

## From the Clinic

### Tubulointerstitial nephritis and uveitis syndrome in an elderly woman

The concomitant presentation of tubulointerstitial nephritis and uveitis is known as tubulointerstitial nephritis and uveitis (TINU) syndrome, also known as the Dobrin syndrome. Since first described in 1975, <300 cases have been reported in the medical literature, most of them in children. Establishing the diagnosis of TINU syndrome may be challenging because concurrent acute interstitial nephritis (AIN) and uveitis manifestations may not occur. This might have led to the under-diagnosis of this syndrome.

A 60-year-old was referred to the nephrology clinic because of abnormal kidney functions. During her routine follow-up, she was found to have elevated serum creatinine (Scr) and blood urea nitrogen (BUN). One month prior, she presented to the ophthalmologist with bilateral eye pain and redness and was diagnosed with anterior uveitis. At that time she was started on oral prednisone 60 mg daily. The patient did not have any complaints of fever, weight loss, headache, fatigue, malaise, arthralgia, myalgia, flank pain or rash. She denied using any antibiotics or nephrotoxic drugs such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, direct renin inhibitors or nonsteroidal anti-inflammatory drugs. Vital signs were within normal. Laboratory investigations showed a Scr of 2.32 mg/dL (205  $\mu$ mol/L). Urinalysis showed proteinuria 100+ and hematuria with a moderate number of intact red blood cells. Urine protein to creatinine ratio was 127.5 mg/g. Renal ultrasound showed normal sized kidneys without gross abnormalities. Renal biopsy revealed diffuse inflammatory infiltrates with lymphocytic predominance affecting the cortex of the renal tubules and the interstitium with associated tubulitis (Figures 1 and 2). The glomeruli appeared nonproliferative and did not show areas of immune complex deposition by immunofluorescence. These pathological features were consistent with active tubulointerstitial nephritis. Given her recent history of uveitis, TINU syndrome was suspected. Antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibody (ANCA), anti Ro/SSA and La/SSB, erythrocyte sedimentation rate (ESR), C reactive protein (CRP), anti-Smith antibody, angiotensin-converting enzyme (ACE) level, liver function tests, glomerular basement membrane antibodies and thyroid function tests were either normal or negative. The patient was diagnosed clinically with TINU syndrome and treated with prednisone 1 mg/kg/day for 3 months. After 2 months, the eye pain and redness resolved with marked improvement of the kidney function tests [Scr was 1.1 mg/dL (97  $\mu$ mol/L) and estimated GFR 51 mL/min/1.73 m<sup>2</sup>]. Six months after treatment, she continued to be asymptomatic with normal blood pressure and improved kidney function tests.

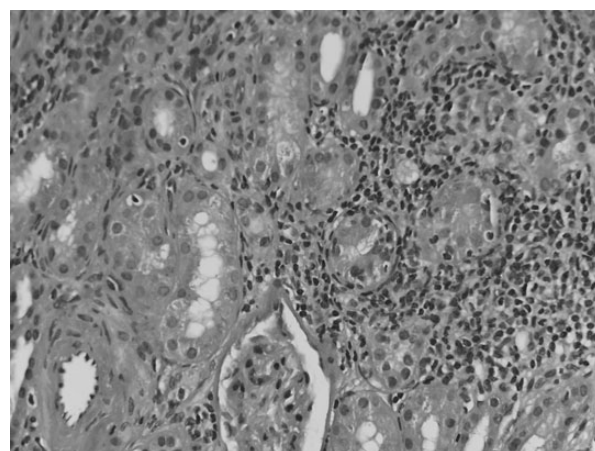
TINU syndrome is defined as tubulointerstitial nephritis associated with uveitis that can occur concurrently, precede or follow the onset of renal dysfunction. Most of the patients with TINU syndrome are children and young adolescents with a median age of 15 years [1] but it has also been reported in adults and in old age. Some of the risk factors for developing TINU syndrome are infection and drug usage such as antibiotics and nonsteroidal anti-inflammatory

drugs [1]. The underlying mechanism for TINU syndrome is not clearly known. Genetically predisposed individuals with HLA-DRB1\*14 (DR6 subtype), DQA1\*01, DQB1\*06(DQ1) may be prone to producing the lesions observed in the TINU syndrome upon activation of their immune system [2].

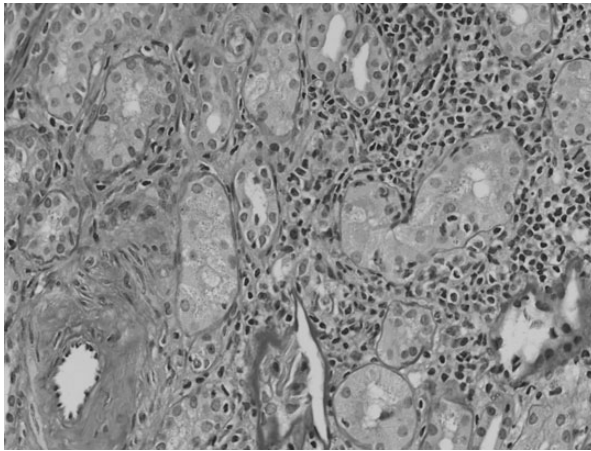
Early diagnosis of TINU syndrome is challenging because patients with this syndrome present with nonspecific systemic manifestations including fever, weight loss, headache, fatigue, malaise, arthralgia and myalgia. Bilateral, or less commonly unilateral, uveitis usually occurs after the onset of AIN but it has been observed to occur 2 months before, concurrently, and up to 14 months after the AIN [1]. Renal manifestations with TINU syndrome may include flank pain, sterile pyuria, hematuria, proteinuria (usually subnephrotic range), renal insufficiency, and/or acute kidney injury (AKI). Renal biopsy is the definitive method of establishing the diagnosis of AIN [3]. TINU syndrome is a diagnosis of exclusion. Other systemic diseases that can cause both uveitis and AIN should be ruled out first. Laboratory findings may include anemia, eosinophilia and elevation of the liver function tests, ESR and urinary beta-2-microglobulin. Krebs von den Lunge-6 (KL-6) glycoprotein, in addition to the mCRP antibodies, might serve as potential laboratory parameters for the diagnosis of TINU syndrome [3].

There is no established standard treatment for TINU syndrome. Early steroid administration (usually prednisone 1 mg/kg/day for 2–3 weeks, followed by gradually tapering dose over 3–4 weeks) is likely to reduce the number and extent of inflammatory infiltrates and subsequent fibrosis [4]. Immunotherapy with methotrexate, cyclosporine A and azathioprine was suggested for the frequent recurrence of ocular involvement [5].

Most reports suggested a good prognosis for TINU syndrome. In contrast, Li *et al.* [3] reported that 92% of patients with TINU had incomplete renal recovery. In this study the authors found that baseline characteristics such as older age, concurrent thyroid diseases, higher levels of



**Fig. 1.** Hematoxylin and eosin (H&E) stained  $\times 40$  objective photomicrograph shows an interstitial inflammatory process with associated tubulitis. The glomeruli show ischemic change with tuft shrinkage and wrinkling of the capillary loops with mild arteriolar intimal wall thickening.



**Fig. 2.** Periodic acid-Schiff (PAS) stained  $\times 40$  objective photomicrograph shows an interstitial inflammatory process with associated tubulitis. The glomeruli show ischemic change with tuft shrinkage and wrinkling of the capillary loops with mild arteriolar intimal wall thickening.

Scr and ESR, and prominent leukocyturia were associated with prolonged renal dysfunction.

Subclinical signs of uveitis should be searched especially in those patients who have tubulointerstitial disease of unknown origin. To our knowledge, only 10 cases of TINU syndrome in older age were reported in the medical literature.

We report a rare case of TINU syndrome in an elderly woman who presented with abnormal kidney functions. One month prior, she was diagnosed with anterior uveitis. Renal biopsy confirmed the diagnosis of tubulointerstitial nephritis. The patient was treated with prednisone. TINU syndrome in old age is extremely rare. This case underlies the importance of early nephrology and ophthalmology referral to diagnose and treat this reversible disease.

An informed consent has been obtained from the patient to report this case.

*Conflict of interest statement.* We confirm that the results presented in this paper have not been published previously in whole or part.

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