

Review Article**Granulomatous Interstitial Nephritis: Histomorphological Features with Review of Literature**Anunayi Jeshtadi^{1*}, Neelaveni Neelala², Sirisha Ommi³, Vijay Sreedhar Veldurthi⁴¹Associate Professor, Upgraded Department of Pathology, Osmania Medical College/General Hospital, Hyderabad, India²Assistant Professor, Upgraded Department of Pathology, Osmania Medical College/General Hospital, Hyderabad, India³Senior Resident, Upgraded Department of Pathology, Osmania Medical College/General Hospital, Hyderabad, India⁴Professor & Head of the Department, Upgraded Department of Pathology, Osmania Medical College/General Hospital, Hyderabad, India***Corresponding author**

Anunayi Jeshtadi

Email: anunavi1990@yahoo.com

Abstract: The term interstitial nephritis denotes inflammation of the interstitium and tubules of the renal parenchyma by inflammatory cells and tubular atrophy with edema hence the term tubule interstitial nephritis is preferable. Chronic tubulo interstitial nephritis presents with prominent fibrosis and few inflammatory cells. Granulomatous interstitial nephritis (GIN) is a rarely encountered special form of chronic tubulo interstitial nephritis with an incidence of 0.5 to 0.9% in routine biopsies and 0.6% in renal transplant biopsies. Many etiological factors are implicated in this disorder like infections, drugs, autoimmune disorders etc. Patients usually present with compromised renal function with either End stage renal disease or chronic renal failure. As GIN is a treatable condition in most of the situations of renal failure, awareness and understanding of the pathophysiological mechanisms along with associated conditions will help in arriving at a definitive diagnosis and treatment.**Keywords:** Interstitial nephritis, Chronic granulomata, drug-induced, Mycobacterial, Giant cells, Tuberculosis.

INTRODUCTION

GIN is defined as Interstitial nephritis in which the inflammatory infiltrate includes distinct aggregates of epithelioid cells with or without multinucleated giant cells. GIN is a rare histological diagnosis. Etiological causes are most commonly drug induced (71.5%), idiopathic, infections, foreign body reactions, Sarcoidosis, crystal induced nephropathy, paraproteinemias and Wegener's granulomatosis being less common causes. Renal transplant cases show causative factors as mycobacteria and fungi [1].

Clinically it can be acute or chronic in presentation. At times they are asymptomatic but when they present the symptoms are varied. They can have mild proteinuria usually less than 1 gram per 24 hours, Nephrotic range of proteinuria is rare. Patients present with fever, rash and enlarged kidneys if the etiology is an allergic reaction. Some people experience dysuria and low back pain. In chronic tubulo interstitial nephritis, patients can experience symptoms such as nausea, vomiting, fatigue and weight loss. In other rare conditions, the patients may develop hyperkalemia, metabolic acidosis and renal failure manifestations [2].

PATHOGENESIS

The pathogenetic mechanism underlying GIN is poorly understood but various observations suggest a T cell mediated delayed hypersensitivity, antitubular basement membrane antibodies and reaginic antibodies [4]. The predominance of mononuclear cells in the infiltrates that is mostly T cells, presence of granulomas and absence of immunoglobulin deposition in the tubules or interstitium supports this evidence [5]. Infection related GIN accounts for only a small percentage of cases. Mycobacteria and fungi are the main etiological causes in renal transplant cases. Histoplasma, Candidal and Cryptococcal fungal infections are common among immunocompromised. Cryptococcal GIN can also occur in immunocompetent individuals [6]. Mycobacterium tuberculosis can spread from lungs, by hematogenous spread to the kidneys after a dormant period and they can present as renal failure. Mantoux test positivity, DNA isolation from the renal biopsy can confirm the diagnosis [7].

The presence of monocytes/macrophages and granulomas with fibrosis are due to overlap that exists between acute and chronic tubulo interstitial nephritis. Immunohistochemistry reveals many T cells in the interstitium. Ultrastructural features may occasionally

reveal electron dense immune deposits along the tubular basement membrane or in the interstitium particularly in SLE. Sarcoidosis is a multisystemic disease of unknown etiology. Renal failure associated with isolated granulomatous interstitial nephritis is extremely rare manifestation with only a few cases reported in the literature [8]. They can present as hypercalcemia and progressive renal failure. Renal sarcoidosis should be considered in the differential diagnosis in such situations. A raised serum ACE levels helps in making the diagnosis and renal biopsy shows granulomatous interstitial changes, Schaumann bodies, asteroid bodies with noncaseating granulomas [9]. Some authors consider granulomatous interstitial nephritis with

sarcoid features ascases of isolated renal sarcoidosis which they have proved by elevated ACE levels and positive response to steroid treatment [10].

In cases of drug induced granulomatous nephritis, noncaseating granulomas are seen with interstitial fibrosis. Tubules may show tubulitis. Glomeruli and vessels are usually spared. In crystal induced granulomatous interstitial nephritis, oxalosis or hyperoxaluria after small intestine bypass is associated with granulomatous reaction to deposited oxalate crystals. The infiltrate is sparse with few granulomas and foreign body giant cells. Intravenous drug abuse and gout can also produce a similar picture.

Table 1: Etiology of GIN [3]

Drug induced
Bacilli Calmette Guerin, intravesical
Antibiotics- Ampicillin, Vancomycin, Cefuroxime, Clarithromycin Rifampicin, NSAIDs (Indomethacin, Diclofenac) Diuretics(Thiazide), Allopurinol, Anticonvulsants (lamotrigine, Carbamazepine),Omeprazole, Bisphosphonate, All trans retinoic acid, Heroine abuse, Sulfasalazine
Infections
Bacterial (E. coli, Rhodococcus, Mycobacterium tuberculosis), leptospirosis, legionella and streptococcus
Viruses(Adenovirus, Human immunodeficiency virus)
Fungus(Histoplasma, Candida, Cryptococcus, Aspergillus)
Inflammatory or systemic conditions like sarcoidosis, Sjogrens syndrome, Wegener’s granulomatosis Tubulointerstitial nephritis and uveitis syndrome(TINU syndrome), Xanthogranulomatous pyelonephritis, Crohn’s disease
Hematologicalmalignancies (Leukemia and Multiple myeloma), IgA nephropathy
Idiopathic
Cystal induced
Oxalosis

PATHOLOGY

Grossly, Kidneys are small, contracted, and pale with variable involvement of papillae, necrosis, sclerosis and calcification. External surface is scarred, finely granular; cortico medullary junction is poorly demarcated. There may be intrarenal vessel prominence with thick walls (Fig. 1 & 2).

Microscopy

All the four components of renal parenchyma should be examined. Variable number of lymphocytes, monocytes/macrophages and plasma cells are seen in the interstitium (Fig. 3). Tubular atrophy and interstitial fibrosis are histologic hallmarks.

Tubular atrophy has 3 morphologic subtypes. The most common type is the classic type atrophic tubule with prominently thickened, frequently wrinkled and lamellated basement membrane. The endocrine type tubule has a narrow lumen or no lumen at all and is usually prominently reduced in diameter and has

simplified epithelium and a thin basement membrane. The thyroid type atrophic tubule has only mildly thickened basement membrane, a simplified flattened epithelium and a lumen filled with eosinophilic PAS positive homogeneous proteinaceous material, therefore the tubule resembles a thyroid follicle. These thyroid type tubules also occur in clusters and in occasional cases of renal scarring, the parenchyma resembles thyroid gland (Fig. 4).The endocrine atrophic tubule is frequently seen in chronic ischemia, including renal artery stenosis. The thyroid type atrophic tubule is a common finding in chronic pyelonephritic scars [11, 12].

Glomerular changes may include focal mild mesangial hypercellularity, crescent formation, endocapillary proliferation, obsolescent glomeruli either focal or global (Fig. 5 & 6). Tubules may show focal lymphocytic infiltration of the epithelial lining, tubular atrophy. Tubular lumina can show hyaline casts and granular debris. In GIN presenting in acute form can

show tubular necrotic changes with neutrophilic debris in the lumina. Blood vessels can show mild hyaline arteriosclerosis changes. Thrombotic phenomena are rarely encountered.

Interstitium shows edematous changes and multiple granulomata formation with distinct aggregates of epithelioid histiocytes, lymphoplasmacytic cuff and presence of necrosis or absence of necrosis (Fig. 7 & 8).

Distinct caseous necrosis with langhans type of giant cells can be seen in mycobacterium tuberculosis infections [13, 14]. Asteroid bodies can be seen in sarcoidosis. Rest of the parenchyma can show mixed inflammatory infiltrate and fibrosis. The degree of fibrosis and density of inflammatory infiltrate needs to be scored as mild, moderate and severe in fibrosis and scanty, moderate and plentiful for inflammatory cells [15].



Fig. 1 & 2: Gross showing irregular, scarred surface with adherent capsule and cut section showing dilated pelvicalyceal system and loss of cortico-medullary differentiation with grey, yellow areas

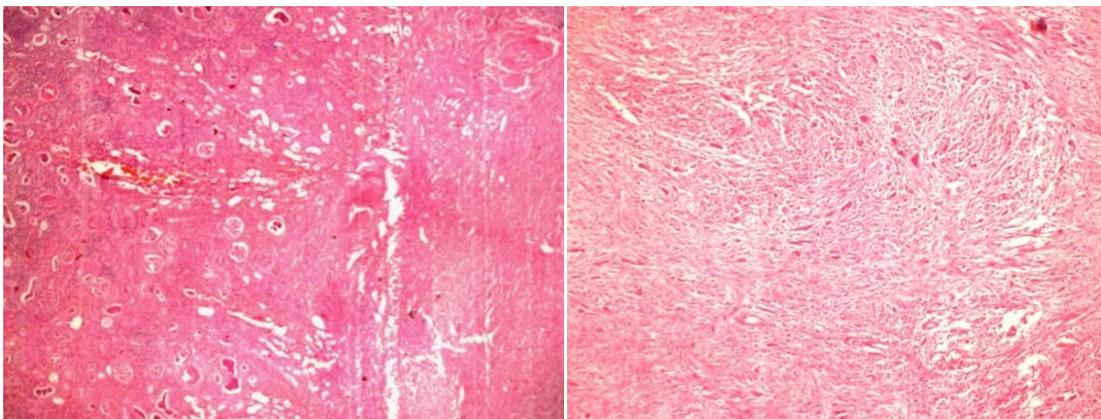


Fig. 3 & 4: Hematoxylin and Eosin stained sections(10X) showing glomeruli, tubules and interstitial inflammation

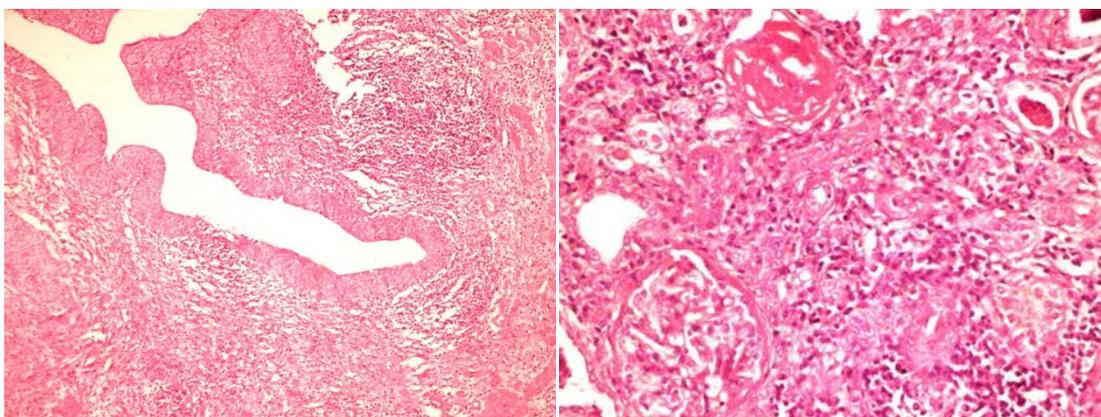


Fig. 5 & 6: Hematoxylin and Eosin stained section(10X) showing peripelvicalyceal dense chronic inflammation and other section(40X) showing sclerosed glomerulus and thyroidization of the tubule

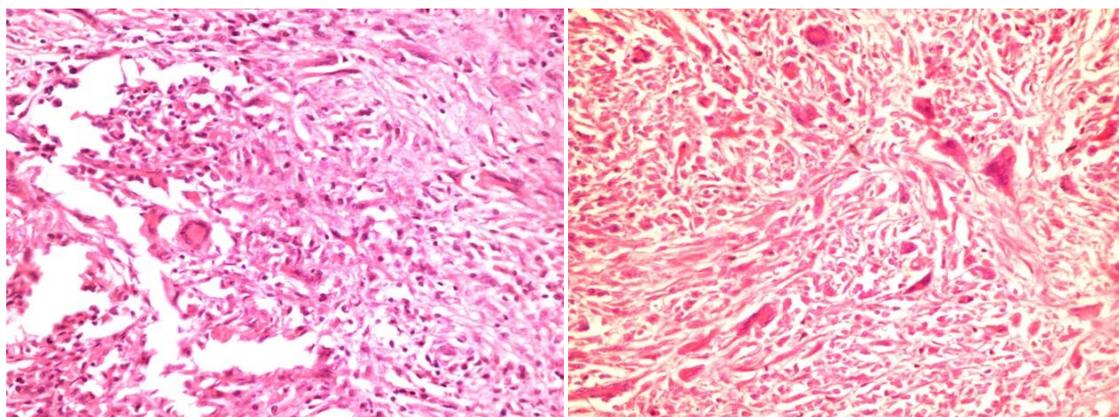


Fig. 7 &8: Hematoxylin and Eosin stained sections(40X) showing granulomas with epithelioid histiocytes and langhans type of giant cells and plentiful multinucleate giant cells

Management depends on confirming the causative mechanism of tubulointerstitial nephritis and for which full renal biopsy workup is needed including immunofluorescence and electron microscopy study and correlating with serum markers and other ancillary techniques wherever applicable [16]. In most of the cases, steroid therapy helps along with treatment of the underlying cause.

CONCLUSION

Granulomatous interstitial nephritis though a rarely encountered histological diagnosis is a treatable condition. It could be the first manifestation of a systemic disease like sarcoidosis and mycobacterial infections. Awareness of this entity helps in proper diagnosis and management.

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