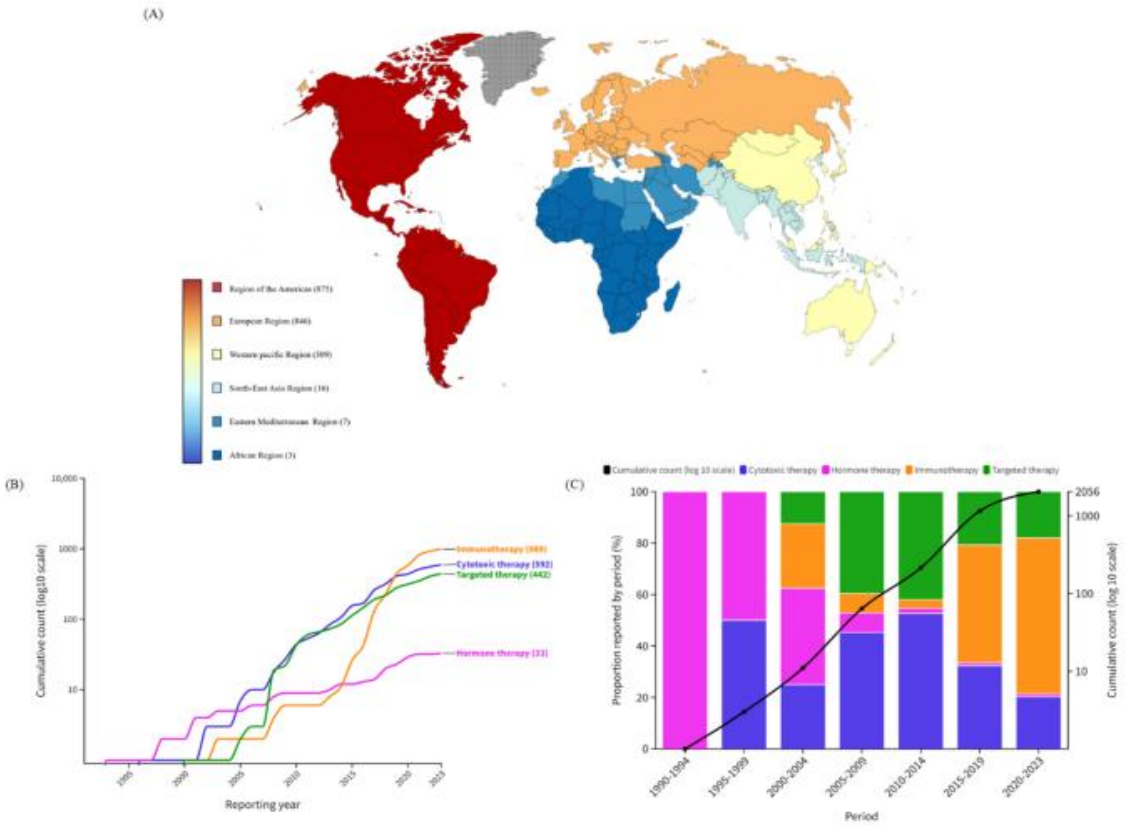

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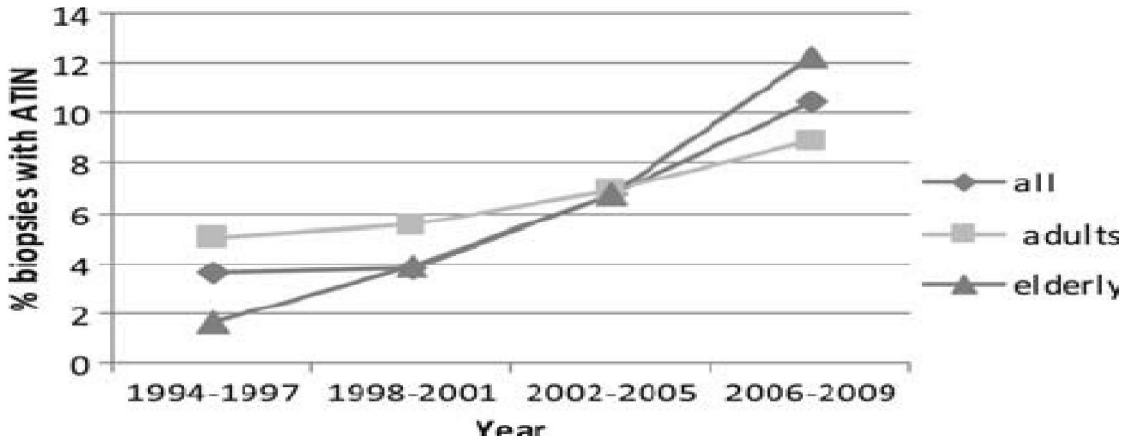

Treatment

Corticosteroids remain the mainstay of ATIN treatment. Therapy usually starts with **oral Prednisolone or Prednisone** at 0.5–1 mg/kg/day (≈60 mg/day). In drug-induced ATIN, treatment typically lasts 1–2 weeks, up to a maximum of 6–8 weeks, with a gradual taper; extending therapy beyond 8 weeks generally offers no additional benefit. In ICPI-associated ATIN, longer courses of 3–6 months may be required, though shorter regimens have also been effective, emphasizing individualized therapy.

For severe acute kidney injury, **intravenous pulse steroids** can be administered, but they have not shown clear advantages over high-dose oral therapy. Patient factors such as age, frailty, comorbidities, and the risk of steroid-related side effects—including infections, diabetes, osteoporosis, hypertension, and thromboembolic events—should guide treatment decisions.

Medications are the leading cause of ATIN, with most patients recovering within 6 months (≈76%), and recovery is higher in drug-related cases (≈81%) than in other causes (≈66%). Poor prognosis is associated with severe interstitial fibrosis, tubular atrophy, or dialysis dependence, where immunosuppressive therapy offers limited benefit.

Other immunosuppressive agents like **Azathioprine, Mycophenolate Mofetil,** and **Infliximab** have been used in select cases, but delayed onset and uncertain efficacy limit their routine use. In corticosteroid-resistant ICPI-associated ATIN, Infliximab or targeted T-cell therapies such as Antithymocyte Globulin may be considered. When advanced fibrosis is present (>50–75%), focus should shift to supportive care and addressing underlying causes rather than aggressive immunosuppression.

Histologic Features of Atin

Kidney biopsy is the gold standard for diagnosing ATIN. Pathologically, ATIN is characterized by interstitial edema, tubulitis, and cellular infiltration predominantly composed of T lymphocytes.40 The composition of inflammatory infiltrates varies between cases and may include macrophages, plasma cells, and eosinophils (Figure 1). However, neutrophils are typically sparse, a feature that generally differentiates ATIN from infection. Cellular infiltrates may involve the entire interstitium or remain patchy, but glomeruli and blood vessels generally appear normal unless there is another concomitant disease.

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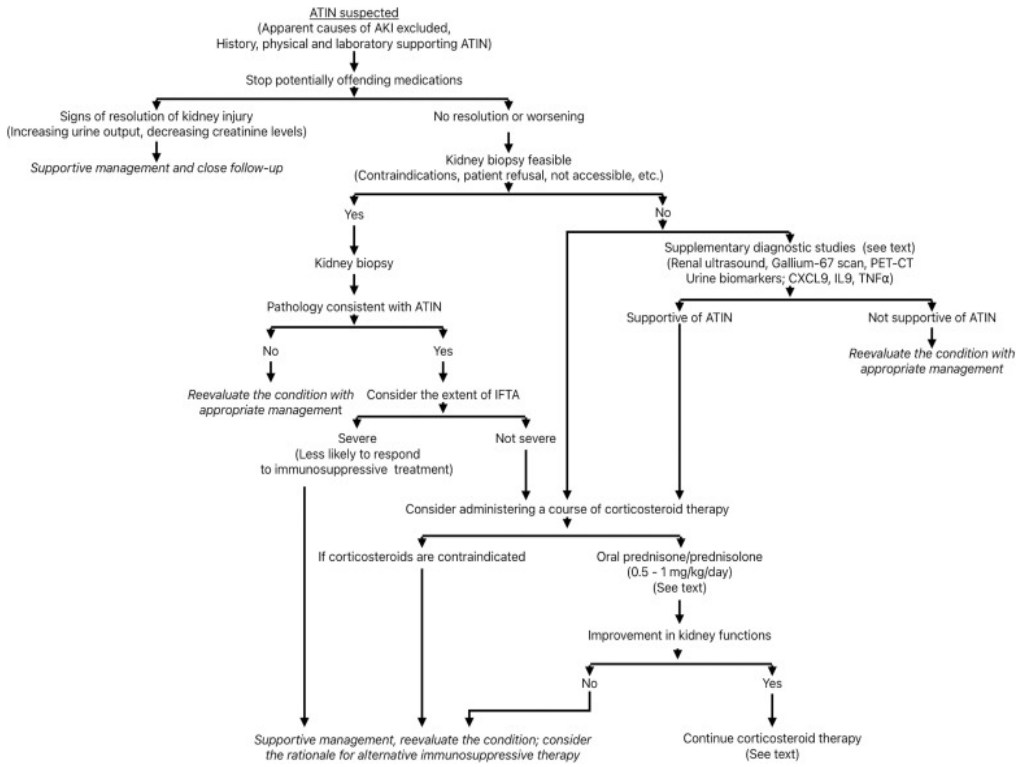

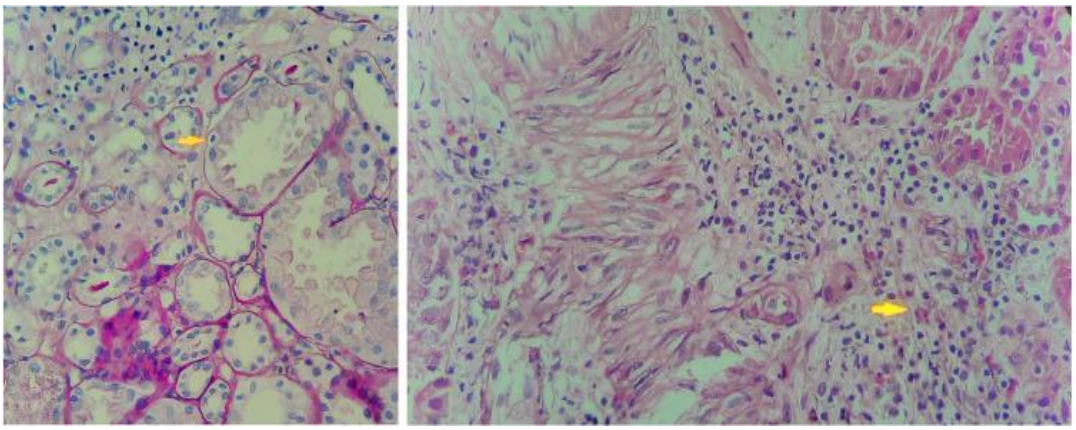

Left image: Shows lymphocytes infiltrating the proximal tubules, a process known as tubulitis (yellow arrow). The surrounding interstitium displays lymphocyte-predominant inflammation, and some tubules appear atrophic (Periodic Acid–Schiff stain, ×100).

Right image: Demonstrates acute hypersensitivity-type tubulointerstitial nephritis. The interstitium contains a mix of inflammatory cells, including eosinophils (yellow arrow), along with tissue swelling (edema) and a neutrophilic cast visible at the 9 o'clock position (Hematoxylin and Eosin stain, ×100).

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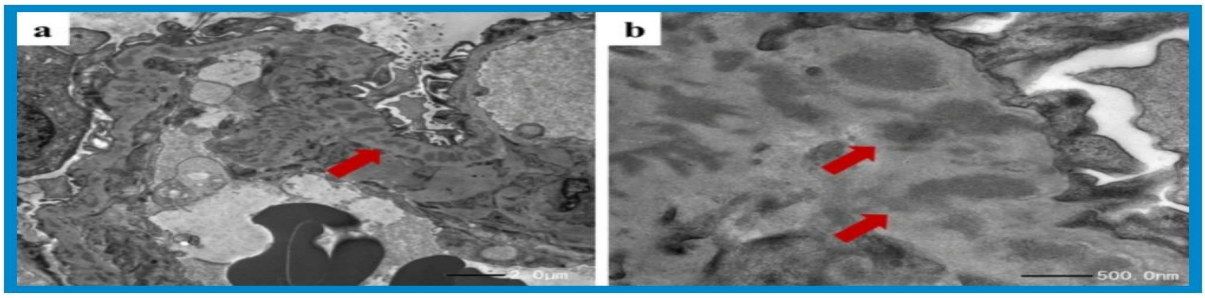

Electron microscopy showed intra-membranous electron-dense deposits (arrow) in glomerular capillary wall, but not in subendothelial or mesangial area

Prognosis

The outlook for tubulointerstitial nephritis (TIN) largely depends on its underlying cause, the management of any related systemic conditions, how quickly treatment is started, the patient's baseline kidney function, and whether any offending agents are removed. Chronic changes are associated with a worse prognosis, and the presence of fibrosis on a kidney biopsy indicates irreversible damage. Early diagnosis of TIN can significantly improve kidney outcomes. Persistent low-molecular-weight proteinuria is linked to a poorer prognosis and reduced glomerular filtration rate. In one review of adults with TIN, about 64% fully recovered, 23% experienced partial recovery, and 13% required ongoing renal replacement therapy.

II. CONCLUSION

At the end after all the research and understanding we can say that Acute tubulointerstitial nephritis (ATIN) is an important cause of acute kidney injury, triggered by a variety of factors such as medications, infections, and systemic diseases. While type IV hypersensitivity plays a central role, a combination of immune reactions often contributes to its complexity. Early recognition and prompt management,mainly by stopping the offending agent and, when appropriate, using corticosteroids are crucial for preserving kidney function. Because its symptoms are often nonspecific, there is a need for advanced biomarkers and individualized treatment strategies. A multidisciplinary approach, along with further research into immune mechanisms and targeted therapies, will help improve outcomes in this challenging condition.

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