Original Article

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Drug Induced Primary Tubulointerstitial Nephritis – A Retrospective Renal Biopsy Study in A Tertiary Care Hospital

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ABSTRACT

Background: Primary Tubulointerstitial Nephritis (TIN) is inflammation of predominantly tubular & interstitial compartment without involving glomeruli and vessels, which may be due to varied etiologies. Drugs are the most common culprit for Primary TIN worldwide. Here we studied a series of primary TIN in renal biopsies at a tertiary care center.

Methods: In this retrospective study of ten year duration, we have studied all cases of primary TIN with history of drug intake. We reviewed these cases for symptoms, etiology and histomorphological features.

Results: A total of 54casesof primary TIN were described. The age range of the patients was 6 to 72 years with mean of 47.8 years. Pedal edema, puffiness of face were the most common symptoms followed by oliguria. Non-Steroidal Anti-Inflammatory (NSAIDs) were found to be the most common group of drugs causing acute TIN resulting in acute kidney injury (AKI). These are followed by antibiotics and ayurvedic/indigenous preparations. Acute TIN was more commonly seen histopathology than chronic TIN.

Conclusion: NSAIDs are most common cause of TIN followed by ayurvedic drugs. Timely diagnosis and withdrawal of offending agent with prompt treatment may help to preserve or improve renal function.

Keywords: *Primary Tubulointerstitial Nephritis, Drug Induced, Renal Biopsy*

Introduction

The term 'Tubulointerstitial Nephritis (TIN)' connotes to inflammatory changes seen predominantly in interstitium & tubules. The history of TIN dates back to 19th century when Biermer first described interstitial inflammation in 1869 and later in 1898, Councilman first reported interstitial edema and inflammation in patients with scarlet fever and diphtheria and termed it as Interstitial Nephritis. TIN may be Primary or secondary. Primary TIN is referred to a condition where inflammation is limited to tubulointerstitial compartment without involving glomeruli and vessels.[1] It is difficult to estimate exact prevalence of TIN, however acute TIN is seen in 0.5-3% of kidney biopsies and seen as prominent finding in 5-27% of kidney biopsies performed for acute kidney injury.[2,3,4]

Previously, infections were the most common etiological agents for TIN, however after the development of antibiotics, rate of infections decreased and antibiotics emerged as predominant cause. Later, in last two to three decades, NSAIDs was the leading cause for drug induced TIN.[2]

As there is paucity of literature of primary TIN in Indian population, we sought to study the drug induced primary TIN to know different etiological agents and to assess histomorphological features with clinicopathological correlation in renal biopsies.

Material and Methods

This is a retrospective kidney biopsy analysis of drug induced TIN, collected from pathological records in the department of Pathology of our tertiary care hospital over a period of ten years. Cases of secondary TIN, a defined underlying glomerular disease or inherited renal disease and renal transplants were excluded from the study. Clinical profile, laboratory investigations, treatment and follow up of patients were obtained from the case records. Histomorphological features of tubular changes like tubular epithelial fraying, denudation, tubular atrophy, necrosis and interstitial changes like edema, inflammation, nature of the inflammatory response, presence of granuloma and fibrosis were noted. These cases were classified as acute, chronic and granulomatous TIN depending on clinical presentation and histomorphological features.

Results

There were total 54 cases of drug induced TIN during ten year period including 32 females and 22 males with the age range from 6 to 72 years. The youngest patient was six year old female and the oldest was 78 year old male with

the mean age of 47.8 years. Predominant distribution of cases was seen in the age group of 41-60 years comprising of 42.9% cases.

Clinical Presentation (Table 2):
The commonest presentation was decreased urine output seen in 72.2% cases followed by pedal edema and puffiness of face in 66.6%. Azotemia was seen in almost all the cases. Proteinuria was also one of the common finding in 16 cases, including five cases of nephrotic range proteinuria.

Etiology:
The most common cause of drug induced TIN was NSAIDS- Non-Steroidal Anti –Inflammatory Drugs (55.5%) followed by antibiotics (22.2%) and ayurvedic or indigenous group of drugs (14.8%). NSAIDs ingestion was seen in patients with orthopedic problems like joint pains, osteoarthritis, osteoma, etc. History Proton pump inhibitors (PPIs) was noted in four cases. Four patients were taking both the drugs - PPIs & NSAIDS. Antibiotics were penicillin, fluoroquinolones, cephalosporin group of drugs and rifampicin. The duration, for which all these drugs were taken, was variable from five days to four years. This duration was more in months to years in cases of NSAIDs, ayurvedic drugs and PPIs whereas it was generally of few days in cases of antibiotics.

Histopathological diagnosis (Table 3)
Based on histomorphological features, all cases were classified as acute, chronic and granulomatous TIN. Acute TIN was most commonly seen in 42 (77.7%) patients followed by chronic TIN in 11 (20.3%) cases. There was a single case of Granulomatous TIN.

Leucocytic infiltrate of lymphocytes, plasma cells and neutrophils was the most common finding, seen in almost 78% patients. Neutrophils were predominantly seen in acute TIN. Lymphocytes and plasma cells were predominant in chronic TIN. Prominent tubular features were tubular damage, atrophy, and necrosis. Occasionally tubulitis was also seen where inflammatory cells were invaded the tubular epithelium. It is stated that eosinophils are the valuable finding in drug induced particularly NSAIDS, but only 4 cases showed eosinophils.

Table 1: Various drugs causing TIN.

Drugs	No. of cases	Acute TIN	Chronic TIN	Granulomatous TIN
NSAIDs	30	24	05	01
Antibiotics	12	08	04	-
Ayurvedic/indigenous	08	06	02	-
PPIs	04	04	-	-

Table 2: Clinical presentation in drug induced TIN.

Clinical presentation	No. of cases
Decreased urine output	46
Pedal edema, puffiness of face	42
Fever	08
Dysuria	05
Others	06

Table 3: Histological features in drug induced TIN.

Histological features	No. of cases
Tubular features	
Tubular damage	36
Tubular atrophy	10
Tubular Necrosis	16
Tubulitis	02
Interstitial features	
Leucocytic infiltrate	24
Interstitial Edema	24
Interstitial fibrosis	04
Infiltrate showing eosinophils	02
Granuloma	01

Discussion

The frequency with which primary TIN affects the kidney is difficult to determine. Retrospective studies of renal biopsies have revealed that 8-22% patients with renal failure have primary TIN.3 In the study by Wilson DB et al., 13% biopsies of patients with acute renal failure revealed acute TIN and in none of them this diagnosis was clinically suspected. [4,5] In another study by Eapen SS et al. acute TIN was diagnosed in 29 cases (13.34%). 5

We noted a wide age range from 6 year to 72 years. Majority (42.5%) of our cases occurred in the age group of 31-50 yrs. Most of these patients (60%) had NSAIDs & PPIs induced TIN. This may be attributable to the common age related problems started in this age group like joint pains due to osteoarthritis, rheumatoid arthritis, etc.

Clinical Presentation:

The most common presentation in our study was decreased urinary output (85.4%) followed by pedal edema and/or puffiness of face (77.4%). As oliguria is one of the common indications for which renal biopsies are being done; we found such a high incidence of oliguria in these patients.

The classic triad of drug induced TIN of low grade fever (70-100%), fleeting maculopapular skin rash (30-50%) and mild arthralgia (15-20%) is not invariably present. The full triad was noted in one third of cases of methicillin induced acute TIN, but only in 5% of cases of acute TIN in general. In our study, skin rash was not present in any case; while 17 of 54 (31.4%) cases had history of fever.

We noted proteinuria in 18.5% cases, out of which nephrotic range proteinuria was 11.1%. Proteinuria is generally mild and rarely exceeds 2gm/day except in NSAIDS induced TIN which show nephrotic range proteinuria in 10-12% cases. NSAIDS cause minimal change disease hence nephrotic range proteinuria is seen in these cases. [6,7]

Eosinophiluria is also the characteristic feature seen in drug induced TIN with 40%-60% sensitivity and 38% positive predictive value.[8] We could detect eosinophiluria in only two cases.

The commonest histomorphological type in our study was acute TIN (74%) followed by chronic TIN (16.8%) and granulomatous TIN (9.2%).

Two studies published in 2000 and 2004 that included a total of 124 patients with AIN found NSAIDs to be the most common culprit class of drugs, whereas a more recent study published in 2008 of 61 patients and 2014 of 134 patients with drug-induced AIN found antibiotics to be the most common cause. [2, 9, 10, 11]

Literature survey indicates that drug induced primary TIN is most often caused by antibiotics. Other drugs responsible are NSAIDS, rifampicin, proton pump inhibitors, lithium, and diphenylhydantoin.

In our study, 30 patients gave history of consuming NSAIDS thus making it, the most common cause amongst drug induced TIN. Twelve out of 30 patients were female taking NSAIDS. These patients were on treatment of NSAIDS for complaints like joint pains due to osteoarthritis and rheumatoid arthritis, backache and generalized bodyache since few days to 4 years. Various studies have emphasized that NSAIDS induced TIN may occur in patients consuming NSAIDS for variable duration ranging from few days to many years. A variety of NSAIDS like salicylates, aspirin, diclofenac, indomethacin, ibuprofen, piroxicams, nimesulides, and COX-2 inhibitors etc. are known to be associated with renal damage.[6, 7]

The histological changes in NSAIDS induced TIN were both acute and chronic. We noted 24 cases of acute TIN and five cases of chronic TIN. One case also showed granulomatous TIN.

It is postulated that NSAIDs induce TIN by inhibiting the synthesis of vasodilatory prostaglandins PGI2 and PGE2 resulting in severe renal vasoconstriction and consequent ischemia. Acute interstitial nephritis may be related to delayed hypersensitive response to NSAIDS. Granulomatous response in NSAIDS induced TIN may be secondary to cell mediated immune response. [6, 7]

It is interesting to note that NSAIDs intake may also result in severe proteinuria and nephrotic range proteinuria was noted four of 30 cases (13.3%) of NSAIDs induced TIN. In these cases, glomeruli were normal and showed no alterations. Three of these cases with severe proteinuria showed acute TIN changes. The remaining one showed chronic TIN. The incidence of NSAIDs induced nephrotic range proteinuria in literature is seen in 10-12% cases. Pathogenic mechanisms of NSAIDs associated nephrotic range proteinuria is due to release of lymphokines and cytokines from interstitial inflammatory cells resulting in increased glomerular permeability. [6, 7]

Interstitial eosinophilic infiltrate is a well-known histological feature of NSAID induced TIN. However we noted them in only four cases. Paucity of interstitial eosinophils in drug induced TIN was also noted in the study by Bender et al. [12]

We noted ayurvedic and indigenous/herbal group of drugs in significant number of eight cases (14.8%). These ayurvedic and indigenous drugs may contain nephrotoxic

substances like heavy metals and they are commonly used by people for the chronic diseases which do not respond to routine treatment. There are few case reports in literature on these drugs.[13]

We had 12 cases of antibiotic associated TIN. These patients had been taking antibiotics for the duration ranging from five days to ten days. These antibiotic were ampicillin, gentamycin, rifampicin and fluoroquinolones, cephalosporins. Analysis of cases reported in the literature noted that antibiotic associated TIN is more common than NSAIDS induced TIN in contrast to our study. The pathogenetic mechanism of developing TIN due to antibiotics is generally an idiosyncratic hypersensitivity reaction, with local activation of drug specific T cells and release of cytokines.[14]

We noted rifampicin associated TIN in three cases giving an incidence of 16.6% of all drug induced TIN. All our cases were on intermittent rifampicin for tuberculosis and leprosy and had been receiving the treatment for minimum 6 months. It is well noted that rifampicin induced TIN usually occur following intermittent dosage for several years in the study by Flynn CT et al and Mutthukumar T et al. Rifampicin induced TIN is thought to be due to antibodies induced mechanism or rarely may be due to intravascular hemolysis resulting in hemoglobinuria and tubular casts.[15, 16]

Drugs causing granulomatous TIN include NSAIDS, penicillins, sulphonamides, carbapenams, allopurinol, furosemide, etc. Clinical history of drug intake is extremely important in drug induced granulomatous TIN. It is to be noted however that interstitial granulomas in the kidneys are also associated with tuberculosis, Wegener's granulomatosis, sarcoidosis, and other infections. Hence special stains for organisms and study of multiple biopsy levels for multiple granulomas around blood vessels and tubules (as seen in Wegener's) are essential. In correlation with this clinical history is essential before the diagnosis of drug induced TIN is diagnosed.[17,18]

One of the limitation of this study is that we have selected only biopsy proven primary TIN in this retrospective study. Renal biopsy is commonly done in patients with more severe & long duration AKI and not all AKI patients, hence we couldn't get exact prevalence of primary TIN.

Conclusion

NSAIDs and ayurvedic/indigenous drugs are still more prevalent cause of TIN in adult population in India as compared to antibiotics and PPIs which are more common in western world. Unwarranted and uncontrolled drug intake for longer period may cause TIN resulting in kidney failure which, if diagnosed and promptly treated at early stage, may be reversible. Hence high clinical suspicion, detailed history of drug intake and early biopsy are needed for accurate identification and diagnosis so that early withdrawal of potential offending agents and prompt treatment help to preserve or recover renal outcome.

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