ORIGINAL RESEARCH PAPER

Pathology

KEY WORDS: Acute Tubular injury , Interstitial nephritis, diabetic nephropathy.

STUDY OF HISTO-MORPHOLOGICAL SPECTRUM OF TUBULO-INTERSTITIAL DISEASES OF KIDNEY IN A TERTIARY CARE HOSPITAL

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ABSTRACT

AIM : To study the various patterns of Tubulo-interstitial diseases of kidney with their clinico-pathological correlation in a tertiary care hospital in North-Karnataka region.

MATERIALS AND METHODS : This study was conducted over a period of eighteen months from july 2017 - December 2018 after approval from the Institutional Ethical Committee . A total of 100 renal samples were studied . Inadequate and samples from the renal transplant patients were excluded from the study .

RESULTS : Out of total hundred renal lesions, twenty one cases were of tubulo -interstitial diseases of kidney . Out of these, thirteen cases were of Acute Tubular Injury , five cases of Acute interstitial nephritis and three cases of chronic interstitial nephritis . Also, in this study, four cases of secondary acute tubular injury were associated with each case of IgA nephropathy, minimal change nephropathy focal segmental glomerulosclerosis and arterio-nephrosclerosis respectively. Diabetic nephropathy was associated with two cases of interstitial nephritis. Most common clinical presentations were deranged renal functions and raised serum creatinine.

Conclusion : This study was undertaken to study histo-morphological patterns, clinical correlation and etiopathogenesis of various Tubulo-interstial diseases of kidney.

INTRODUCTION

Acute kidney injury is one of the rising problem in the world, most common cause of it being acute interstial nephritis. Tubulo-interstitial nephritis (TIN) is well-described entity. Patients present with non-specific signs and symptoms, leading to delay in diagnosis. It is associated with increased morbidity and mortality, constituting major health problem.[1,2]

Tubulo-interstitial nephritis (TIN) can be categorized based on underlying etiology, histology, or duration (acute versus chronic).[3]Acute tubulo-interstitial nephritis is seen in patients exposed to various medications. Other causes include infections, autoimmune and systemic diseases, environmental exposures etc. Chronic tubulo-interstitial nephritis develops in patients with previous acute tubulo-interstitial nephritis or it can be the initial manifestation of an autoimmune, environmental, metabolic or systemic process.[4]

Thus its challenging for clinicians to differentiate various causes of acute and chronic kidney diseases particularly distinguishing acute tubular interstitial nephritis from rapidly progressive glomerulonephritis or acute tubular necrosis. It is important as treatment and prognosis differs. [5]

This study was undertaken to emphasize the diagnosis of Tubulo-interstitial diseases of kidney and its clinical correlation, and to study various types including Acute Tubular injury , Acute Interstitial nephritis and Chronic Interstitial nephritis in a tertiary care hospital in North -Karnataka region. [4,6]

MATERIALS AND METHODS

This study was conducted in the department of pathology, Mahadevappa Rampure Medical college, Kalaburagi over a period of eighteen months from July 2017 to December 2018. Approval from the Institutional Ethical Committee was taken prior to the study.

A total of hundred renal samples were analysed. Clinical details were obtained from medical records. Patients with uncorrected bleeding diasthesis, polycystic kidney disease, biopsies from transplanted kidney and incomplete biopsies and samples were excluded from the study.

RESULTS

A total of hundred renal samples were studied using light microscopy. Immunoflorescence and electron microscopy were used as required . Out of total cases, twenty one cases were of Tubulo-interstitial diseases, in which Acute Tubular Injury was most common(61.90%), followed by Acute Interstitial Nephritis(23.80%) and Chronic Interstitial Nephritis(14.28%)[TABLE-1].

TABLE-1 : DISTRIBUTION OF TUBULO-INTERSTITIAL DISEASES OF KIDNEY

TUBULO INTERSTITIAL DISEASES	CASES	PERCENTAGE
ACUTE TUBULAR INJURY	13	61.90%
ACUTE INTERSTITIAL NEPHRITIS	05	23.80%
CHRONIC INTERSTITIAL NEPHRITIS	03	14.28%
TOTAL	21	100%

Mean age of diagnosis of acute tubular injury was 35.50 years, whereas in acute interstitial nephritis it was 56.50 years and in chronic interstitial nephritis it was 57.67 years respectively. Interstitial diseases were common in older age group with male predominace whereas acute tubular injury was common in younger age group. [TABLE-2]

TABLE-2 : MEAN AGE AND SEX WISE DISTRIBUTION OF CASES WITH TUBULO-INTERSTITIAL DISEASES

TUBULO-INTERSTITIAL DISEASES	MALE (n=15)	FEMAL (n=6)	MEAN AGE (YEARS)
ACUTE TUBULAR INJURY	08	05	35.50
ACUTE INTERSTITIAL NEPHRITIS	04	01	56.50
CHRONIC INTERSTITIAL NEPHRITIS	03	00	58.85

Most common clinical presentation in all tubulo-interstitial diseases was deranged renal function tests with increased serum creatinine, followed by proteinuria and RBCs in urine. Four cases of acute tubular injury also presented with edema. All cases of chronic interstitial nephritis and one case acute interstitial nephritis were associated with diabetes mellitus. Hypertension was associated with two cases of acute interstitial nephritis [TABLE-3]

TABLE-3 : CLINICAL PRESENTATION OF CASES

CLINICAL PRESENTATION	ACUTE TUBULAR INJURY (n=13)	ACUTE INTERSTITIAL NEPHRITIS (n=5)	CHRONIC INTERSTITIAL NEPHRITIS (n=3)
FLANK PAIN	05	03	01
EDEMA	04	--	--
HYPERTENSION	--	02	01
DIABETS MILLITUS	--	01	03
DREANGED RENAL FUNCTIONS	09	04	02
RAISED SERUM CREATININE	10	04	03
HEMATURIA	01	--	--
PROTEINURIA	06	02	01
RBCs IN URINE	06	01	--

Out of twenty one cases, seven cases were associated with multiple diagnosis. Five cases had primary glomeular pathology associated with tubulo –interstitial or vascular lesions. One case had primary vascular pathology and single case of primary tubular pathology was seen.

One case of 54 year old male was diagnosed with acute tubular injury along with acute interstitial nephritis. Three cases of secondary acute tubular injury was associated with IgA nephropathy, minimal change nephropathy and focal segmental glomerulosclerosis respectively. Diabetic nephropathy was associated with two cases of interstitial nephritis. One case of 60 year old male with acute tubular injury was associated with arterio-nephrosclerosis . [TABLE-4]

TABLE-4: CASES WITH MULTIPLE DIAGNOSIS

CASE	AGE (YEAR)	SEX	PRIMARY DIAGNOSIS	SECONDRY DIAGNOSIS
1	54	M	ACUTE TUBULAR INJURY	ACUTE INTERSTITIAL NEPHRITIS
2	29	F	IgA NEPHROPATHY	ACUTE TUBULAR INJURY
3	34	F	MINIMAL CHANGE NEPROPATHY	ACUTE TUBULAR INJURY
4	71	M	DAIBETIC NEPHROPATHY	CHRONIC INTERSTITIAL NEPHRITIS
5	65	M	DIABETIC NEPHROPATHY	ACUTE INTERSTITIAL NEPHRITIS
6	47	M	FOCAL SEGMENTAL GLOMERULOSCLEROSIS	ACUTE TUBULAR INJURY
7	60	M	ARTERIO-NEPHROSCLEROSIS	ACUTE TUBULAR INJURY

DISCUSSION

Renal biopsy helps to establish or refute a suspected clinical diagnosis. It has become gold standard for diagnosis of glomerular diseases and also plays an important role in diagnosis of tubulo-interstitial and renal vascular pathology. The present study was done to study various histo-morphological patterns of renal tubulo-interstitial diseases diagnosed over a period of eighteen months.[1,2]

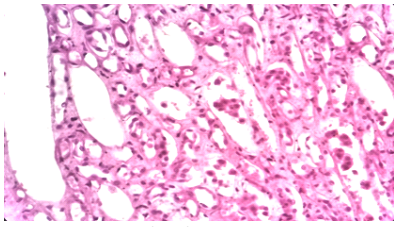
Tubules and interstitium makes up approximately 80% of the renal volume and diseases involving this compartment can be due to primary injury or secondry to glomeruar or vascular pathology. Broadly classified into acute tubular injury(toxic or ischaemic) and tubule-interstitial nephritis (acute and chronic).[3,4]

Various etiological factors for tubulo-interstitial diseases include infections (acute bacterial pyelonephritis, chronic pyelonephritis and reflux nephropathy), drugs (non steroidal anti- inflammatory drugs-NSAIDS, proton pump inhibitors, anti-diuretics, lead, cadmium etc.), autoimmune diseases (Sjogren's syndrome, sarcoidosis, IgG4 tubulo-interstitial nephritis, systemic lupus erythematousis, tubule-interstitial nephritis uveitis-TINU, vasculitis), systemic diseases (Lymphoproliferative diseases, paraproteinemias, inflammatory bowel disease, athero-embolic disease, drug related eosinophilia systemic syndrome-DRESS, microangiopathies, hemolytic uraemic

syndrome, Disseminated intravascular coagulation) and metabolic disorders (acute oxalate nephropathy).[5]

Acute tubular injury is characterised by swelling of tubular epithelium, detachment of epithelium from underlying basement membrane, attenuation of brush border of proximal convoluted tubule cells, thinning of tubular epithelium, dilation of tubular lamina, interstitial edema and casts (hyaline, pigmented, eosinophilic, cellular, granular debris) in distal tubules. Necrosis and rupture of tubular basement membranes (tubulorrhexis) can also be seen.[FIGURE-1]

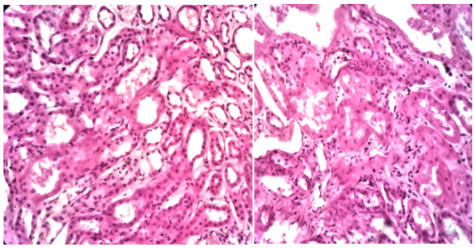
FIGURE 1: Acute tubular injury with irregular dilated tubules and sloughing of epithelial cells in tubules.



Acute interstitial nephritis(AIN) is characterized by the presence of inflammatory infiltrates and edema within the interstitium, usually associated with an acute deterioration in renal function, First defined by Councilman in 1898 and is known to be a serious cause of acute kidney injury (AKI). Prevalence of Acute interstitial nephritis is 1%–3% of all kidney biopsies. However, when it is limited to patients with Acute kidney injury it accounted for 15%–27%.. In children, Tubulo-interstitial nephritis (both acute and chronic) accounts for 1-7% of the histological diagnoses in renal biopsies.[6]

The characteristic inflammatory cell infiltrates of Acute interstitial nephritis can be diffuse or patchy with interstitial edema, lymphocytes (CD4+T cells being the most abundant type), polymorphs, eosinophils and plasma cells , whereas glomeruli and vessels are distinctly normal. [FIGURE-2]. Interstitial granulomas with possibility ofsarcoidosis and tuberculosis should be looked for. Immunofluorescence studies are negative in most patients, although granular or linear deposits of IgG or complement along the tubular basement membrane(TBM) can occasionally be observed. Electron microscopy reveals non-specific lesions. In those patients with NSAIDs induced acute interstitial nephritis accompanied by nephritic syndrome, diffuse effacement of podocyte's foot processes is observed.[7]

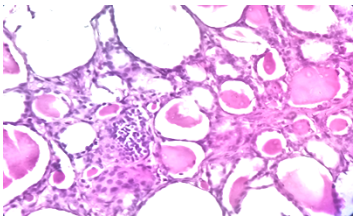
FIGURE 2: Acute tubular necrosis of proximal convoluted tubules



Chronic interstitial nephritis is a non-specific diagnosis of a pattern of kidney injury, which may occur due to any of many conditions that initially cause an acute interstitial nephritis. The diagnosis is made when specific underlying causes cannot be identified. Patients may present at any age, usually with low-grade proteinuria and slowly progressive decline in glomerular filtration rate, and may reach end-stage kidney disease.[4] On light microscopy it shows lympho-plasmacytic infiltrate out of proportion to the degree of interstitial fibrosis and tubular atrophy.

The infiltrate consists of CD4/CD8 T-cells, B-cells, and plasma cells, with scattered tubulitis. Glomeruli are initially unremarkable, but may show peri-glomerular fibrosis and ischemic wrinkling of glomerular basement membranes and even sclerosis in advanced cases. Vascular sclerosis and hyalinosis may be present. No specific changes on immunoflorescence and on electron micro scopy.[8][FIGURE-3]

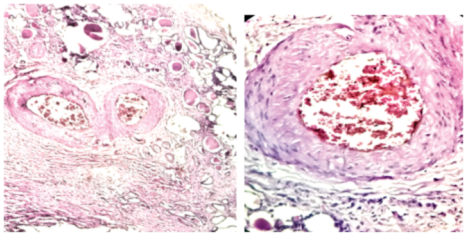
FIGURE 3: Chronic interstitial nephritis with dilated tubules containing hyaline cast and lymphocytic infiltrates.



Tubulo-interstitial diseases are associated with primary pathologies in glomeruli and renal vessels.. Renal lesions include tubulointerstitial nephritis (TIN), which may occur synchronously or metachronously with lesions in other organs like auto-immune pancreatitis.[9] Immunoglobulin G4-related disease (IgG4-RD) is a systemic, immune-mediated disorder associated with high serum IgG4 levels (in approximately 70–80%)

In this study, four cases of secondary acute tubular injury were associated with IgA nephropathy, minimal change nephropathy, focal segmental glomerulosclerosis and arterio-nephrosclerosis respectively. Diabetic nephropathy was associated with two cases of interstitial nephritis. [FIGURE-4][10]

FIGURE 4: Arterionephrosclerosis with hyperplasia of tunica media



CONCLUSION

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REFERENCES

1. Zohre Khodamoradi1, Maryam Pakfetrat , Simin Torabinezhad, Mohammad Mahdi Sagheb; Acute interstitial nephritis in the south of Iran- an observational study, J Nephropathol. 2017;6(3):225-230, DOI: 10.15171/jnp.2017.37
2. Nasar Yousuf Alwahaibi, Taiseer Ahmed Alhabsi, Samira Abdullah Alrawahi , Pattern of Glomerular Diseases in Oman: A Study Based on Light Microscopy and Immunofluorescence Saudi J Kidney Dis Transpl 2013;24(2):387-391.
3. Alastair J. Rankin, David Kipgen, Colin C. Geddes, Jonathan G. Fox, Gordon Milne, Bruce Mackinnon and Emily P. McQuarrie; Assessment of active tubulointerstitial nephritis in non-scarred renal cortex improves prediction of renal outcomes in patients with IgA nephropathy, Clinical Kidney Journal, 2018, 1–7.
4. Eduardo Verde, Borja Quiroga , Francisco Rivera, Juan M. López-Gómez; Renal Biopsy in Very Elderly Patients: Data from the Spanish Registry of Glomerulonephritis, Am J Nephrol 2012;35:230–237, DOI: 10.1159/000336307.
5. Emily Joyce , Paulina Glasner, Sarangarajan Ranganathan , and Agnieszka Swiatecka-Urban, Tubulointerstitial Nephritis: Diagnosis, Treatment and Monitoring, Pediatr Nephrol. 2017 April ; 32(4): 577–587. doi:10.1007/s00467-016-3394-5.
6. Mark A. Perazella , Clinical Approach to Diagnosing Acute and Chronic Tubulointerstitial Disease, Adv Chronic Kidney Dis. 2017;24(2):57-63
7. Praga M, González E. Acute interstitial nephritis. Kidney Int. 2010; 77(11):956-61. doi: 10.1038/ ki.2010.89.
8. Agnes B. Fogo, Mark A. Lusco, Behzad Najafian, Charles E. Alpers, AJKD Atlas of Renal Pathology : Chronic Interstitial Nephritis , Am J Kidney Dis. 2017;70(1):e1-e2
9. Korivi D, Billa V, Patel K, Madiwale C. Renal disease masquerading as pyrexia of unknown origin. Indian J Nephrol 2013;23:312-5.
10. Clement Wilfred Devadass, Vijaya Mysorekar V, Gireesh MS, Mahesh E , Gurudev K C, Radhika K, REVIEW OF RENAL BIOPSY DATABASE: A SINGLE CENTRE SOUTH INDIAN STUDY , Int J Med Res Health Sci.2014;3(4):959-966
11. Kamal V. Kanodia, Aruna V. Vanikar, Lovelesh K. Nigam, Rashmi D. Patel, Kamlesh S. Suthar, Dinesh N. Gera, Hargovind L. Trivedi; Nephro Urol Mon. 2015 July; 7(4): e25473.
12. Matthai S M, Mohapatra A, Palak R, Basu G. Immunoglobulin G4-related tubulointerstitial nephritis: A not to be missed diagnosis. Indian J Pathol Microbiol 2017;60:577-80.
13. A. VALLURI , L. HETHERINGTON , E. MCQUARRIE , S. FLEMING , D. KIPGEN , C.C. GEDDES , B. MACKINNON and S. BELL1 , Acute tubulointerstitial nephritis in Scotland , Q J Med 2015; 108:527–532, doi:10.1093/qjmed/hcu236.
14. Vinita Agrawal, Anupama Kaul, Narayan Prasa, Kusum Sharma and Vikas Agarwal, Etiological diagnosis of granulomatous tubulointerstitial nephritis in the tropics, Clinical Kidney Journal, 2015, vol. 8, no. 5, 524–530
15. Richard J. Baker and Charles D. Pusey, The changing profile of acute tubulointerstitial nephritis, Nephrol Dial Transplant (2004) 19: 8–11 , DOI: 10.1093/ndt/gfg464.
16. Chih-Wei Yang, Leptospirosis Renal Disease: Emerging Culprit of Chronic Kidney Disease Unknown Etiology, Nephron 2018;138:129–136, DOI: 10.1159/000480691
17. in a single center of south India: 19 years, experience. Indian J Nephrol 2011;21:250-7.
18. Gianluigi Zaza, Patrizia Bernich, Antonio Lupo, Renal Biopsy in Chronic Kidney Disease: Lessons from a Large Italian Registry , Am J Nephrol 2013;37:255–263 , DOI: 10.1159/000348566.
19. Aleckovic-Halilovic et al. Granulomatous interstitial nephritis: a chameleon in a globalized world. Clin Kidney J (2015) 8: 511–515 .
20. Shah et al. Granulomatous interstitial nephritis. Clin Kidney J (2015) 8: 516–523.
21. Yang J, Liang D, Zhang H, Liu Z, LeW, Zhou M, HuW, Zeng C, Liu Z: Long-term renal outcomes in a cohort of 1814 Chinese patients with biopsy-proven lupus nephritis. Lupus 24: 1468–1478, 2015