Tubulointerstitial nephritis and uveitis syndrome in an adolescent female: a case report

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Abstract

Background: Tubulointerstitial nephritis with uveitis syndrome is a rare disease affecting mainly children and young women. Tubulointerstitial nephritis with uveitis is a diagnosis of exclusion, requiring a high degree of clinical suspicion. Studies report recent infections or certain drugs as precipitating factors of a lymphocytic oculorenal immune response. The prognosis is usually favorable with topical and systemic corticosteroid therapy.

Case presentation: We report a literature review and the case of a 14-year-old white girl, who presented to the ophthalmology department with features of one-sided uveitis. Upon transfer of patient to nephrological care, diagnostic work-up revealed renal involvement. Renal biopsy showed a mixed-cell and granulomatous tubulointerstitial nephritis with some noncaseating granulomas, leading to a diagnosis of tubulointerstitial nephritis with uveitis syndrome. With topical ocular and systemic corticosteroid therapy, the patients' condition improved over several weeks.

Conclusions: Our case highlights the importance of early recognition and treatment of this syndrome, where cross-specialty care typically leads to a favorable outcome.

Keywords: Tubulointerstitial nephritis with uveitis, Acute tubular injury, Bilateral uveitis, Renal biopsy
endocrinological and dietary assessment, and was continued to be seen by our pediatric nephrologist twice per year.

In October 2018, aged 14 years, she presented to the Department of Ophthalmology with 1 week of redness, pain, epiphora, and loss of visual acuity of the right eye. She denied any recent drug exposure, allergy, infection, or symptoms of systemic illness. A diagnosis of acute anterior uveitis was made, followed by topical corticosteroid and cycloplegic treatment, which led to symptom alleviation.

**Investigations**

A broad diagnostic work-up was performed. Renal ultrasound was normal. Also, chest radiography was also normal (Fig. 1), which in conjunction with a normal serum angiotensin-converting enzyme level and absence of cough excluded sarcoidosis, a known oculorenal offender. However, upon laboratory evaluation, marked elevation in erythrocyte sedimentation rate (ESR, 98 mm/hour), mild elevation of serum C-reactive protein (CRP, 13 mg/L), mild normocytic anemia (Hb, 113 g/L), elevated serum creatinine (80 µmol/L), mild proteinuria (0.38 g/day), microalbuminuria (urine albumin-to-creatinine ratio, 58 mg/g), elevated values of alpha-1 microglobulin (urine alpha-1-microglobulin-to-creatinine ratio, 3.24 mg/g), and normoglycemic glycosuria (1+) were observed. Immunological screening revealed elevated C3 complement fraction (C3, 2.01 g/L), with negative antinuclear antibodies (ANA), anti-extractable nuclear antigen antibodies (ENA), anti-deoxyribonucleic acid antibodies (anti-DNA) and antineutrophil cytoplasmic antibodies (ANCA) antibodies. These values indicated mild renal involvement and prompted a referral to our nephrology unit.

Upon admission, she had no history of unexplained fevers, weight-loss, or other systemic symptoms. She had a pulse of 100 beats/minute, blood pressure of 126/81 mmHg, and body temperature of 36.5 °C. Her review of systems was negative, with a gradual improvement of symptoms and vision of the right eye. She continued both-sided topical cycloplegic and topical corticosteroid therapy. Borderline blood pressure values with repeated and persistent abnormal values of ESR, serum urea and creatinine, proteinuria, and glucosuria, indicating kidney injury, prompted a kidney biopsy.

Histopathology revealed focal tubulointerstitial nephritis. Interstitial inflammatory cell infiltrate was composed of lymphocytes, macrophages, fewer neutrophils, eosinophils, and plasma cells and rare noncaseating granulomata, with foci of invasion of lymphocytes into the tubules (tubulitis). Tubules in the affected areas showed signs of acute tubular injury—flattened, irregular, and vacuolated tubular epithelium. Glomeruli and vessels were unremarkable (Figs. 2, 3). Immunofluorescence was negative. Electron microscopy showed no specific pathological findings. On the day of renal biopsy, 1 month after first symptom presentation, she also developed contralateral, left-sided anterior uveitis. A diagnosis of TINU syndrome was confirmed, based upon histopathological findings.

DNA typing of HLA loci showed the subtype HLA-B*07, *51; DRB1 *11, *13; DQA1 *05:05/05:09; DQB1...
*03:01, negative for uveitis-related HLA-B27 genotype. Next-generation sequencing did not demonstrate any disease-related variants.

**Treatment**
The patient was started on methylprednisolone 60 mg daily, which improved the laboratory markers of kidney injury and allowed us to continue an alternate-day corticosteroid therapy regimen. She also received pantoprazole 40 mg daily, trimetoprim–sulfametoxazole 480 mg twice daily every other day for *Pneumocystis carinii* pneumonia prevention, and vitamin D supplementation 2000 units daily, together with topical ocular therapy (scopolamine, nepafenac, dexamethasone). Because of elevated blood-pressure readings, she began therapy with ramipril 2.5 mg and later 5 mg daily and received regular follow-up.

**Outcome and follow-up**
After 3 months, upon evaluation at our out-patient clinic, her ocular symptoms improved, although she started having pain in her lumbar spine. Clinical examination showed a Cushingoid appearance with a 4 kg increase in body weight since discharge. Blood pressure values with antihypertensive therapy were normal. Lumbosacral spine X-ray imaging was normal, without signs of osteopenia (Fig. 4). This allowed a slow reduction in corticosteroid therapy upon following weeks and motivated her for implementation of healthy lifestyle measures.

At the most recent ambulatory office visit, two and a half years after onset of TINU, the patient denied any further ocular exacerbations, but she gained weight and had a body mass index of almost 35 kg/m². Her 24-hour ambulatory blood pressure values were normal, as well as renal ultrasound examination, without presence of renal scarring. She was receiving ramipril 2.5 mg and metformin 500 mg twice daily each, together with education on necessary lifestyle changes.

**Discussion and conclusions**
Our article presents, to the best of our knowledge, the first Slovene case of TINU syndrome in a 14-year-old girl in published literature. The diagnosis was suspected by the presence of renal and ocular findings, combining acute interstitial nephritis and anterior uveitis, and confirmed by renal biopsy. Current literature suggests that approximately 300 cases have been published [2]. We present a literature review of 580 described cases. Table 1 presents the case series published in the last 10 years. Countries with published case series are presented in Fig. 5 and in greater detail in Table 2.

**Pathophysiology**
In 2001, Mandeville *et al.* [3] proposed diagnostic criteria for TINU syndrome, comprising clinical and histopathologic features. Since then, studies have tried to elucidate the underlying mechanism of disease. Limited data suggest that modified C-reactive protein (mCRP), a uveal and renal tubular autoantigen, might play a role in
| No. of patients | Presentation | Laboratory findings | Renal biopsy | Treatment | Outcome | Important contribution |
|----------------|--------------|---------------------|--------------|-----------|---------|------------------------|
| 5              | Four women and one man aged 18-64 years with systemic symptoms, all with renal and two with ocular involvement at initial presentation | Moderate-to-severe renal dysfunction, proteinuria, elevated ESR, anemia | Renal biopsy in all patients, with moderate-to-severe interstitial nephritis | All Pt on systemic steroids, three on either cyclosporin or azathioprine | Uveitis relapse in 3/5 Pt after corticosteroid cessation, necessitating immune-modulatory agents | Adult patients with TINU had more severe uveitis than previously reported |
| 2              | 13-year-old boy and 5 years later 17-year-old girl with acute anterior uveitis | Pt 1: systemic inflammation, renal dysfunction; Pt 2: elevated serum β-2 microglobulin, proteinuria | Pt 1: interstitial nephritis. Pt 2: no signs of interstitial nephritis on repeated renal biopsies | Pt 1: topical and systemic steroid; mycophenolate-mofetil after frequent relapses. Pt 2: topical prednisolone | Frequent relapses of acute uveitis in 1/2 Pt | Two familial TINU cases with specific HLA-DQB1 and -DRB1 alleles |
| 9              | Seven female and two male Pt; mean age 45.2 years | Acute kidney injury (mean serum creatinine 241 µmol/L), mCRP serum autoantibodies in all Pt | Renal biopsy in all TINU cases; all samples positive for mCRP immunohistochemistry in tubules and interstitium | Topical ocular steroid in all patients, oral prednisone in 8/9 patients (median 30 mg/day), cyclophosphamide in 2/9 patients | Serum creatinine of all Pt normalized within 2–4 months after therapy initiation | High prevalence of serum anti-mCRP autoantibodies in patients with TINU syndrome |
| 4              | Three male and one female Pt aged 13–36 years | NA | Lymphocyte-dominant interstitial inflammation accompanied by lymphocytic tubulitis | NA | NA | TINU is usually not associated with IgG4 sclerosing disease |
| 2              | 5-year-old and 51-year-old patient. Rash in 1/2 Pt | Both Pt with elevated serum β-2 microglobulin | NA | NA | None had active chronic disease | Simultaneous-onset bilateral acute anterior uveitis is more common in younger patients and in TINU |
| 20             | Ten male and ten female Pt; median age 12.8 years. Anterior uveitis in 20/20 Pt. Two Pt had uveitis prior to nephritis, 11 simultaneous with and 7 Pt ≥1 month after nephritis onset | NA | Biopsy-proven AIN (not otherwise specified) | NA | All Pt followed-up by a pediatric ophthalmologist and monthly by a pediatric nephrologist for at least 12 months | Strong associations exist between certain HLA genotypes in TINU patients |
| No. of patients | Presentation | Laboratory findings | Renal biopsy | Treatment | Outcome | Important contribution |
|-----------------|--------------|---------------------|--------------|-----------|---------|------------------------|
| 16              | Eight male and eight female Pt. Median age of uveitis onset 12 years and 9 months: Bilateral uveitis in all Pt. No ocular symptoms in 8/16 Pt | NA | Biopsy-proven AIN (not otherwise specified) | All 16 Pt received topical steroids. Mydriatics and antiglaucoma therapy used in 9/16 and 6/10 Pt, respectively. Prednisone or placebo per trial protocol | Follow-up duration between 6 and 48 months | No statistically significant difference in occurrence of uveitis in AIN patients, treated with prednisone or placebo |
| 2               | 12-year-old girl and a 12-year-old boy with probable TINU syndrome | Important elevation of urinary β-2 microglobulin in both patients | Not performed | Pt 1: after several ocular inflammatory exacerbations with systemic steroid therapy, intravitreal bevacizumab proved useful Pt 2: topical and systemic corticosteroid | Pt 1: without choroidal neovascularization in 5 years’ time Pt 2: NA | Two cases of choroidal neovascularization in TINU, one successfully treated with intravitreal bevacizumab injection |
| 31              | Mean age 47 years, with a 5.2:1 female predominance. Median time from onset of symptoms to renal biopsy was 30 days | Increased serum creatinine, increased urinary α-1 microglobulin excretion and decreased urine osmolality in all Pt. Approximately 50% of Pt had elevated urinary NAG excretion and leukocyturia | Performed in all patients, together with mCRP-antibody and Krebs von den Lungen-6 assays | Systemic prednisone for 6–8 weeks and subsequently tapered. 10/31 Pt received methylprednisolone pulse therapy. Cyclophosphamide used in 11/31 Pt | Median follow-up period 37 months. Approximately one-third of patients had relapses during follow-up, and most had incomplete renal recovery | Uveitis in TINU can present well after onset of AIN, leading to misdiagnosis. Elevated mCRP-antibody levels may be useful to predict late-onset uveitis occurrence |
| 6               | Four boys and two girls with definite TINU, median age of 11 years. Diagnosis of renal disease before uveitis by a median of 3 months | NA | NA | All Pt received oral corticosteroids. 3/6 Pt treated with methotrexate and 4 Pt with mycophenolate mofetil, and one each received infliximab or cyclosporine | Median follow-up was 35 years. 2/6 Pt who completed therapy were successfully weaned from immunosuppressive therapy. | Panuveitis is underappreciated as a manifestation of TINU |
| No. of patients | Presentation | Laboratory findings | Renal biopsy | Treatment | Outcome | Important contribution |
|-----------------|--------------|---------------------|--------------|-----------|---------|------------------------|
| **Ali et al. (2014), Oregon [40]** | 4 | One Pt with definite and three with ‘possible or probable’ TINU diagnosis, aged 10–31 years | Pt 1: mild anemia, elevated ESR and CRP, normal urinalysis. Pt 2: elevated serum creatinine. Pt 3: elevated serum creatinine and urine leukocyte esterase. Pt 4: normal lab values | 1/4 Pt with biopsy-proven interstitial nephritis | Pt 1: topical and systemic steroid. Pt 2: systemic steroid and oral methotrexate. Pt 3: oral steroid, switched to methotrexate. Pt 4: topical steroid, mydriatic, subsequently oral steroid | Regular follow-up for up to 3 years | Chorioretinal lesions should be recognized as a component of TINU |
| **Hettinga et al. (2015), Netherlands [41]** | 8 | Two definite and six probable TINU cases, aged 12–20 years. | All Pt had increased serum creatinine values, 7/8 Pt had increased urinary β-2 microglobulin levels. | 2/8 with biopsy-proven AIN. | NA | NA | Urinary β-2 microglobulin and serum creatinine are a simple diagnostic screening tool for detecting renal dysfunction in TINU. Use of oral corticosteroids in TINU was associated with fewer uveitis relapses, but not better kidney function. |
| **Legendre et al. (2016), France [42]** | 41 | 25 females and 16 males with biopsy-proven TINU. Median age at disease onset 46.8 years. 29/41 Pt had a bilateral anterior uveitis, and 24/41 presented with deterioration in general health | Moderate proteinuria in 32/41 Pt, sterile leukocyturia in 25/36 Pt. Median estimated GFR was 27 ml/min per 1.73 m². | All Pt had AIN, 19/39 with light-to-moderate fibrosis and 5 Pt with acute tubular necrosis. | 36/41 Pt treated with oral corticosteroids, median duration of 8.0 months. | After 1 year of follow-up, 32% of patients suffered from moderate-to-severe chronic kidney disease, and 40% of Pt had uveitis relapses | TINU syndrome characterized by limited responsiveness to corticosteroid therapy and less by severe complications |
| **Sobolewska et al. (2016), Germany [28]** | 9 | Five female and four male Pt mean age 16.7 years. All presented with bilateral uveitis | Elevated urinary β-2 microglobulin levels in 8/9 Pt. | 3 Pt with biopsy-proven AIN. In 2 pediatric cases, parents declined renal biopsy | Mean follow-up of 19.6 months. 1 Pt with recurrences after 133 months of treatment | Mean follow-up period was 54.8 years | TINU syndrome characterized by limited responsiveness to corticosteroid therapy and less by severe complications |
| **Sawai et al. (2016), Japan [43]** | 2 | Two 14-year-old girls. Pt 1 had systemic symptoms and low back pain 4 days after third dose of HPV vaccination. Pt 2 had anterior uveitis 10 weeks after third dose of HPV vaccine. | Pt 1: elevated CRP, serum creatinine, leukocyturia, glycosuria, and proteinuria. Pt 2: elevated serum creatinine, glycosuria, proteinuria, hematuria. | Renal biopsy-proven AIN in 1/2 Pt | Topical and systemic steroid in both cases | Pt 1 has stable renal function and long-term topical steroid therapy for uveitis. Pt 2 without symptoms after steroid therapy cessation | HPV vaccine might be causally related to TINU syndrome. |
| No. of patients | Presentation | Laboratory findings | Renal biopsy | Treatment | Outcome | Important contribution |
|-----------------|--------------|---------------------|--------------|-----------|---------|------------------------|
| Ariba et al. (2017), Tunisia [44] | Two male and two female patients aged 41–70 years, 1/4 Pt had fever, 3/4 Pt weight loss | Acute renal injury in 4/4 Pt, ESR elevated in all Pt, CRP in 3/4 Pt, ANCA positive 1:80 in 1/4 Pt | Renal biopsy performed in 1 Pt, consistent with AIN, without interstitial fibrosis | All patients initially received topical steroids. Systemic steroid started at onset of renal symptoms with tapering over 5-month period. | Renal outcome favorable in all Pt | The presentation and recognition of TINU in adult patients is probably underestimated |
| Nagashima et al. (2017), Japan [45] | Pt 1: 15-year-old boy with bilateral anterior uveitis, Pt 2: 14-year-old girl with bilateral papilledema, Pt 3: 49-year-old woman with panuveitis | Pt 1: elevated IgG, elevated ESR and CRP, azotemia, elevated urinary β2-microglobulin and NAG, Pt 2: normal at initial visit, Pt 3: mild increase in serum creatinine | Pt 1: biopsy-proven AIN, Pt 2: no biopsy approach, Pt 3: biopsy-proven AIN 12 months before admission | Pt 1: pulse of methylprednisolone 1 g/day for 3 days, tapering of dose, Pt 2: topical steroid, triamcinolone ace-tonide, Pt 3: topical and systemic steroid | Pt 1: continued topical and oral steroids needed due to relapse, Pt 2: no relapse, Pt 3: no relapse | In addition to anterior uveitis, TINU may present also with fundal features |
| Jia et al. (2018), People's Republic of China [22] | NA | All Pt with clinicopathologically diagnosed AIN | NA | NA | NA | Patients with drug-induced AIN or TINU have genetic susceptibility in HLA-DQA1, -DQB1, and DRB1 alleles |
| Provencher et al. (2018), Iowa [46] | 9 TINU Pt with iridocyclitis and elevated urinary β2-microglobulin, 9/9 met full diagnostic criteria | Mean urinary β2-microglobulin at presentation was 6536 μg/L (40.9 times the upper limit of normal), elevated serum creatinine in 7/9 Pt, proteinuria in 9/9 Pt | Performed in 3/9 Pt, all biopsies showed acute TIN | All Pt were treated with topical steroids, and oral steroids were used in 8/9 Pt. Two Pt were also treated with mycophenolate mofetil | Mean follow-up was 36.2 months. Relapse occurred once in two different Pt. An exacerbation occurred in 7/9 Pt within the first year | Urinary β2-microglobulin correlates with uveitis activity and trends down over the course of TINU |
| Kanno et al. (2018), Japan [47] | Two male and three female Pt, mean age of 15.8 years. First presentation to ophthalmology in 4/5 Pt, pediatrics 1/5 Pt | Serum creatinine slightly increased in 2/5 Pt, proteinuria in 3/5 Pt, glycosuria in 4/5 Pt, elevated urinary β2-microglobulin in all Pt | 2/5 Pt underwent renal biopsy, showing focal AIN | All Pt received topical steroids, 3/5 needed also systemic steroid because of renal manifestations | Mean follow-up of 54.0 months. Two Pt had recurrence of nephritis after steroid tapering. One Pt developed ocular hypertension on steroid therapy. Recurrence-free periods ranged from 12 to 71 months | Urinary β2-microglobulin level and HLA typing (especially HLA-DR4 or DRB1) may help in the diagnosis of TINU |
| No. of patients | Presentation | Laboratory findings | Renal biopsy | Treatment | Outcome | Important contribution |
|----------------|--------------|---------------------|--------------|-----------|---------|------------------------|
| Zhang et al. (2018), People’s Republic of China [48] | 4 | Age 10.8–13.6 years | All Pt presented with proteinuria and elevated urinary α-1-microglobulin. The ratio of urinary α1-microglobulin to microalbumin was greater than 1 | NA | NA | All Pt seen within a 3-year period | A ratio of urinary α1-microglobulin to microalbumin greater than 1 can be used as a diagnostic criterion for tubuloproteinuria |
| Pereira et al. (2018), Portugal [49] | 3 | Pt 1: 13-year-old female presenting with bilateral anterior uveitis | Pt 1: hypertension, raised inflammatory markers, decreased GFR, hypokalemia, metabolic acidosis, leukocyturia, glucosuria, hematuria, non-nephrotic proteinuria, and raised urine β2-microglobulin levels |
| | | Pt 2: 12-year-old female presenting with bilateral and intermediate uveitis | Pt 1: diffuse mononuclear cell interstitial infiltrates, consistent with AIN |
| | | Pt 3: 12-year-old female presenting with systemic symptoms | Pt 1 and 3: mydriatics, topical corticosteroids, oral deflazacort |
| | | | Pt 2: oral prednisolone, amlodipine, and potassium citrate. Afterwards methotrexate |
| | | | Pt 2: at 18 months receiving methotrexate, on remission |
| | | Pt 3: one episode of recurrent uveitis within 5 months observation period | Patients with uveitis need to be screened for renal disease |
| Yang et al. (2019), People’s Republic of China [30] | 32 | Female-to-male ratio was 1.46, mean age of onset 41.1 years. 20/32 Pt had uveitis after AIN. Fatigue was most common systemic symptom (30/32 Pt) and polyuria most common renal symptom (20/32 Pt) | 2/32 Pt had anemia. Other laboratory data are NA |
| | | Diagnoses of AIN were all confirmed by renal biopsy | Topical and systemic steroids in all Pt, from 2 to 38 months. Immunomodulatory agents administered to 18/32 Pt |
| | | Mean duration of follow-up was 31.6 years. 50% of recurrences occurred during the first year | Ultra-wide-field fluorescence is sensitive in detecting the activity of uveitis and might be useful in monitoring disease progression |
| No. of patients | Presentation | Laboratory findings | Renal biopsy | Treatment | Outcome | Important contribution |
|----------------|--------------|---------------------|--------------|-----------|---------|------------------------|
| Takeuchi et al. (2019), Japan [50] | 8 Eight TINU Pt within a cohort of 156 Pt with noninfectious uveitis | NA | Topical steroid monotherapy in 6/8 Pt, other 2 Pt received long-term steroids | NA | Betamethasone eye drops, topical triamcinolone acetonide, and long-term, systemic corticosteroids were the major therapeutic strategies used for uveitis relapse or exacerbation |
| Abd et al. (2020), Egypt [51] | 8 Eight TINU Pt within a cohort of 781 Pt with intermediate uveitis | NA | Full-dose steroid treatment was maintained for 1 month in all Pt, followed by gradual tapering. Steroid treatment was continued for 6.0 months | NA | 40% of patients with intermediate uveitis had identifiable a systemic disease |
| Clave et al. (2019), France [25] | 7 Five male and two female Pt, aged 10.1–14.5 years, all with bilateral uveitis and renal involvement | All Pt with elevated serum creatinine and lower GFR, other laboratory data | All Pt showed a gradual improvement of renal function | NA | Children with idiopathic AIN and prompt treatment have a better prognosis, and chronic kidney disease occurrence justifies long-term follow-up |
| Çakan et al. (2019), Turkey [52] | 4 Three male and one female Pt, median age at diagnosis of uveitis 13.4 years. Bilateral anterior uveitis in 3/4 Pt. All had systemic manifestations | All Pt had renal manifestations as microscopic hematuria, glycosuria, and mild proteinuria | All Pt received topical steroids and 1 Pt needed systemic steroids and methotrexate. | NA | A simple urine test may help in establishing the diagnosis of TINU syndrome in uveitis patients |
| Cao et al. (2020), Ohio [53] | 10 Six female and four male Pt with TINU and posterior ocular segment inflammation. Age distribution was bimodal (10–46 years and 77–83 years) | Mean urinary β-2-microglobulin levels were more than tenfold upper limit of normal. Serum creatinine was elevated in 6/10 Pt. Urinalysis was abnormal in 9/10 Pt | 11 of 20 eyes were initially treated with topical steroids only, and 2 Pt received oral steroids alone due to posterior segment involvement | Visual acuity was stable or improved for all but one patient who had a subretinal macular scar | Posterior segment inflammation in the setting of TINU is not uncommon |
| Roy et al. (2020), United Kingdom [54] | 6 Pt from a cohort of 10 Pt with AIN, age range 6–16 years, male-to-female ratio 1:9 | Lowest GFR in TINU Pt ranged from 7 to 30 ml/min/1.73 m² | All Pt had biopsy-proven AIN | Visual acuity was stable or improved for all but one patient who had a subretinal macular scar | There is a high proportion of TINU in a UK case series of biopsy-proven AIN in children |
| No. of patients | Presentation | Laboratory findings | Renal biopsy | Treatment | Outcome | Important contribution |
|----------------|--------------|---------------------|--------------|-----------|---------|------------------------|
| 4              | 4 Pt with TINU from a cohort of 98 Japanese uveitis Pt | NA                      | NA           | 48% of the 98 Pt received only topical steroids, whereas 39/98 Pt received some form of systemic antiinflammatory therapy | 80.9% of the eyes maintained a visual acuity of 20/20 at the final visit | Hypotony, serous retinal detachment, and pupil disorders can lead to visual loss in uveitis patients, including TINU |

Total 306

NA data not available, No. number, Pt patient, ESR erythrocyte sedimentation rate, HLA human leukocyte antigen, NAG N-acetyl-(β-D)-glucosaminidase, mCRP modified C-reactive protein, AIN acute interstitial nephritis, GFR glomerular filtration rate, HPV human papilloma virus, ANCA antineutrophil cytoplasmic antibodies, UK United Kingdom
eliciting an IgG-mediated oculorenal immune response [4]. A novel human glycoprotein, Krebs von den Lungen-6, was also observed to be significantly increased in sera and distal renal tubules of TINU patients [5]. Furthermore, certain interleukin-10 polymorphisms have been found to be more prevalent in TIN/TINU patients, broadening our understanding of the genetic basis of the disease [6].

Differential diagnosis and epidemiology

TINU syndrome was shown to represent 15–65% of cases of acute interstitial nephritis (AIN) in pediatric renal care centers [7, 8]. It is essential to distinguish it from other causes of AIN, either drug-induced, autoimmune, metabolic, malignant, or consequential to a variety of infectious causes [9–11].

A large case series [3] suggests TINU shows a 3:1 female-to-male predominance, with a median age of 15 years. A UK-based study estimated the incidence as 1 per 10 million population per year [12]. Several recent reviews confirmed peak incidence in adolescence and a female-to-male predominance [9, 13–16]. Genetic studies indicate a strong association with certain HLA haplotypes, especially variants DQA1, DQB1, DRB1, and DR14 [17–21]. No disease-associated HLA variants were confirmed in our patient.

Clinical presentation

TINU patients typically present with a viral-like illness, after which renal dysfunction is discovered. Alternatively, in about 20% of cases (including this case), the patient presents with symptoms of burning eyes and/or visual blurring [9, 13–16] and is subsequently discovered to have renal manifestations. This asynchrony prompts a high degree of clinical suspicion in treating young, female patients with AIN or acute uveitis. In a Finnish study [2], which prospectively evaluated the presence of acute uveitis in biopsy-proven AIN at onset, at 3 and at 6 months afterwards, 16/19 (84%) of pediatric patients had uveitis within the observation period, half (8/16) without ocular symptoms. However, there are no guidelines or recommendations regarding ocular screening in patients with AIN.

Acute kidney injury is nearly universal in the setting of TINU and is usually in the mild-to-moderate range. It may be complicated with hypertension, which was also the case in our patient. In literature, cases of Fanconi syndrome and nephrogenic diabetes insipidus in association with TINU have been described [23, 24], as well as progression to chronic kidney disease in adult and pediatric patients [25]. Table 3 presents TINU characteristics in comparison with disease manifestations, seen in our patient.

Pathohistological findings

Upon light microscopy, features of a predominantly CD3-positive lymphocytic infiltrate with fewer plasma cells and macrophages are present. A prominent eosinophilic infiltrate may be seen initially, as well as interstitial granulomas that can become confluent. Upon disease progression, the inflammation subsides, while variable amounts of interstitial fibrosis appear. The CD4-to-CD8 ratio varies. However, studies indicate a reciprocal T-cell profile in the kidney as compared with what is seen in peripheral
Table 2  Reported case series of tubulointerstitial nephritis with uveitis, sorted by country and year of publication

| Country (city) | Author and year of publication (ref.) | No. of patients |
|---------------|---------------------------------------|-----------------|
| France        |                                       |                 |
| NA            | Azar 2000 [56]                         | 2               |
| Dijon         | Legendre 2016 [42]                    | 41              |
| Marseille     | Clavé 2019 [23]                       | 7               |
| USA           |                                       |                 |
| California    | Mandeville 2001 [3]                   | 133             |
| California    | Levinson 2003 [19]                    | 18              |
| Oregon        | Mackensen 2007 [57]                   | 33              |
| Oregon        | Houghton 2012 [36]                    | 4               |
| Illinois      | Binbaum 2012 [37]                     | 2               |
| Virginia      | Reddy 2014 [21]                       | 6               |
| Oregon        | Ali 2014 [40]                         | 4               |
| Iowa          | Provencher 2018 [46]                  | 9               |
| Ohio          | Cao 2020 [53]                         | 10              |
| Serbia        |                                       |                 |
| NA            | Nikolić 2001 [58]                     | 8               |
| Spain         |                                       |                 |
| Madrid        | Gorrono-Echebarria 2001 [17]          | 3               |
| Sevilla       | Sanchez Burson 2002 [59]              | 6               |
| Japan         |                                       |                 |
| Hirosaki      | Tanaka 2001 [60]                      | 2               |
| Hirosaki      | Suzuki 2004 [33]                      | 2               |
| Okayama       | Matsuo 2002 [61]                      | 4               |
| Nagasaki      | Deguchi 2003 [62]                     | 2               |
| Hokkaido      | Goda 2005 [63]                        | 12              |
| Sapporo       | Kase 2006 [5]                         | 17              |
| Tokyo         | Yanagihara 2009 [32]                  | 3               |
| Sapporo       | Takemoto 2013 [38]                    | 2               |
| Kanazawa      | Sawai 2016 [43]                       | 2               |
| Yokohama      | Nagashima 2017 [45]                   | 3               |
| Gifu          | Kanno 2018 [47]                       | 5               |
| Saitama       | Takeuchi 2019 [50]                    | 8               |
| Tokyo         | Kitano 2020 [55]                      | 4               |
| Germany       |                                       |                 |
| Essen         | Hudde 2002 [64]                       | 4               |
| Tübingen      | Biester 2010 [35]                     | 2               |
| Tübingen      | Sobolewska 2016 [28]                  | 9               |
| United Kingdom|                                       |                 |
| London        | Baker 2004 [29]                       | 6               |
| Southampton   | Howarth 2004 [65]                     | 2               |
| Scotland      | Joss 2007 [56]                        | 2               |
| Liverpool     | Roy 2020 [54]                         | 6               |
| Australia     |                                       |                 |
| Melbourne     | Lim 2005 [67]                         | 2               |
| Adelaide      | Li 2008 [68]                         | 2               |
| Czech Republic|                                       |                 |
| NA            | Svozilkova 2006 [69]                  | 5               |
| Prague        | Dusek 2008 [70]                       | 2               |
Table 2 (continued)

| Country (city)          | Author and year of publication (ref.) | No. of patients |
|-------------------------|---------------------------------------|-----------------|
| Morocco                 | Mortajil 2006 [71]                    | 2               |
| People's Republic of China |                                      |                 |
| NA                      | Yao 2007 [72]                        | 2               |
| Beijing                 | Tan 2011 [4]                         | 9               |
| Beijing                 | Li 2014 [39]                         | 31              |
| Beijing                 | Jia 2018 [22]                        | 38              |
| Beijing                 | Zhang 2018 [48]                      | 4               |
| Beijing                 | Yang 2019 [30]                       | 32              |
| Israel                  | Weinstein 2010 [34]                  | 5               |
| Finland                 | Peräsaari 2013 [18]                  | 20              |
| Oulu                    | Saarela 2013 [2]                     | 16              |
| Netherlands             | Hettinga 2015 [41]                   | 8               |
| Tunisia                 | Ariba 2017 [44]                      | 4               |
| Portugal                | Pereira 2018 [49]                    | 3               |
| Egypt                   | Abd 2020 [51]                        | 8               |
| Turkey                  | Çakan 2019 [52]                      | 4               |
|                         |                                       | 580 in total    |

NA data not available

Table 3  Comparison of clinical characteristics of tubulointerstitial nephritis and uveitis with our patient

| Clinical characteristics† | Our patient |
|---------------------------|-------------|
| AIN in TINU               | Mild elevation of serum creatinine. AH treated with lifestyle interventions already before disease onset |
| 1. Abnormal renal function| Mild proteinuria, microalbuminuria, elevated α1 microglobulin, normoglycemic glycosuria |
| 2. Abnormal urinalysis   | No history of systemic symptoms |
| Low-grade proteinuria, glycosuria, urinary eosinophilia, hematuria, sterile pyuria, and presence of white cell casts, as well as phosphaturia and aminociduria. Elevated urinary NAG, α1 and β2 microglobulin | Marked elevation of ESR, mild elevation of CRP, mild anemia |
| 3. Systemic illness lasting ≥ 2 weeks | (a) Signs and symptoms: fever, rash, weight loss, anorexia, malaise, fatigue, flank pain, arthralgia or myalgia |
| (b) Blood and urinary findings: anemia, eosinophilia, elevated ESR and CRP, abnormal LFT, acid–base disorders | |
| Uveitis in TINU           | Unilateral anterior uveitis at presentation and contralateral anterior uveitis after 1 month |
| 1. Classical bilateral, anterior uveitis with ocular redness, pain, and photophobia | |
| 2. Atypical uveitis: intermediate and/or posterior involvement | |
| 3. Complications: posterior synechiae, cystoid macular edema, disc edema, elevated intraocular pressure, cataract formation | |

†The renal and ocular course are thought to be independent, and neither the severity nor prognosis of nephritis is influenced by the presence of uveitis [16]. AIN acute interstitial nephritis, AH arterial hypertension, NAG N-acetyl-β-glucosaminidase, ESR erythrocyte sedimentation rate, CRP C-reactive protein, LFT liver function tests. Adopted from [3, 9].
blood, indicating that cellular immunity is active at the tissue level and decreased systemically [9]. Tubular atrophy or tubulitis is also characteristic for TINU and is in accordance with clinical evidence of tubular dysfunction, reported in our patient and many cases of TINU [9, 26].

**Treatment**

As in other uncommon disorders, there are no evidence-based treatment protocols, so the decision whether to initiate systemic corticosteroid or immunosuppressive therapy depends on renal and ocular involvement. If nephritis is mild or in remission, topical steroids may be used to treat uveitis, though not efficient in posterior intraocular segment involvement [9]. Systemic corticosteroids are generally reserved for cases of progressive renal involvement [3] and are needed in about 80% of patients [27]. Oral prednisone or prednisolone with a dosage of 1–1.5 mg/kg/day is usually used. The duration and schedule for tapering of steroid dose depends mainly on patient response [9, 13, 15, 16, 27]. Because of frequent relapses and recurrences of disease, some authors suggest at least 12 months of oral corticosteroid therapy [28], while others advocate an early and short course [29], which was the case in our patient. We believe that, in the absence of evidence-based treatment protocols, a case-by-case management may be adopted [27].

In a pediatric case series [2], all 16 patients with TINU received topical ocular steroids. Mydriatic therapy was necessitated in 9/16 patients and antiglaucoma therapy in 6/16 cases. Surprisingly, oral prednisone did not influence occurrence of uveitis. In steroid-resistant cases or in exacerbation of disease after weaning from corticosteroid therapy, immunosuppressive medications such as cyclophosphamide, cyclosporine, methotrexate, or mycophenolate mofetil may be used [9, 13, 15, 16].

**Prognosis**

Ocular and renal outcomes are usually good with appropriate treatment, as most respond to initial topical or systemic therapy. The disease may remit altogether or run a chronic or recurrent course, usually appropriately controlled through judicious use of immunosuppressive agents [9, 20, 30]. Though early TINU literature held that renal disease often resolved spontaneously, repeat renal biopsy studies reported cases of continued nephritis after pulse corticosteroids [31, 32], mandating close follow-up of patients for several years after disease onset. Prompt corticosteroid therapy initiation also seems to play a role as demonstrated in a small case series, where a patient with delayed treatment demonstrated persistent elevations of beta-2-microglobulin and renal inflammation with subsequent renal damage [33]. Additionally, severe TINU can lead to end-stage renal failure requiring dialysis and kidney transplant [16].

Most patients will maintain or improve eyesight from presentation. However, ocular disease recurs in up to 50% of patients after corticosteroid withdrawal [16]. Younger age was identified as a risk factor for chronic uveitis, though few studies have evaluated the impact of systemic therapy on reducing that risk [16]. Vision is seldom severely impaired, as demonstrated in a case series of 133 patients [3], where vision outcome was rarely worse that 20/40. Therefore, optimal care incorporates joint nephrological and ophthalmic input, which was done in our patient.

**Conclusion**

This case highlights the need to maintain a high degree of suspicion and close follow-up in young, female patients who present with features of tubulointerstitial nephritis or uveitis. As there are no evidence-based protocols for treating TINU, management relies on case reports and case-series. The recommended treatment for uveitis is topical steroids. However, most cases necessitate systemic therapy with corticosteroids owing to renal involvement or in cases of posterior ocular involvement.

Immunomodulatory drugs may be used in resistant cases. With prompt therapy, prognosis of both renal and ocular involvement is usually favorable, though relapses might occur. Therefore, combined nephrological and ophthalmological care is warranted. Furthermore, there is a need for a multicenter study and registry formation to obtain important clinical data regarding follow-up and treatment of these patients, and a frameshift for implementation of multinational guidelines of treatment and prognosis.

**Learning points**

- In patients presenting with uveitis and/or acute interstitial nephritis, a suspicion of TINU syndrome should be made, especially if young and/or female.
- Even when histological features of important tubulointerstitial nephritis and noncaseating granuloma can be found, as in our case, the urinalysis can show only mild urine changes with proteinuria and glucosuria, with no hematuria. In our patient with bilateral uveitis and marked elevation of ESR, a renal biopsy proved useful in guiding therapy.
- With prompt ocular and systemic corticosteroid therapy, prognosis of TINU is favorable, despite occasional relapses.
Patient’s perspective

I have to say that the overall care from both the Nephrology and Ophthalmology department was very professional. At first, I was quite shocked after I developed an inflammation of my eye, which did not allow me to see properly. Also, I was surprised that I had additional problems with my kidneys that I did not even notice. After several weeks of staying in the hospital, my nephrologist told me that I would have to undergo a kidney biopsy, the thought of which was quite scary. However, as I had already known the department staff for years, I trusted them fully and was not too worried after the diagnosis of TINU came. The therapy which was offered to me was quite tolerable, though I did not like gaining even more weight after being put on corticosteroids, which the doctors told me could happen. Coming home after more than a month, I am very happy to again attend school, and try to maintain a healthy lifestyle as recommended.

Abbreviations
TINU: Tubulointerstitial nephritis with uveitis; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; ANA: Antinuclear antibodies; anti-ENA: Anti-extractable nuclear antigen antibodies; anti-DNA: Anti-deoxyribonucleic acid antibodies; HLA: Human leukocyte antigen; mCRP: Modified C-reactive protein; AIN: Acute interstitial nephritis.

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TP and NMV managed the patient, and MF performed the pathological assessment of renal biopsy samples. TP wrote the original manuscript, MF provided pathological images with descriptions, and NMV performed clinical supervision and edited the manuscript. All authors read and approved the final manuscript.

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Competing interests
The authors declare that they have no competing interests.

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