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The Eye and Kidney Connect: Tubulointerstitial Nephritis and Uveitis Syndrome

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Abstract
Tubulointerstitial nephritis with uveitis syndrome (TINU) and is a largely an under diagnosed entity. The renal course is independent of the ocular disease. This article highlights the course, presentation, diagnosis, pathogenesis and the current treatment modalities offered for the disease.

Keywords: Eye, Kidney, Tubulointerstitial Nephritis, India

Introduction
Uveitis in association with acute tubulointerstitial nephritis is a relatively rare entity. It is commonly known as tubulointerstitial nephritis with uveitis syndrome (TINU) and is a largely an under diagnosed entity. It was first described by Dobrin and associates in 1975. Only 200 cases have been described in literature since its first description, 45 years ago. It comprises of patients with acute interstitial nephritis which can be drug induced, infectious or idiopathic [1]. About 10- 15 % of individuals with acute renal failure are patients with acute interstitial nephritis [2, 3]. However, it may represent up to a third of bilateral acute-onset anterior uveitis in patients younger than 20 years [4-8].

Presentation
Patients with TINU most commonly present with complaints of eye pain and redness (77%), decreased vision (20%), and photophobia (14%) [6]. The presentation is usually bilateral, acute onset non-granulomatous anterior uveitis [4, 6, 9]. Due to less awareness of the syndrome among ophthalmologists and under reporting of the disease the ocular features are less well defined than the renal disease. These findings include anterior chamber cells and flare, conjunctival injection, fine keratic precipitates, posterior synechiae, cystoid macular edema, disc edema (especially in the young), elevated intraocular pressure, and cataract [4, 6, 10]. Granulomatous keratic precipitates has also been reported in two cases [11, 12]. One of these two cases also had iris busacca nodules [12].
However, the renal course of the disease is independent of the ocular disease. Ocular findings in some cases preceded, in some occurred concurrently and in some developed after the onset of interistial nephritis [4, 6]. Tubulointerstitial Nephritis can present with systemic symptoms like fever, weight loss, and fatigue and malaise. Other common initial symptoms were anorexia, weakness or asthenia, abdominal or flank pain, and arthralgias or myalgias [6]. The patient may also present with rash [9].
TINU can occur at any age. However, the median age reported in literature is 15 years ranging from 9 to 74 years of age [6]. Awareness among clinicians to the syndrome has led to earlier diagnosis of this entity. Thus, the median age of diagnosis has shifted from 20years in the 1990s to 15 years post the 90 era.
Females were thought to be more predisposed to the disease than males, with a ratio of 3:1. However, in the recent literature, there has been increasing reports of male patients with TINU syndrome, and therefore no gender predilection [4, 6, 7, 9, 13]. No ethnic preponderance has been noted either [6].
There have been several human leukocyte antigens (HLA) associated with TINU syndrome. However, these studies had limited sample size and significant variations in the studied population [14-20]. Mandeville *et al* suggested a common association of HLA-A2 and HLA-A24 in Japanese subjects with this syndrome [6]. These antigens as reported by Matsumoto *et al*. was commonly present in the healthy Japanese controls [20]. Mackensen *et al*., in a European population found HLA-DRB1*0102 allele (RR = 14.3) and HLA-DRB1*08 (RR = 4.0) allele associated with patients with sudden-onset, anterior bilateral uveitis but without TIN than TIN without uveitis [16].

Reddy *et al*. thereafter reported HLA-DRB1*01-HLADQB1*05 haplotype (high risk haplotype for TINU in the Levinson study [15]) in 14/15 paediatric patients with unexplained panuveitis with no evidence of interstitial nephritis, again raising the possibility that some of these alleles are risk factors for uveitis rather than specifically for TINU [19].

In most recent literature, TINU patients, apart from the above manifestations have presented with other rare descriptions of posterior findings such as small hypopigmented chorioretinal scars [21, 22], delayed multifocal choroiditis [23], acute posterior multifocal placoid pigment epitheliopathy [24], choroidal neovascular membranes [25], and neuroretinitis [26, 27].

It must be remembered that TINU is a diagnosis of exclusion. It can present with a large spectrum of signs, non-granulomatous anterior uveitis being the most predominant.

Diagnosis

TINU has been identified in approximately 1/3 of patients less than 20 years of age with bilateral sudden-onset anterior uveitis [4].

It can be labeled as "Definitive", "Probable" and "Possible" TINU syndrome depending on the criteria published in 2001 [6]. The diagnosis of TINU syndrome requires the presence of both uveitis and acute interstitial nephritis (AIN), without any other condition that can cause either AIN or uveitis.

Typical uveitis was defined as bilateral anterior uveitis with or without intermediate uveitis or posterior uveitis diagnosed two months prior or 12 months after AIN. While atypical uveitis was defined as unilateral anterior uveitis or intermediate uveitis or posterior uveitis or a combination of these categories 2 months before or 12 months after AIN.

A definitive diagnosis of AIN is on the basis of histopathological confirmation or extensive clinical evidence of the disease (abnormal renal function; abnormal urinalysis; and history of acute systemic illness that lasted at least 2 weeks, characterized by various signs, symptoms and laboratory findings.) [6]

Definitive TINU syndrome - AIN (diagnosed histopathological /complete clinical criteria) and typical Uveitis.

Probable TINU syndrome- AIN diagnosed histopathologically and atypical uveitis or AIN diagnosed clinically (incomplete criteria) and typical uveitis

Possible TINU syndrome- AIN diagnosed clinically (incomplete criteria) and atypical uveitis [6].

The laboratory investigations in a patient suffering TINU syndrome are [4, 6]:

1. Deranged renal function tests- These include elevated blood urea nitrogen (BUN) and serum creatinine levels and a low creatinine clearance level. However, renal function typically returned to normal or near-normal values upon recovery.
2. Urinanalysis often shows low grade protienuria. Microscopic hematuria and urinary leukocytes may also be found in a few cases. A urinary beta-2 microglobulin level, a marker for interstitial nephritis, is usually elevated, often to markedly high levels [5-8]. Urinary eosinophils, pyuria or hematuria without infection, urinary white cell casts, or normoglycemic glucosuria may also be present.

Other nonspecific findings indicating systemic inflammation are an elevated ESR, an elevated serum IgG and circulating immune complexes in some patients [6].

Differential Diagnosis

Uveitis and interstitial disease can be found together in a number of diseases. Various immunologically mediated syndromes such as collagen vascular disorders (systemic lupus erythematosus, Wegener's granulomatosis, Behchet and Sjo¨gren syndromes), sarcoidosis, and infectious diseases (syphilis, toxoplasmosis, brucellosis, tuberculosis, infectious mononucleosis, leprosy and yersinia enterocolitica, cytomegalovirus, herpes simplex virus, Chlamydia psittaci infection) have both these components. However, many of these diseases do not present with acute anterior uveitis alone which is the most common presentation of TINU. They also present with different characteristic systemic signs and symptoms which make them readily distinguishable from TINU.

Since the pediatric population does not commonly present with pulmonary symptoms, Sarcoidosis can be particularly difficult to rule out. Granulomas are an uncommon finding in patients with isolated interstitial nephritis [28], hence a renal biopsy is very helpful. They are the defining lesions in sarcoidosis and an exception in cases with TINU. Approximately 20%of patients with Sarcoidosis will develop granulomatous interstitial nephritis along with ocular symptoms [29, 30]. Mandeville *et al* [6] found only 15 patients (13%) had evidence of non-caseating granulomas on renal biopsy out of 118 biopsied TINU cases before 2001, and nearly half of them had evidence of granuloma in the liver and the bone marrow. Hence to differentiate sarcoidosis from TINU a renal biopsy is a must and the evidence of granulomas elsewhere in the body should weigh more towards Sarcoidosis than TINU. We must remember TINU is a diagnosis of exclusion.

Pathogenesis

The pathogenesis of TINU has been associated with a wide variety of drugs, genetic mutations, infectious agents, autoimmune diseases, toxins or it being idiopathic [5, 6, 31, 32].

Drug induced interstitial nephritis is thought to be an immune mediated allergic reaction [31]. TIN occurs only in a small proportion of individuals taking a certain medication which can recur after re-exposure to the same drug, they manifest as a hypersensitivity reaction which is not dose – dependent and eosinophils are often present on renal biopsies thus substantiating the above view [28]. Many drugs have been implicated in the precipitation of TINU, beta-lactam antibiotics and non-steroidal anti-inflammatory (NSAID) drugs being the most common. Drug-induced TIN has been noted in 7-27 % of adult patients with unexplained non-oliguric or oliguric acute kidney injury [28].

Both humoral and cellular immune mechanisms have been promising areas of interest in the pathogenesis of TINU.

The characteristic findings consistent with tubulointerstitial nephritis in patients with TINU syndrome are interstitial edema and infiltration by inflammatory cells with relative sparing of the glomerular and vascular structures [11, 33-35]. The inflammatory infiltrate in kidneys affected by TINU syndrome consists primarily of mononuclear cells, including lymphocytes, plasma cells, and histiocytes. The majority of lymphocytes were found to be T-lymphocytes expressing IL-2 receptors, indicating an activated state [36]. Multiple population-based studies have suggested a strong link between TINU and certain class II HLA [6, 14-20]. They point

towards cellular immunity which is widely believed to be the central to the pathogenesis of TINU.

Circulating immune complexes in a patient with TINU, suggesting a humoral mechanism first came to light in 1985 [37]. Serologic evidence of auto-antibodies has been found in several patients with TINU syndrome, including anti-nuclear antibodies [11, 38-41] rheumatoid factor [1, 42-43], anti-DNA antibodies [40], anti-cardiolipin antibodies [11], and cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) [44-46] Conz *et al*, in 2001, described a 48-year-old woman who demonstrated a transiently reduction in C4 concentration., during the acute phase of TINU [47]. A study in 2008, found that serum from TINU patients reacted against healthy kidney, retinal, and ciliary tissue [48].

In another study serum from active patients with isolated acute interstitial nephritis (AIN, idiopathic or drug-related), ANCA-vasculitis, IgA-nephropathy, minimal change disease, Sjogren's syndrome, or amyloidosis and healthy subjects were tested. They found the titres of anti-mCRP to be significantly higher in the patients with TINU syndrome (9/9,100%) but it was not limited to the group. AIN (4/11, 36%) was the only other disease entity with more than two patients with elevated titres suggesting a disease specific relevance. Anti–mCRP was interestingly not present in any other form of kidney disease other than interstitial nephritis. The authors also showed an increase in the mCRP (in addition to increased serum Anti-mCRP) found by immunohistochemistry in kidney biopsies when compared to normal kidneys. It was also found in ocular tissue (iris and ciliary body collected at the time of trabeculectomy) by immunohistochemistery [49]. mCRP was colocalised in normal tissues in patients with active TINU suggesting a link between this protein and the disease pathogenesis [49, 50]. mCRP is the dissociated monomer of the parent C-reactive protein (acute phase reactant pentamer). It has no tissue specific role but is involved in the activation and regulation of the complement pathway. Another study showed a recurrence of TINU in a patient of renal allograft similar to the native disease suggesting the target renal antigen is a wild-type (not genetically aberrant) endogenous protein [51].

An interesting insight into the pathogenesis of the disease whether the organs involved share a common target or is it one primary organs being affected first and in turn inciting a cascade of events, thus involving the other organ. Evidence says that kidney is the primary target organ and it is hypothesized that once exposed to the inciting agent it stimulates a HLA class II response which targets a common antigen in both the organs. This antigen could be an acute phase reactant or a native protein that shares a common epitope in the uvea and renal interstitium. However, more studies are required to validate it.

Treatment

The prognosis of patients with ocular and renal symptoms is usually good when treated appropriately and promptly. Cases with ocular disease presenting as anterior uveitis are most commonly treated with topical steroids and cycloplegic agents. A few patients have been treated with periocular injection of corticosteroids [52]. Systemic corticosteroids are reserved for the severe (bilateral, intermediate, or posterior disease), chronic and recurrent cases of ocular disease. Maintaining quiescence in the eye can be challenging with nearly 50% of patients recurring after corticosteroid withdrawal [6]. Earlier studies also underestimated the need for chronic therapy as they had short follow up periods and/or were managed by non-uveitis specialists [21].

Immunomodulatory agents like azathioprine [11, 53, 54], methotrexate [11, 55], cyclosporine [11, 53, 56], and mycophenolate mofetil [52] have been used in patients to treat uveitis that was not responding to systemic corticosteroids or out of concern for the systemic or ocular toxicities of corticosteroids in the young population who are more prone to a chronic course. This was further substantiated by a recent study that followed 9 TINU patients for a median of 3 years after their initial diagnosis. There was a recurrence in 56% of patients after tapering of the corticosteroids, thus prompting the authors to use immunomodulatory therapy (IMT). The authors found a significant decrease in uveitis recurrence in patients with adequate control for at least 12 months (mean: 29.5 months; range: 13-40 months) [21]. They followed an aggressive inflammatory control and routinely started IMT early in the disease.

Patients could also present with only the kidney disease. Severe cases could also need IMT during their course of treatment. Earlier literature emphasized that patients with acute interstitial nephritis would resolve spontaneously once the inciting agent (drug or infection) was removed. Systemic corticosteroids were reserved generally for cases with progressive renal failure [6, 8, 41]. However later there have been reports of cases with continued nephritis on biopsies after short term pulse corticosteroid therapy [57, 58]. Hence it was substituted with longer therapy in selected cases. The duration of therapy was also taken into consideration. No consensus has been established regarding the dose or duration of the systemic steroid therapy. In one series, three patients with prompt therapy showed improved short-term urinary β2M levels and inflammatory signs on repeat biopsy while one with a delayed treatment progressed to permanent renal damage with persistent high levels of β2M and renal inflammation [59]. However, in a retrospective of 60 adults suffering from TIN from different etiologies showed no difference in the serum creatinine levels at 1, 6 and 12 months in the group being treated with corticosteroid versus the ones on supportive care [60]. Similar results were seen in prospective study in patients suffering from TIN or TINU with comparable renal parameters at 6 months. But the patients on corticosteroids showed a quicker recovery from TIN, particularly the ones with more severe disease [61].

Hence, both ocular and renal disease warranty prompt diagnosis, removal of the offending agent, early and aggressive control of inflammation. This should warranty at least a 12-month period of quiescence before withdrawal of treatment whether steroids or IMT. Ophthalmologist should always treat in collaboration with our nephrology colleagues.

Conclusion

TINU is a relatively underdiagnosed entity. Ophthalmologists should have a high index of suspicion for patients (pediatric and adults) presenting with acute anterior uveitis, with the common entities ruled out. It should be kept in mind that TINU is a diagnosis of exclusion. Patients should be managed in conjunction with the nephrology department. The ocular as well renal conditions have a good prognosis when treated promptly and adequately. The uveitis is known to recur on decreasing the steroids hence patients should be on long follow up with the ophthalmologist and on immunomodulatory therapy with

close monitoring if required.

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