The Syndrome of Tubulointerstitial Nephritis With Uveitis (TINU)

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The syndrome of tubulointerstitial nephritis and uveitis (TINU) is a multisystemic autoimmune disorder that may occur in response to various environmental triggers, including drugs and microbial pathogens. Evidence exists of HLA antigen–related genetic predisposition to developing TINU. The resulting inflammation affects chiefly the ocular uvea and renal tubules, although other organs may be involved. TINU is uncommon; only about 200 cases are on record since its original description 40 years ago, although it is possible that new ones are no longer being reported. Although its incidence is highest in children and adolescents, all ages may be affected. Renal and ocular inflammation may be clinically severe and persistent, but the prognosis for the majority of patients with TINU is favorable. Owing to its low prevalence, no standard therapeutic protocols have been established, but most reported cases have been treated with corticosteroids or other immunomodulatory agents. TINU has many features in common with sarcoidosis, the main clinical entity from which it must be distinguished. This article begins with an illustrative case vignette, followed by an overview of the syndrome and current theories regarding its pathogenesis.

Complete author and article information provided before references.

Am J Kidney Dis. 72(1): 118-128. Published online February 8, 2018.

doi: 10.1053/j.ajkd.2017.11.013

Case Vignette: *A 30-year-old previously healthy woman developed an upper respiratory tract infection associated with mild conjunctivitis. Her symptoms abated with no medication after a week, but 1 month later, she was found at a routine medical checkup to have a serum creatinine concentration of 1.8 mg/dL, corresponding to estimated glomerular filtration rate of 44 mL/min/1.73 m^2 by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Two years previously, her creatinine concentration had been 0.8 mg/dL. Her medical history was remarkable only for dry eyes, not believed to represent Sjögren syndrome, and childhood asthma. Physical examination was normal except for elevated blood pressure (190/110 mm Hg), which had previously been normal. Urinalysis results were unremarkable and her kidneys appeared normal by sonography. She was referred to a nephrologist.*

*Two weeks later, the patient experienced burning in her eyes associated with blurring of vision, and bilateral acute uveitis was diagnosed. HLA typing revealed DQA1*01 and 02:01 and DQB1*02:02 and 05:01 genotypes. Percutaneous kidney biopsy revealed an active TIN with predominantly lymphocytes (Fig 1) and a mild degree of nephron loss, including 8% glomerulosclerosis and 5% to 10% interstitial fibrosis. No granulomas or immune complexes were present and lymphocytes and plasma cells showed no predominant immunoglobulin G (IgG) subclass or light chain restriction.*

The patient was treated with prednisone (1 mg/kg/d), lisinopril, and topical ophthalmic prednisone. Over the ensuing year, her uveitis resolved and serum creatinine concentration decreased to 0.9-1.0 mg/dL. Prednisone dosage was slowly tapered and her blood pressure improved, allowing discontinuation of lisinopril treatment.

Introduction

Only 40 years have passed since the syndrome of tubulointerstitial nephritis (TIN) and uveitis (TINU) was first described by Dobrin et al.[1] TINU is uncommon, which may explain the relative recency of its recognition. Nevertheless, TINU may hold important clues to understanding the pathogenesis of other multiorgan inflammatory conditions. Although the TINU record now comprises many case reports and several reviews,[2-7] the preponderance of this information resides in the ophthalmologic literature. Furthermore, the most comprehensive review to date, that of Mandeville et al,[7] is already 15 years old. The purpose of this article is to offer clinicians an updated summary of the existing TINU knowledge base, beginning with a case illustrating many of the clinical features of this interesting syndrome.

Epidemiology

The incidence of TINU is unknown, but a few epidemiologic generalizations can be made. Case reports have emanated from all parts of the globe and involved patients of all races.[8-41] TINU most often occurs in children, although many adult cases have been recorded,[18,20,23-26,30,31] including some of patients older than 60 years.[24-26] Female patients outnumber males by a factor ranging from 2.5 to 5.[28,29] TINU has been reported to account for <2% of uveitis cases seen in ophthalmology clinics[5,6] and <15% of cases of acute TIN in a pediatric renal care center.[8] As a practical consideration, it should be mentioned that it is unclear how often children evaluated for de novo uveitis are referred for renal evaluation, or vice versa. Between 1975 and 2015, the rate at which TINU cases were reported increased steadily. Although this increase could reflect a natural uptick in its incidence, growing recognition is more plausible. It would therefore seem premature to relegate TINU to the category of extremely rare conditions.

Etiologic Factors

Evidence suggests that TINU arises from a confluence of host susceptibility factors and environmental triggers.

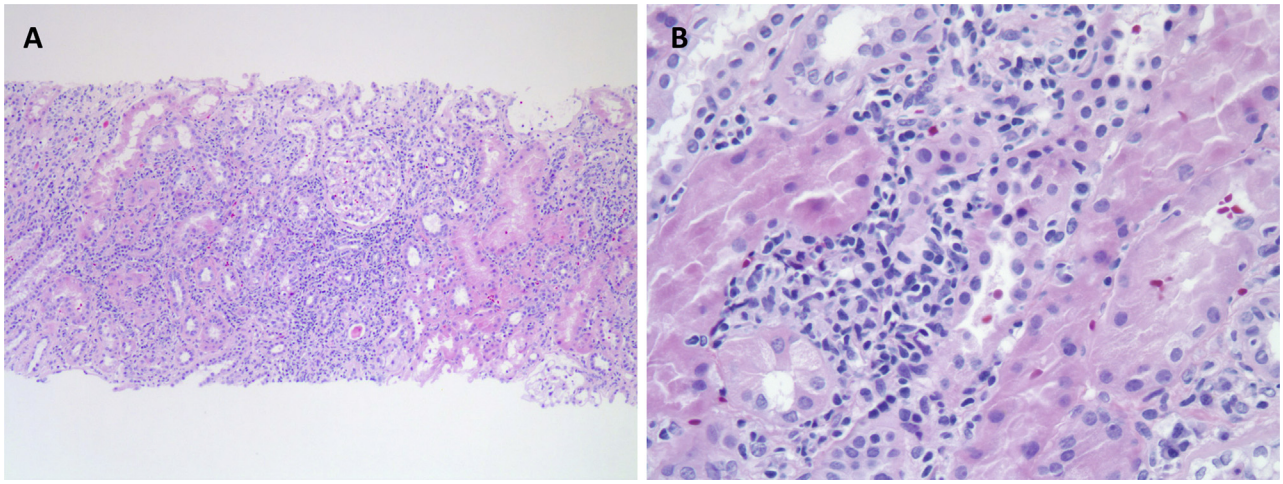

Figure 1. Histopathologic photomicrographs from ultrasound-guided percutaneous needle biopsy of the left kidney of the patient described in the case vignette. (A) Renal cortex contains extensive interstitial inflammation separating apart tubules without granulomas. Glomeruli shown are viable and not directly affected by inflammation (light microscopy; hematoxylin and eosin [H&E]; original magnification, ×100). (B) The infiltrate is composed predominantly of lymphocytes with several plasma cells, occasional monocytes, and only isolated eosinophils. Some lymphocytes are directly in contact with tubular epithelial cells (tubulitis), with associated signs of tubular injury, including attenuation and sloughing of the tubular epithelium (light microscopy; H&E; original magnification, ×400).

Infectious Triggers

TINU usually presents following a constellation of flu-like symptoms including fever, malaise, anorexia, arthralgia, and weakness. Because positive microbial cultures and localizing signs of infection are generally absent, TINU is unlikely to represent an infectious illness per se, but rather an inflammatory response to an external trigger, analogous to reactive arthritis. TINU has been diagnosed in a patient with hepatic tuberculosis,[37] patients with serologic evidence of recent Epstein-Barr virus infection,[38,39] a patient with serologic evidence of active chlamydial infection,[40] and 2 carriers of human T-lymphotropic virus type 1.[41] Fujita et al[42] diagnosed TINU in a 14-year-old boy with acute *Campylobacter jejuni* enteritis and pre-existing IgA nephropathy. In none of these cases has a direct causal relationship been established between the infecting pathogen and the development of TINU. Voghenzi et al[43] reported the development of acute mastitis in a 14-year-old girl during the course of TINU. The authors note that her breast inflammation may have represented a new manifestation of the same process occurring in the patient's eyes and kidneys or an altogether unrelated process.[43] Because mastitis is generally a bacterial infection, it may also be that the breast infection, initially subclinical, incited the oculorenal autoimmune response.

Chemical and Pharmacologic Triggers

In some case reports, TINU is attributed to a pharmacologic exposure, including nonsteroidal anti-inflammatory drugs,[23,30,44] a mixture of paracetamol and codeine phosphate,[45] and the herbal formulation Goreisan.[31] In none of these reports has the causal relationship been proved, and the possibility remains that the medication in question may have been taken to treat the prodromal symptoms of already evolving TINU. Whereas nonsteroidal anti-inflammatory drug–induced acute interstitial nephritis is a well-recognized entity, the case reports in the literature differ from TINU in manifesting heavy proteinuria and no apparent association with uveitis.

Genetic Susceptibility

One of the more intriguing pathogenetic aspects of TINU is evidence of genetic associations. At least 4 reports document the occurrence of TINU in multiple members of a single family. In one such report, a mother and her son were affected.[46] The other 3 involved sibling pairs,[47-49] including a pair of monozygotic twin boys.[49]

The search for genetic susceptibility markers, as with other autoimmune diseases, has to date focused on HLA genes. The results of these investigations are summarized in Table 1. In some, HLA typing was performed in small cohorts of patients with TINU and shared alleles identified, with the presumption that these may represent TINU risk alleles.[47,48,50-52] In other generally larger cohort studies, the frequency with which certain HLA alleles occur in the cohort was compared with their frequency in case-control groups or in a normative population database.[53-56] Based on sample size and the strength of their controls, 3 of these studies are particularly informative. Perasaari et al[54] genotyped 31 patients presenting with TIN, 20 of whom had TINU. Haplotypes DRB1*14, DQA1*01:04, and DQA1*04:01 were statistically more prevalent among the whole cohort than in an apparently healthy reference population. In addition, the subset of patients with TINU showed an increased prevalence of DQA1*01:04 and DRB1*14.[54] Levinson et al[55] found an increased frequency of the DRB1*0102 allelic variant in 18 patients with TINU, as well as associations with DQB1