Ulusal ROMATOLOJİ Dergisi
Journal of Turkish Society for Rheumatology www.romatolojidergisi.org

Case Report / Olgu Sunumu

DOI: 10.4274/raed.galenos.2022.87597
Ulus Romatol Derg 2022;14(3):146-149

Tubulointerstitial nephritis and uveitis (TINU) syndrome; an underrecognized entity

Tubulointerstisyel nefrit ve üveit (TİNU) sendromu; az bilinen bir olgu

Reşit Yıldırım, Nazife Şule Yaşar Bilge, Timuçin Kaşifoğlu

Eskişehir Osmangazi University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Eskişehir, Turkey

Abstract

Tubulointerstitial nephritis and uveitis syndrome is a rarely seen multi-systemic disease with autoimmune features. Renal and ocular involvement generally occurs asynchronously therefore leads to late diagnosis. Renal manifestations generally precede ocular involvement. Eye disease is almost always of recurrent bilateral anterior uveitis. Renal disease is generally mild, self-limited and rarely requires immunosuppression. Definitive diagnosis is based on histopathological evaluation in the presence of clinical features and exclusion of masquerading disorders. Steroid is the most preferred first line agent, usually suggested for at least 3 to 6 months. Here, our objective with this case report is to attract attention to this uncommon entity in the rheumatology literature.

Keywords: Tubulointerstitial nephritis, uveitis, TINU syndrome, rheumatology

Öz

Tubulointerstiyel nefrit ve üveit (TİNU) sendromu, otoimmün özellikler barındıran, nadir bir multisistemik hastalıktır. Renal ve göz tutulumu çoğunlukla aynı zaman diliminde ortaya çıkmaz, bu nedenle tanıda gecikmelere neden olur. Genellikle, böbrek tutulumu göz tutulumundan önce görülür. Göz tutulumu, hemen daima tekrarlayıcı ve bilateral anterior üveit şeklindedir. Renal tutulum sıklıkla kendini sınırlayıcıdır ve nadiren immünosüpresif tedavi ihtiyacı olmaktadır. Kesin tanı, klinik ve histopatolojik bulguların yanı sıra taklitçi hastalıkların dışlanması ile konur. Steroid en sık tercih edilen ajan olmakla beraber en az 3-6 ay kadar kullanımı önerilmektedir. Burada TİNU sendromu tanısı konan bir olgu ile romatoloji literatüründe bu hastalık ile ilişkili farkındalığı artırmayı amaçladık.

Anahtar Kelimeler: Tubulointerstisyel nefrit, üveit, TİNU sendromu, romatoloji

Introduction

The association between tubulointerstitial nephritis and uveitis (TINU) was firstly described by Dobrin et al.[1] in two cases presented with similar features, including eosinophilic nephritis, bilateral anterior uveitis, increased sedimentation rate and granuloma formation in the bone marrow. Organ involvement may be variable that kidney precedes the eye in 65% of the patients.[2] Renal involvement mostly has a mild course with spontaneous improvement. Bilateral granulomatous anterior uveitis is the most common eye involvement, seen approximately in 80 to 90% of patients.[3] Fever, fatigue, arthralgia may accompany. After excluding mimickers such as sarcoidosis, Sjogren's syndrome, granulomatosis with polyangiitis (GPA), histopathologic evidence of tubulointerstitial nephritis in a patient with compatible clinical features is mandatory for definitive diagnosis. No treatment guidelines are currently available. Steroids are generally recommended, particularly in the presence of active uveitis and/or renal insufficiency.[4] Our goal with the report of this case is to increase the awareness of this rare entity among rheumatologists.

Case Report

A 20-year-old man with a previous diagnosis of autoimmune hypothyroidism was admitted to an opthalmology clinic with acute vision loss in both eyes.

Correspondence / İletişim:
Reşit Yıldırım MD, Eskişehir Osmangazi University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Eskişehir, Turkey
Phone: +90 533 379 12 94 **E-mail:** celeng18@gmail.com **ORCID ID:** orcid.org/0000-0003-4040-0212
Received / Geliş Tarihi: 18.01.2022 **Accepted / Kabul Tarihi:** 22.09.2022

Cite this article as / Atıf: Yıldırım R, Yaşar Bilge NŞ, Kaşifoğlu T. Tubulointerstitial nephritis and uveitis (TINU) syndrome; an underrecognized entity. Ulus Romatol Derg 2022;14(3):146-149

On ocular examination, the best-corrected visual acuity was 8/10 in the right eye and 7/10 in the left eye. Slit-lamp examination of the right eye was remarkable for granulomatous keratic precipitates, 3^+ cells in the anterior chamber with fibrinoid reaction. In the left eye, there were 2^+ cells in the anterior chamber, and the posterior synechiae. A dilated fundus examination revealed a fainted optic disk with increased venous fullness. The patient was consulted due to the differential diagnosis of panuveitis. On admission, systemic rheumatologic questionaire was inconclusive. He reported neither history of recurrent oral ulcers, genital ulcer, osteofollicular lesions, thrombosis, hemoptysis, cough, hearing loss nor the recent medication intake or infectious contact. Laboratory investigations showed an erythrocyte sedimentation rate of 80 mm/h (0-10), C-reactive protein (CRP) of 47 mg/dL (0-5), serum creatinine level of 1.63 mg/dL (0.7-1.20), serum glucose of 80 mg/dL (70-126), serum pH of 7.32, serum bicarbonate (HCO_3) level of 20 mEq/L (22-26), serum potassium of 5.0 mEq/L (3.5-5.3), and urine pH of 6. Hematuria, glycosuria, and mild proteinuria (328 mg/g on spot urine protein/creatinine) were found on urinalysis. Microscopic examination of urine showed eosinophiluria and granular cast, but no dysmorphic erythrocytes. His recent serum creatinine level was 0.8 mg/dL two months ago. Serum complement levels were normal, and anti-nuclear antibody and anti-neutrophilic cytoplasmic antibody (ANCA) tests were negative. All possible infectious causes were excluded and the chest X-ray was normal. Serum angiotensin-converting enzyme (ACE) levels were not studied in our clinic. Renal biopsy revealed interstitial lymphocytic infiltration with focal tubular atrophy and interstitial fibrosis, consistent with acute tubulointerstitial nephritis (ATIN) (Figures 1, 2). Based on the clinical features and histopathologic findings, a diagnosis of TINU syndrome was considered. He was started on high dose methylprednisolone (1 mg/kg/day) due to bilateral panuveitis and renal insufficiency. At the first month visit, eye examination was normal, as well, serum creatinine and acute phase parameters returned to normal reference values. At the fourth month, while receiving 4 mg methylprednisolone, the patient presented with an acute panuveitis attack in the left eye. Therefore, azathioprine (AZA) (2.5 mg/kg/day) was added along with escalating steroid dosage. The patient is currently on AZA without any eye attack in the last 11 months.

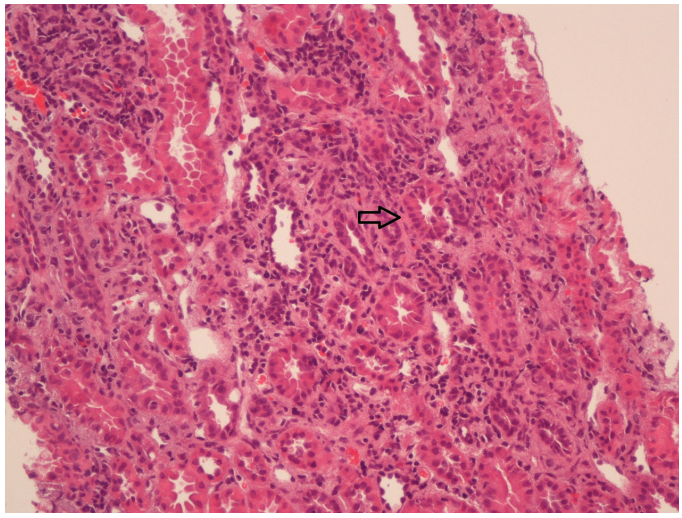

Figure 1. Interstitial lymphocytic infiltration with focal tubular atrophy and interstitial fibrosis (H&Ex100)
H&E: Hematoxylin and eosin

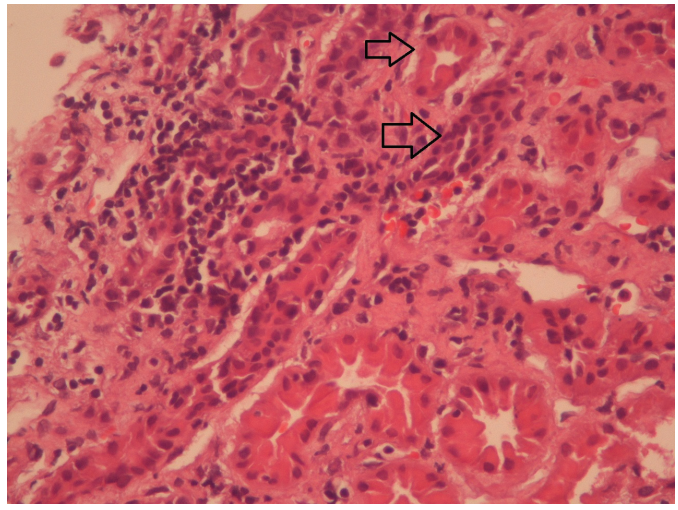

Figure 2. Interstitial inflammatory infiltrate and tubulitis (H&E x400)
H&E: Hematoxylin and eosin

Discussion

Uveitis is an inflammatory ocular disease that may lead to vision loss if left untreated. It is well-known that nearly 40% of uveitis is associated with a systemic autoimmune disease.[5] Therefore, all uveitis cases should be evaluated by a rheumatologist especially in terms of Behcet's syndrome (BS), spondyloarthropathies, sarcoidosis, systemic lupus erythematosus, GPA and relapsing polychondyritis. Despite an extensive investigation, the etiology still may not be well-clarified nearly in half of the patients. To date date, the prevalence of TINU syndrome has not been truly estimated because of its rarity. According to some recent observational studies, 2% of uveitis and 15% of ATIN population were found to fulfill the diagnosis of TINU syndrome.[6,7]

In an early observational study, TINU syndrome was reported to be more frequent in females (female to male ratio 3:1) with a mean age of 15 years for disease onset, and mostly presenting with anterior uveitis (80%).[2] However,

a recent study has demonstrated that it may not be as common in females (female/male 1.6:1) as previous reports and the disease might be seen more frequently in the adult population (mean age of 46 years) as well.[8] This change can be explained by the increased disease awareness in the recent years. Our case was of a young man with acute onset bilateral panuveitis. In our region, BS indeed should be placed among differential diagnoses, especially in a young male with panuveitis. The absence of other clinical components of BS, presence of granulomatous inflammation in the eye and negative pathergy test were the elements used for ruling out this possibility.

Based on the analysis of published cases, there is a unique relationship between the time in the emergence of renal and eye disease. The eye is typically involved in a period of 2 months before and 14 months after renal manifestations. As in our case, the synchronous presentation was seen only in 15% of patients.[2] Interestingly, in a recent study, it has been demonstrated that asymptomatic uveitis may be detected in 50% of cases if ocular examination is performed regularly regardless of the symptoms.[9] Therefore, all individuals should be investigated attentively in terms of each component of the disease at each outpatient visit. With better understanding of the disease nature in the last decade, prevalence rates have been relatively changed compared to earlier reports. This difference might be explained by the asynchronous pattern of the clinical features, which were not well-known previously. However, subsiding of each component after initiating steroid might be another possible explanation for the diagnostic delays.

Sarcoidosis is of important mimicking clinical condition that should be excluded before diagnosing TINU syndrome. Some experts have speculated that TINU syndrome might be an atypical form of extrapulmonary sarcoidosis according to the described granuloma formation in the kidney, eye and bone marrow in previous reports.[1] Literature data regarding methods used for excluding sarcoidosis are not homogenous, mainly determined by normal chest X-ray and serum ACE levels. However, it has been well-identified that pulmonary involvement may not be evident in 10% of sarcoidosis and serum ACE levels can be seen normally in nearly half of the patients.[10] In a study including 45 patients, it was found that combinating high levels of serum creatinine with urinary beta2-microglobulin has a predictive value of 100% for diagnosing TINU syndrome.[11] We were not able to measure serum ACE and beta2-microglobulin levels in our center. Thus, we excluded sarcoidosis based on normal chest X-ray and serum calcium level, and with no evidence of a granulomatous lesion in the renal specimen. Additionally, ANCA-associated vasculitides should also be considered when a patient manifests with simultaneous eye and renal involvement, but urinalysis and ANCA profile were nonsupporting in this case.

To date, the pathogenesis of TINU syndrome has not been well-addressed. Evidence of infiltration of T-cells and lymphoplasmacytes on renal biopsy, established familial forms of TINU, and case reports seen post infections are some footprints of cellular immunity.[12-17] On the other hand, IgG antibodies detected against ciliary and tubular cells, high levels of circulating modified CRP (mCRP) in the sera of TINU cases as well as antibodies demonstrated against mCRP in the renal and eye tissue of TINU patients suggest the role of humoral immunity.[18,19]

No consensus on treatment is currently available. Steroids are the most common preferred first line agent in the setting of acute eye involvement and/or profound renal insufficiency. This recommendation is based on observational experience from the literature of ATIN. Renal prognosis is generally good in contrast to eye disease, which may show high recurrence rates (70%) despite steroid monotherapy.[20] Therefore, addition of an immunosuppressive agent such azathioprine, mycophenolate mofetil and methotrexate may be considered for favorable long-term outcome.[21]

Conclusion

TINU syndrome should be considered in the differential diagnosis of a young male with uveitis and renal involvement. Of note, it should not be forgotten that each component of this unusual disease may not be seen simultaneously. Therefore, the clinician should perform a thorough examination of each manifestation at each visit. Data on this issue is insufficient in rheumatology. We believe that this disease deserves more interest than being an "orphan" among rheumatologists.

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: R.Y., N.Ş.Y.B., T.K., Design: R.Y., N.Ş.Y.B., T.K., Data Collection or Processing: R.Y., Analysis or Interpretation: R.Y., N.Ş.Y.B., T.K., Literature Search: R.Y., Writing: R.Y., N.Ş.Y.B., T.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that they have no relevant financial disclosures.

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. Bodakçi E , Üsküdar Cansu D , Korkmaz C. Tubulointerstitial Nephritis and Uveitis (TINU) Syndrome: A Case Report and Review of Literatüre. Osmangazi Tıp Dergisi 2019;41:187-91.
4. Clive DM, Vanguri VK. The Syndrome of Tubulointerstitial Nephritis With Uveitis (TINU). Am J Kidney Dis 2018;72:118-28.
5. Tsirouki T, Dastiridou A, Symeonidis C, et al. A Focus on the Epidemiology of Uveitis. Ocul Immunol Inflamm 2018;26:2-16.
6. Kump LI, Cervantes-Castañeda RA, Androudi SN, Foster CS. Analysis of pediatric uveitis cases at a tertiary referral center. Ophthalmology 2005;112:1287-92.
7. Kobayashi Y, Honda M, Yoshikawa N, Ito H. Acute tubulointerstitial nephritis in 21 Japanese children. Clin Nephrol 2000;54:191-7.
8. Legendre M, Devilliers H, Perard L, et al. Clinicopathologic characteristics, treatment, and outcomes of tubulointerstitial nephritis and uveitis syndrome in adults: A national retrospective strobe-compliant study. Medicine (Baltimore) 2016;95:e3964.
9. Saarela V, Nuutinen M, Ala-Houhala M, Arikoski P, Rönnholm K, Jahnukainen T. Tubulointerstitial nephritis and uveitis syndrome in children: a prospective multicenter study. Ophthalmology 2013;120:1476-81.
10. Jain R, Yadav D, Puranik N, Guleria R, Jin JO. Sarcoidosis: Causes, Diagnosis, Clinical Features, and Treatments. J Clin Med 2020;9:1081.
11. Hettinga YM, Scheerlinck LM, Lilien MR, Rothova A, de Boer JH. The value of measuring urinary β2-microglobulin and serum creatinine for detecting tubulointerstitial nephritis and uveitis syndrome in young patients with uveitis. JAMA Ophthalmol 2015;133:140-5.
12. Suzuki K, Nakahata T, Tanaka H, Waga S. Repeat renal biopsy in tubulointerstitial nephritis and uveitis syndrome: report of a case. Nihon Jinzo Gakkai Shi 2003;45:445-8.
13. Dusek J, Urbanova I, Stejskal J, Seeman T, Vondrak K, Janda J. Tubulointerstitial nephritis and uveitis syndrome in a mother and her son. Pediatr Nephrol 2008;23:2091-3.
14. Tanaka H, Waga S, Nakahata T, et al. Tubulointerstitial nephritis and uveitis syndrome in two siblings. Tohoku J Exp Med 2001;194:71-4.
15. Cigni A, Soro G, Faedda R, et al. A case of adult-onset tubulointerstitial nephritis and uveitis ("TINU syndrome") associated with sacroiliitis and Epstein-Barr virus infection with good spontaneous outcome. Am J Kidney Dis 2003;42:E4-E10.
16. Grefer J, Santer R, Ankermann T, Faul S, Nölle B, Eggert P. Tubulointerstitial nephritis and uveitis in association with Epstein-Barr virus infection. Pediatr Nephrol 1999;13:336-9.
17. Stupp R, Mihatsch MJ, Matter L, Streuli RA. Acute tubulointerstitial nephritis with uveitis (TINU syndrome) in a patient with serologic evidence for Chlamydia infection. Klin Wochenschr 1990;68:971-5.
18. Abed L, Merouani A, Haddad E, Benoit G, Oligny LL, Sartelet H. Presence of autoantibodies against tubular and uveal cells in a patient with tubulointerstitial nephritis and uveitis (TINU) syndrome. Nephrol Dial Transplant 2008;23:1452-5.
19. Tan Y, Yu F, Qu Z, et al. Modified C-reactive protein might be a target autoantigen of TINU syndrome. Clin J Am Soc Nephrol 2011;6:93-100.
20. Joyce E, Glasner P, Ranganathan S, Swiatecka-Urban A. Tubulointerstitial nephritis: diagnosis, treatment, and monitoring. Pediatr Nephrol 2017;32:577-87.
21. Amaro D, Carreño E, Steeples LR, Oliveira-Ramos F, Marques-Neves C, Leal I. Tubulointerstitial nephritis and uveitis (TINU) syndrome: a review. Br J Ophthalmol 2020;104:742-7.