A case of adult-onset tubulointerstitial nephritis and uveitis syndrome presenting with granulomatous panuveitis

Kemal Tekin1*, Yasemin Ozdamar Erol2, Olcay Kurtulan3, Dilek Ertoy Baydar3

Abstract:
The tubulointerstitial nephritis and uveitis (TINU) syndrome is a rare disorder that is probably underdiagnosed in clinical practice. Ocular involvement in TINU syndrome not only presents with the nongranulomatous anterior uveitis in 80% of patients but also manifests as intermediate, posterior, or panuveitis. This case report mentions an adult male patient who presented with granulomatous iridocyclitis with panuveitis and mild renal insufficiency. Workup for connective tissue and infectious diseases was negative for the patient. He was diagnosed with TINU syndrome based on the findings of renal biopsy. Both the uveitis and nephritis promptly responded well to steroid treatment, and there was no recurrence during the follow-up of 24 months.

Keywords:
Granulomatous iridocyclitis, tubulointerstitial nephritis, uveitis

Introduction

The tubulointerstitial nephritis and uveitis (TINU) syndrome is a rare disorder which was first described in 1975 by Dobrin et al., in two adolescent female patients with concomitant acute interstitial nephritis, anterior uveitis, and bone marrow granulomas. In 2001, Mandeville et al. reviewed 133 published cases with TINU syndrome showing a median age at presentation of 15 years with a 3:1 female-to-male predominance. Since then, few small case series and reports in the nephrology and ophthalmology literature tried to better explain the clinical and histopathologic characteristics of this inflammatory disease. The diagnosis of TINU syndrome is based on the presence of both acute interstitial nephritis and uveitis in the absence of any other disease which may cause either manifestation. A definite diagnosis requires the findings of consistent histopathologic changes on renal biopsy. TINU syndrome typically presents with an acute-onset bilateral nongranulomatous anterior uveitis.

Herein, we report the long-term follow-up of an adult patient who presented with acute granulomatous iridocyclitis and panuveitis associated with constitutional symptoms. He was diagnosed with TINU syndrome based on renal histopathologic findings and successfully treated with systemic and topical steroids.

Case Report

A previously healthy 49-year-old male was admitted with a 1-month history of extreme fatigue, anorexia, and nearly 10 kg weight loss. He had also blurred vision for 15 days. He did not have any significant
past medical or ocular history as well as family history, and there was no history of any drug use. On the first physical examination, his height was 172 cm (75 percentile), weight was 55 kg (3–10 percentile), and blood pressure was 130/90 mmHg. Other physical examination findings were unremarkable. On ocular examination, the best-corrected visual acuity (BCVA) was 20/30 in the right and 20/25 in the left eyes. Intraocular pressures were 9 mmHg and 11 mmHg for the right and left eyes, respectively, and there was no evidence of an afferent pupillary defect in either eye. Slit-lamp examination of the right eye showed medium granulomatous keratic precipitates in the Arlt’s triangle, 3+ cells in the anterior chamber [Figure 1], and 2+ cells in the anterior vitreous. In the left eye, there were granulomatous keratic precipitates, 2+ cells in the anterior chamber, and 1+ cells in the anterior vitreous. Dilated fundus examination revealed 1+ vitreous haze in both eyes and a few snowball opacities, which were distributed in the inferior quadrant in the right eye [Figure 2]. His complete blood count findings showed 9.2 g/dL hemoglobin (normal [N]: 14–17), 27.6% hematocrit (N: 41%–50%), and white blood cell count 8600 µL (N: 4000–11,000) with 75% neutrophil, 20% lymphocytes, 4% monocytes, and 1% eosinophils. The erythrocyte sedimentation rate was 110 mm/h (N: 0–22), and C-reactive protein was 1.63 mg/dL (N: <0.05). His renal laboratory findings were compatible with mild renal insufficiency as follows: serum creatinine was 171 µmol/L, blood urea nitrogen was 6.7 mmol/L, and uric acid was 152 µmol/L, all of which were elevated. Arterial blood gas analysis revealed pH 7.40 (N: 7.38–7.42), pCO₂ 38 mmHg (N: 38–42), and HCO₃⁻ 22 mEq/L (N: 22–28). Serum immunoglobulin (Ig) G, IgM, and IgA levels were within the normal limits. Similarly, serum complement levels were also normal. Moreover, antinuclear antibody, anti-DNA antibody, rheumatoid factor, and antineutrophil cytoplasmic antibody were negative. Viral and brucellosis, chlamydia, toxoplasma, and syphilis serologies were all unremarkable. Quanti-FERON test was negative. Serum angiotensin-converting enzyme (ACE), lysozyme levels, and chest X-ray were also normal. Urinalysis showed a pH of 5.1, specific gravity 1019, glucose 102 mg/dL, protein 24 mg/dL, 6–8 red blood cells/high-power field, and β2-microglobulin was 22 mg/L (N: <0.10). The urinary total protein/creatinine ratio was elevated, 1.5 (N: <0.2). Urine protein analysis showed a tubular pattern, and the creatinine clearance was approximately 50 mL/min. Due to a normal urinary tract ultrasonography, renal biopsy was performed. The biopsy specimen showed diffuse interstitial inflammatory infiltrate with tubulitis, consistent with acute TIN [Figure 3]. Majority of inflammatory cells were CD4-positive T lymphocytes (T helper cells), although accompanying CD8 (+) T-cells, plasmacytes, and scattered eosinophils were also present [Figure 4]. Granuloma formation was not seen. Glomeruli showed...
nonspecific changes secondary to TIN. In addition, immunofluorescence microscopy revealed negative staining for IgG, IgA, IgM, complements (C3, C4, and C1q), kappa, and lambda light chains in glomeruli. There were no vascular lesions and immune-complex nephritis. In light of the clinical data and patient’s history without other underlying causes that may lead to acute TIN, the patient was diagnosed with TINU syndrome. Topical 1% prednisolone acetate and 1% cyclopentolate applied to both eyes for uveitis and oral corticosteroids (1 mg/kg prednisone/day) were prescribed to the patient. Systemic treatment continued for 3 weeks with the same dose, and then the dose was tapered and discontinued within 2 months. His renal functions normalized after the steroid therapy. In addition, uveitis promptly responded to systemic and local steroid treatment and BCVAs increased to 20/20 in both eyes within 15 days. After about 3 weeks of the treatment, β2-microglobulin, erythrocyte sedimentation rate, and C-reactive protein levels returned to normal limits. Serum creatinine levels decreased to 145 µmol/L. There were no relapses of uveitis and ocular or renal complications during the follow-up period of 24 months.

**Discussion**

Clinical findings of TINU syndrome are variable, and systemic symptoms may include fever, fatigue, anorexia, and weight loss. Renal presentations include sterile pyuria, hematuria subnephrotic proteinuria, and renal insufficiency. On the other hand, clinical features of the ocular disease in TINU syndrome are less well defined than the renal features; ocular manifestations were seen as uveitis which is generally limited to anterior chamber and acute-onset bilateral nongranulomatous type. However, granulomatous anterior uveitis can also be seen in TINU syndrome, similar to the case described herein. The most common ocular findings of anterior uveitis are anterior chamber flare and cells. However, as seen in this case report, vitreous involvement and also posterior uveitis may rarely occur in TINU syndrome. In addition, in contrast with initial reports of TINU manifesting exclusively as an anterior uveitis in pediatric patients, more recent reports have identified TINU in patients of all ages with a wide range of ocular manifestations. In the review of 120 patients with TINU syndrome, only in two cases, the keratic precipitates were described as having the granulomatous appearance, and 20% of the patients had posterior or panuveitis. In addition, this review demonstrated that 10 patients had vitreous humor cells as a posterior segment finding, five patients had pars plana exudates and cells in the anterior vitreous body, and features of an intermediate uveitis. TINU syndrome may probably be an underdiagnosed disorder, especially in the cases, if the associated interstitial nephritis was not clinically evident or resolved by the time uveitis had developed. These cases may be supposed as idiopathic uveitis. In view of the fact that 50% or more of the uveitis cases have no identified cause, it is important to consider other associations that might lead to diagnosis or suggest pathophysiological mechanisms of the disease.

There are no diagnostic criteria or test for the TINU syndrome, and the diagnosis necessitates the exclusion of other conditions that manifest with tubulointerstitial nephritis and uveitis such as Sjogren’s syndrome, systemic lupus erythematosus, Wegener’s granulomatosis, rheumatoid arthritis, sarcoidosis, Behcet’s disease, and infectious diseases (e.g., tuberculosis, toxoplasmosis, herpes, and brucellosis). No sign of any systemic disease has been detected in the case described herein, and all of the medical researches, including autoantibody screen, complement and immunoglobulin concentrations, infectious serology, Quanti-FERON test, ACE, and lysozyme enzyme levels were negative or normal. In addition, clinical and laboratory features of the case were compatible with mild renal failure associated with tubular dysfunctions (tubular glucosuria and proteinuria and elevated β2-microglobulin levels) without any sign of glomerular involvement (normal serum immunoglobulin and complement levels). The kidney biopsy confirmed that acute tubulointerstitial nephritis with negative staining for immunoglobulins, complements, kappa, and lambda light chains in glomeruli. As seen in this case report, biopsy allows the confirmation of nephritis; however, the diagnosis of TINU syndrome might be established without the aid of biopsy if the clinical criteria for tubulointerstitial nephritis are present. Goda et al. analyzed clinical features of 12 patients with TINU syndrome in Japan and reported that the levels of urinary β2-microglobulin which is a valuable marker of proximal renal tubular dysfunction.
function were increased in 11 patients, with values at least 10 times higher than the upper normal limits in eight patients. In the present case, β2-microglobulin level was detected as 22 mg/L (N: <1.0) at the admission.

The uveitis in TINU syndrome responds well to topical or systemic steroids in the majority of the cases but tends to recur. In some cases, it may become chronic and treatment-resistant which requires the use of immunomodulatory agents. Although there is no prospective, randomized clinical report regarding the treatment of TINU syndrome in the literature, steroids are commonly recommended as the treatment choice of uveitis. As the inflammation is mainly anterior, topical corticosteroid and cycloplegic agents may be sufficient; however, oral, periocular, or even intravitreal corticosteroids may be required for posterior segment involvement, and in chronic disease, the use of an antimetabolite or other corticosteroid-sparing immunomodulatory agents may be indicated. Sobolewska et al. evaluated the response to treatment in nine patients with TINU syndrome over a long-term follow-up period and revealed that TINU syndrome is characterized by limited responsiveness to corticosteroid therapy and a long-term course of immunosuppressants or biologics is necessary to control the uveitis and leads to induction of remission. On the contrary, Yang et al. analyzed the clinical features and long-term prognosis of uveitis in TINU syndrome in 32 Chinese patients. They concluded that uveitis in TINU syndrome is mild and corticosteroids are efficient in most cases; however, a slower tapering and long-term treatment were required. Our adult patient had ocular symptoms, including bilaterally granulomatous anterior uveitis, vitreous haze, and snowball opacities which occurred after systemic symptoms and nephritis that were successfully treated with systemic and topical steroids. In addition, it should be kept in mind that renal disease may coexist and may benefit from systemic treatment. In the present case, our patient responded well to the combined use of systemic and topical steroids. His renal functions normalized and uveitis resolved shortly after the treatment. There was no recurrence of either nephritis or uveitis during tapering or after discontinuation of the treatment.

As distinct from classical demographic and clinical findings of TINU syndrome, our case has differed in terms of advanced age, panuveitis with granulomatous involvement, and presenting with ocular findings. In addition, further investigations, including renal biopsy, could be required for definitive diagnosis.

To conclude, TINU syndrome is a rare disorder that is probably underdiagnosed in clinical practice. Due to the increasing number of TINU reports in the world, we suggest that it should be considered in differential diagnosis of patients presenting with nonspecific constitutional, visual, and renal manifestations. It should be kept in mind that although TINU syndrome typically presents with an acute-onset bilateral nongranulomatous anterior uveitis, it may manifest as granulomatous anterior, intermediate, posterior, or panuveitis.

Informed consent
It was taken. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that name and initial will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Financial support and sponsorship
Nil.

Conflicts of interest
The authors declare that there are no conflicts of interests of this paper.

References
1. Dobrin RS, Vernier RL, Fish AL. Acute eosinophilic interstitial nephritis and renal failure with bone marrow-lymph node granulomas and anterior uveitis. A new syndrome. Am J Med 1975;59:325-33.
2. Mandeville JT, Levinson RD, Holland GN. The tubulointerstitial nephritis and uveitis syndrome. Surv Ophthalmol 2001;46:195-208.
3. Mackensen F, Billing H. Tubulointerstitial nephritis and uveitis syndrome. Curr Opin Ophthalmol 2009;20:525-31.
4. Barut K, Razyet T, Canpolat N, Ozturk Y, Tugal-Tutkun I, Kasapcok O, et al. Acute granulomatous iridocyclitis in a child with tubulointerstitial nephritis and uveitis syndrome. J Ophthalmic Inflamm Infect 2015;5:3.
5. Weinstein O, Tovbin D, Rogachev B, Basok A, Vorobiev M, Kratz A, et al. Clinical manifestations of adult tubulointerstitial nephritis and uveitis (TINU) syndrome. Int Ophthalmol 2010;30:621-8.
6. Goda C, Kotake S, Ichishi A, Namba K, Kitaichi N, Ohno S, et al. Clinical features in tubulointerstitial nephritis and uveitis (TINU) syndrome. Am J Ophthalmol 2005;140:637-41.
7. McCannel CA, Holland GN, Helm CJ, Cornell PJ, Winston JV, Rimmer TG, et al. Causes of uveitis in the general practice of ophthalmology. UCLA community-based uveitis study group. Am J Ophthalmol 1996;121:35-46.
8. Pakzad-Vaezi K, Pepple KL. Tubulointerstitial nephritis and uveitis. Curr Opin Ophthalmol 2017;28:629-35.
9. Kaynar K, Ersoz S, Akyol N, Ersoz O, Unlu O, Ozbay T, et al. Adult onset tubulointerstitial nephritis and uveitis syndrome. Nephrology (Carlton) 2005;10:418-20.
10. Rueda-Rueda T, Sánchez-Vicente JL, Moruno-Rodriguez A, Castillo-Martino M, López-Herrero F, Contreras-Díaz M, et al. Tubulointerstitial nephritis and uveitis syndrome (TINU). Treatment with immunosuppressive therapy. Arch Soc Esp Oftalmol 2018;93:47-51.
11. Gion N, Stavrou P, Foster CS. Immunomodulatory therapy for chronic tubulointerstitial nephritis-associated uveitis. Am J Ophthalmol 2000;129:764-8.

12. Joyce E, Glasner P, Ranganathan S, Swiatecka-Urban A. Tubulointerstitial nephritis: Diagnosis, treatment, and monitoring. Pediatr Nephrol 2017;32:577-87.

13. Lei WH, Xin J, Yu XP, Li J, Mao MF, Ji JS, et al. Tubulointerstitial nephritis and uveitis syndrome in an elderly man: Case report and literature review. Medicine (Baltimore) 2015;94:e2101.

14. Levinson RD. Tubulointerstitial nephritis and uveitis syndrome. Int Ophthalmol Clin 2008;48:51-9.

15. Sobolewska B, Bayyoud T, Deuter C, Doycheva D, Zierhut M. Long-term follow-up of patients with tubulointerstitial nephritis and uveitis (TINU) syndrome. Ocul Immunol Inflamm 2018;26:601-7.

16. Yang M, Chi Y, Guo C, Huang J, Yang L, Yang L, et al. Clinical profile, ultra-wide-field fluorescence angiography findings, and long-term prognosis of uveitis in tubulointerstitial nephritis and uveitis syndrome at one tertiary medical institute in China. Ocul Immunol Inflamm 2017;1-9. doi: 10.1080/09273948.2017.1394469. [Epub ahead of print].