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A Rare Case of Tubulointerstitial Nephritis and Uveitis Syndrome Treated with a Multi-Specialty Approach

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Patient: Female, 23
Final Diagnosis: Tubulointerstitial nephritis and uveitis syndrome
Symptoms: Abdominal pain • eye redness
Medication: —
Clinical Procedure: —
Specialty: Opthalmology

Objective: Rare disease

Background: It is important for an ophthalmologist and nephrologist to look for hidden causes of uveitis and nephritis, respectively. Delay in diagnosis leads to increased morbidity and failure to systemically manage the patient results in future recurrence of disease. It is likely that TINU remains underdiagnosed and could potentially account for some of the cases of idiopathic uveitis, especially when greater than 50% of uveitis cases have no identifiable cause.

Fewer than 300 cases of tubulointerstitial nephritis and uveitis (TINU) syndrome have been reported. In TINU syndrome, inflammation affects the renal tubules, interstitial tissue, and uveal tract. Its pathogenesis remains poorly understood.

Case Report: We report a rare case of TINU syndrome in a 23-year-old female who was treated using a multispecialty approach. Her primary care physician diagnosed her with proteinuria and acute kidney injury and referred her to the nephrologist, who later referred her to the ophthalmologist. A left kidney biopsy confirmed acute interstitial nephritis. Following the discovery of a "pink eye", the patient was referred to ophthalmology and diagnosed with anterior uveitis, confirming TINU syndrome. Without the additional findings of uveitis, the diagnosis would have been missed. Resolution was obtained through steroid therapy.

Conclusions: Correctly diagnosing TINU syndrome requires a multispecialty approach and may not be obvious upon initial presentation. Therefore, the ophthalmologist needs to consider TINU in the differential diagnosis for a patient with bilateral uveitis and evaluate a urinalysis for proteinuria as part of the work up.

MeSH Keywords: Glucocorticoids • Nephritis, Interstitial • Uveitis, Anterior

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/900701

Background

In tubulointerstitial nephritis and uveitis (TINU) syndrome, inflammation is two-fold, since it affects the renal interstitium and uveal tract [1,2]. TINU syndrome was first described in 1975, and since then, fewer than 300 cases have been reported, mostly in children [1]. Standard diagnostic criteria for this syndrome do not exist, thus under-diagnosed cases are likely. However, according to Mandeville et al., interstitial nephritis must meet the following criteria: abnormal renal function, abnormal urinalysis, and a systemic illness lasting two or more weeks with a combination of various signs and symptoms such as fever, rash, malaise, weight loss, anorexia, fatigue, myalgias, arthralgias, and abdominal or flank pain [2,3]. In addition, a renal biopsy is essential for definitively diagnosing of interstitial nephritis [3]. Uveitis may not affect both eyes, but it must occur within a 12-month period of interstitial nephritis [3]. TINU predominantly affects females at two different peak age ranges: 11–20 years and 31–35 years [2]. Although the etiology of TINU remains uncertain, it has been associated with multiple immunologic conditions and HLA proteins, suggesting an immunologic abnormality [4].

We report a rare case of TINU syndrome in a young female who had systemic symptoms and was treated using a multi-specialty approach.

Case Report

A 23-year-old female presented initially to her PCP with complaints of nausea, vomiting, and abdominal pain. A past medical history of allergic asthma and gastroesophageal reflux disease was noted. She had no past surgical history. She had no history of tobacco, alcohol, or recreational drug abuse. Her PCP completed a thorough workup for evaluation of her vomiting, including MRCP, all of which were negative, and she was placed on pantoprazole 40 mg once a day and metoclopramide 10 mg twice a day. A week later, she still had symptoms and a complete blood count (CBC), complete metabolic panel (CMP), and urine analysis (UA) were repeated. All were normal except for an increase in creatinine of 2.35 mg/dL and 4+ proteinuria. She was felt to be dehydrated and consequently sent to the ER, where she received IV fluids and potassium. A week later, repeat labs showed a still elevated serum creatinine of 2.17 mg/dL and she was consequently referred to nephrology for evaluation.

Nephrologic evaluation revealed an elevated Alb/Cr ratio 130, urine β2-microglobulin 33,100 µg/L (normal <300 µg/L), ESR 81, Cr 2.2, CRP 5.3, HgA1c 5.7, and proteinuria (100 mg/dL). The elevated Alb/Cr ratio and β2-microglobulin levels suggest tubular injury, with the possibility of pantoprazole-induced acute interstitial nephritis (AIN) [5–8]. Subsequently, pantoprazole was discontinued and the patient was started on sucralfate and sodium bicarbonate 650 mg po bid. Trending serum creatinine showed an initial level of 2.2 mg/dL (as above), which decreased to 1.8 mg/dL over the 3-month follow-up period before re-peaking at 2.5 mg/dL during conservative management. Serologic studies, including ANCA, cryoglobulin, complement, anti-RNP, anti-SSA/B, anti-Smith, anti-dsDNA, C3, C4, were negative. Renal nuclear scan was within normal limits. She was subsequently scheduled for kidney biopsy to investigate the etiology of proteinuria and elevated serum creatinine, which showed "marked interstitial infiltrate with tubulitis and focal tubular epithelial cell necrosis, as well as an admixture of eosinophils in a background of otherwise T-cells with rare admixture of B-cells within the interstitium". This pattern is consistent with the diagnosis of AIN.

One week after the biopsy, she revealed that over the past 8–9 days, she had developed progressively worsening bilateral eye redness. At this time, urinalysis revealed a protein of 900 mg/dL; serum creatinine was 2.5. The next day she was examined by an ophthalmologist, who determined that there was anterior uveitis present in both eyes with keratic precipitates and posterior synechiae present bilaterally as seen in Figure 1. Visual acuity declined from her pre-inflammation baseline of 20/20 with correction in both eyes to 20/30-2 in her right and 20/20-2 in her left eye. With the diagnosis of anterior uveitis, TINU syndrome was confirmed. She was started on 60 mg of prednisone daily for three weeks and prednisolone acetate ophthalmic one drop every two hours while awake. Three weeks later, proteinuria improved to 100 mg/dL, serum creatinine improved to 1.8. Thus, we began to taper the steroids, decreasing prednisone to 60 mg every other day for two months. After those two months, urine was negative for protein and serum creatinine was 1.1. Prednisone was decreased to 10 mg every other day for one month (after which creatinine was 1.0), then decreased to 5 mg every other day for three months, then stopped. Visual acuity returned to her normal baseline. She has not had recurrence of either ocular or abdominal symptoms at six months after resolution.

Discussion

It is rare for patients with interstitial nephritis to have TINU syndrome [4], however, acute interstitial nephritis (AIN) accounts for 10–15% of patients with acute renal failure. It is likely that TINU remains underdiagnosed. It could potentially account for some of the cases of idiopathic uveitis, especially if the renal component was not evident during initial evaluation. This is especially important considering that greater than 50% of uveitis cases have no identifiable cause [9].

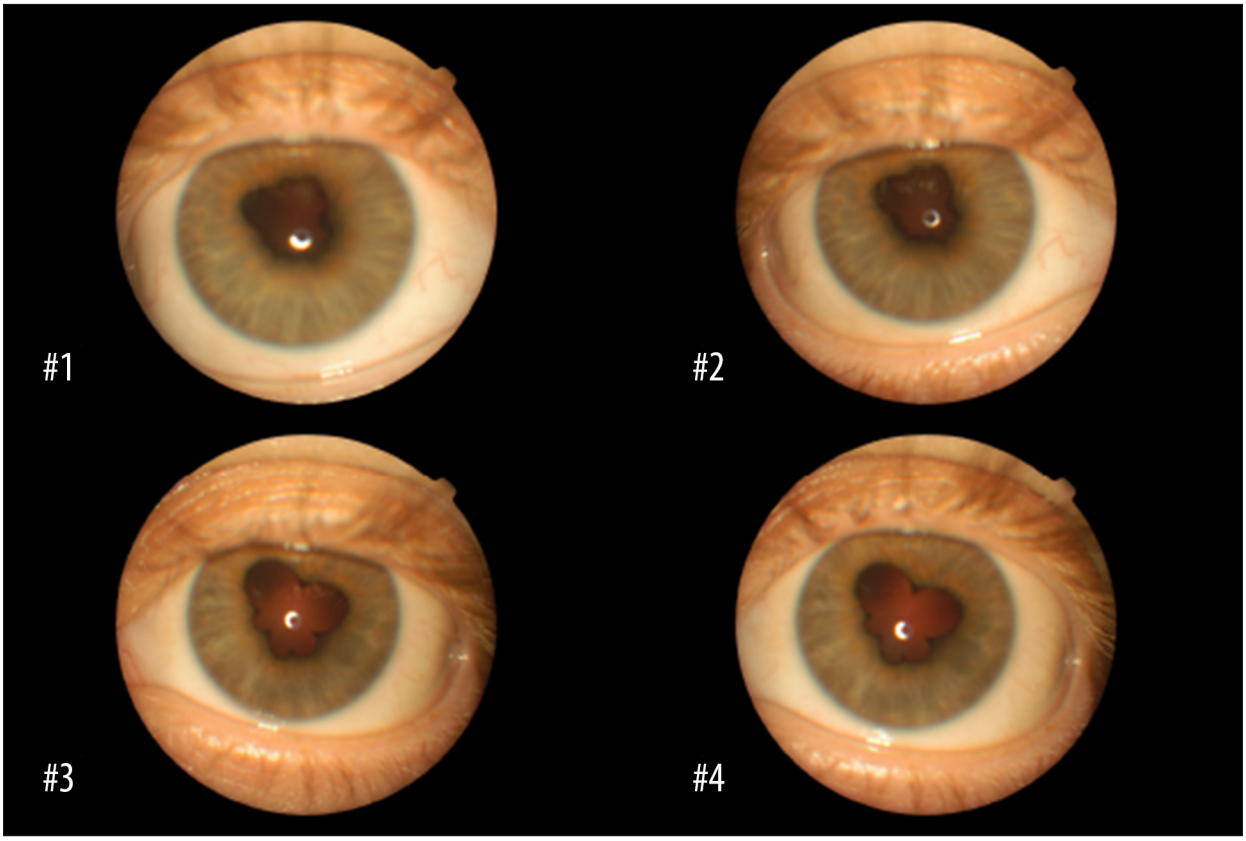

Figure 1. These are photographs taken upon initial presentation to ophthalmology after administration of dilating drops (with associated blanching of superficial blood vessels). Posterior synechiae are visible. There is 2+ anterior chamber cell and flare, but it is difficult to visualize in these photographs.

Inflammation in TINU syndrome is isolated to the kidneys and uveal tissue. Many risk factors have been proposed, none of which has been clearly associated with TINU syndrome. Most patients diagnosed with TINU are children and females, with a median age of 15 years [3,4]. However, a study done in 2007 by Mackensen et al. contradicts this belief, reporting a male: female ratio of 3: 2 [10]. TINU has no particular affinity with race, familial inheritance, genetics, or geographic clustering [3]. Ocular symptoms include redness, photophobia, decreased visual acuity, and pain. Ocular physical exam findings include anterior chamber cell, flare, keratic precipitates, and redness [2]. Renal manifestations are typical for AIN and include flank pain, acute kidney injury, proteinuria, and sterile pyuria. In addition, proximal and distal tubular defects have been reported and can result in aminoaciduria, glucosuria, phosphaturia, and acidification defects [11,12]. Table 1 shows the varying presentations and outcomes of some of the cases of TINU syndrome reported previously. It is important to note that uveitis occurs after onset of renal disease in most cases [13].

The pathogenesis of TINU syndrome remains poorly understood. In some cases, prior infections or drug use have been implicated as the cause. Many studies have reported a genetic basis for disease, namely associations with HLA-DQA1*01, HLADQB1*05, and HLA-DQB1*01 [3,14]. Other studies have proposed various immunologic etiologies. The authors of one such study demonstrated that patients with TINU had a significantly elevated level of antibodies to modified C-reactive protein (mCRP) compared to disease controls (patients with AIN, IgA nephropathy, minimal change disease, ANCA-associated vasculitis, Sjögren's syndrome, and renal amyloidosis) [15]. On the other hand, Gafter et al. linked TINU to suppression of cell-mediated immunity. They reported that TINU patients had a normal T-cell population, but decreased secretion of lymphokines and anergy to skin tests compared to normal controls. They also reported a possible link with HLA-DR6 [16]. There have also been reports of associations with ANCA [17], ANA [18], and hypocomplementemia [19].

Unfortunately, recurrence of uveitis in TINU syndrome is common and is often more severe, warranting close follow-up [2]. According to a study, 41% of cases (52/126) have a high recurrence of uveitis [3]. In another study of 12 cases of TINU syndrome, half experienced recurrence or exacerbation of uveitis during follow-up [2]. With such potential complications, regular monitoring of renal function, proteinuria, and uveitis is essential

Table 1. Case-reports on TINU presentation and management.

Number	1st Author	Gender	Age	Initial presentation	Bilateral/ unilateral uveitis	Treatment	Outcome	Comorbidities
1	Cigni [20]	F	48	4 months of Uveitis, then Nephritis	Bilateral	Ophthalmic steroids	Normal within 6 months	Bilateral sacroiliitis
2	Kaynar [21]	F	44	Nephritis and Uveitis simultaneously	Unilateral	Systemic steroids and ophthalmic steroids	Normal 2 weeks after treatment	Contralateral chorioretinal scarring and unilateral sacroiliitis
3	Koike [12]	F	32	Nephritis, then Uveitis 1 day after renal biopsy	Bilateral	Systemic steroids	Normal within 3 months	Fanconi syndrome
4	Liakopoulos [22]	F	52	Nephritis and Uveitis simultaneously	Unilateral	Systemic steroids	Recovered in 6 weeks	
5	Mortajil [23]	F	35	3 months of Nephritis, then Uveitis	Bilateral	Systemic steroids and ophthalmic steroids	Normal within 24 months	
6	Mortajil [23]	F	44	1 month of Nephritis, then Uveitis	Bilateral	Systemic steroids and ophthalmic steroids	Normal within 27 months	
7	Nakai [24]	M	48	10 months of Nephritis, then Uveitis	Bilateral	Systemic steroids	Improvement in Cr after 1 year	
8	Savaj [25]	M	23	Uveitis	Bilateral	Systemic steroids	No recurrence at 1 year follow-up	
9	Thomassen [26]	M	11	1 week of Nephritis, then Uveitis	Bilateral	Systemic steroids and ophthalmic steroids	Normal within 10 weeks. No recurrence at 18 months	
10	Wen [27]	M	40	Nephritis and Uveitis simultaneously	Bilateral	Systemic steroids	Normal after 4 weeks	Ankylosing spondylitis and Fanconi syndrome

in patients with TINU syndrome. Thus, a multispecialty approach to treatment can be advantageous. Fortunately, most patients regain renal and ocular function after successful treatment. With patients often presenting with either uveitis or nephritis, it is essential that both ophthalmologists and nephrologists be suspicious for TINU syndrome. An ophthalmologist should inquire about urinary symptoms when patients present with uveitis and perform a urinalysis as part of the uveitis workup.

Our patient initially presented with vague symptoms of nausea, vomiting, and abdominal pain. She matches the more common young female demographic for TINU. However, our patient had none of the serologic associations and she had been taking pantoprazole, which has been linked to AIN [5–8]. Like 65% of patients [3], our patient developed uveitis after nephritis. It was only after a thorough workup ruling out more common causes of her symptoms that she was referred to nephrology. Due to early suspicion for systemic disease on the part of the nephrologist, our patient was promptly referred to an ophthalmologist. Following treatment, her visual acuity returned to 20/20 in both eyes using her previous correction and her uveitis and renal disease resolved. Successful management depended on suspicion for TINU syndrome for prompt referral to ophthalmology. She will need continued follow-up for early detection of relapse.

Conclusions

The current case highlights the need for a multispecialty approach to treat patients with TINU as well as suspicion to look

for hidden causes of interstitial nephritis. Even without symptoms, physicians must still be mindful of TINU and work with members of other specialties in the care of our patients. The disease does not begin with a finding specific to any medical specialty. Rather, as seen in Table 1, uveitis and nephritis often presents weeks or months before the other. It remains important to perform an ophthalmic and nephrologic evaluation, even for an asymptomatic patient, to prevent delay in treatment. This case demonstrates that clinically significant uveitis can be present without the medical team being aware. Ophthalmic examination not only improves patients' outcomes, since significant uveitis can cause major morbidity, but it also improves the medical team's ability to diagnose TINU. An ophthalmologist played a key role in diagnosing TINU in our patient.

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Conflict of interest

The authors declare no conflicts of interest.

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