Acute tubulointerstitial nephritis-uveitis (TINU) syndrome developed secondary to paracetamol and codeine phosphate use: two case reports

Demet Alaygut[1], Meral Torun-Bayram[1], Mehtat Ünlü [2], Alper Soylu[1], Mehmet Türkmen[1], Salih Kavukçu[1]

Departments of [1]Pediatric Nephrology and [2]Pathology, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey. E-mail: alaygutdemet@gmail.com

SUMMARY: Alaygut D, Torun-Bayram M, Ünlü M, Soylu A, Türkmen M, Kavukçu S. Acute tubulointerstitial nephritis-uveitis (TINU) syndrome developed secondary to paracetamol and codeine phosphate use: two case reports. Turk J Pediatr 2014; 56: 92-96.

Tubulointerstitial nephritis (TIN) refers to a group of heterogeneous diseases affecting the interstitial compartment of the kidney. It might be primary or can develop secondary to many urinary systemic diseases. Primary TIN develops mainly following drug usage, exposure to toxins, and also infections and humoral and cell-mediated immune reactions. In some patients, signs of systemic inflammatory reactions can be the first presenting symptoms. Histopathological evaluation reveals mononuclear cells and lymphocytes in the interstitium and tubuli. Acute and chronic TIN can resolve after elimination of the culprit destructive factors, as drugs, toxins and immune reaction. Combination of tubulointerstitial inflammation and uveitis is termed as tubulointerstitial nephritis-uveitis (TINU) syndrome. Uveitis might occur before, after, and also concomitantly with TIN. Herein, two adolescent cases of TIN and TINU, seemingly developed secondary to paracetamol and codeine phosphate use, are presented.

Key words: tubulointerstitial nephritis, codeine phosphate, paracetamol, over-the-counter drugs, uveitis, children.

Tubulointerstitial nephritis (TIN) is an important cause of acute renal failure in children and adults. TIN was indicated as an etiological factor in 10-25% of the adults and in 7% of the children with acute renal failure[1]. It is especially characterized by infiltration of the interstitium and tubular structures with inflammatory cells, which are rich in lymphocytes[2]. However, spontaneous progression of the renal disease in both adults and children and the inability to perform routine renal biopsy may preclude adequate reporting of the diagnosis[1]. In some cases, renal changes are accompanied by uveal inflammation, and the term "tubulointerstitial nephritis and uveitis (TINU) syndrome" was used for this condition. In many cases, its etiology cannot be defined. Many bacterial and viral infections, various drugs (especially antibiotics), and non-steroidal antiinflammatory drugs (NSAIDs) have been suggested as triggering factors[2]. Renal involvement can show changes ranging from asymptomatic urinary findings and mild azotemia to non-oliguric or oliguric acute renal failure[1]. Causative agents of TIN in children are drugs rather than infections. The major category of drugs in both children and adults involves antibiotics, NSAIDs, anticonvulsants, and diuretics[1]. It is possible for patients to purchase over-the-counter (OTC) drugs (analgesics, decongestants, antitussives, expectorants, and mucolytic drugs) without the need of prescription, and while they are easily accessible, they have many side effects. This report presents two adolescent cases of TIN and TINU developing due to use of paracetamol and codeine phosphate.

Case Reports

Case 1

A 17-year-old male patient had complaints of malaise, fatigue, weight loss of 5 kg in the previous month, and many daily vomiting

episodes for the last two days. His medical history revealed use of paracetamol and codeine phosphate three weeks ago for symptomatic relief of his coughing and high fever complaints. It was learned that he had taken a drug consisting of 500 mg paracetamol and 10 mg codeine phosphate, three times a day for two days. His personal and familial medical history was otherwise unremarkable. His weight was 72 kg (75th percentile), and his height was 169 cm (25th percentile). His physical examination did not show any signs of fever, hypertension or edema. His biochemical test results were compatible with acute renal failure (creatinine clearance, 51 ml/min/1.73 m^2; blood urea nitrogen [BUN]: 25 mg/dl; creatinine, 2.77 mg/dl). Results of liver function tests and serum calcium, phosphorus, other electrolytes, and blood gas values were within normal limits. Whole blood counts showed leukocytosis (WBC, 16,300/mm^3) without any evidence of anemia or thrombocythemia. Differential counts evaluated on peripheral blood smear slides presented normochromic and normocytic red blood cells, dominance of neutrophils (78%), and eosinophils (8%). Test results for erythrocyte sedimentation rate (ESR, 76 mm/h), C-reactive protein (54 mg/L), immunoglobulin (Ig)A (133 mg/dl [63-484]), IgG (842 mg/dl [540-1822]), and IgE (820 IU/ml [0-100]) were determined as indicated in parentheses. Although there were higher blood eosinophil counts (500/mm^3) in the patient, no eosinophils were determined in urine samples. Urinalysis revealed normal urinary density, pH, leukocyturia, leukocytes, and hyaline cylinders. No microbial growth was detected in urine cultures. Tubular function tests demonstrated non-nephrotic proteinuria (24 mg/m^2/h) and a decrease (74%) in tubular resorption of phosphorus. On ultrasonographic examination, a slight increase was detected in bilateral renal echogenicity. Histopathological examination of percutaneous renal biopsy specimens displayed diffuse interstitial nephritis with eosinophils, neutrophils and mainly lymphocytes. No evidence regarding granuloma, glomerulosclerosis, or tubular atrophy was found (Figs. 1, 2). All these findings revealed the presence of acute interstitial nephritis. Tests and anteroposterior (AP) chest X-rays were performed to make a differential diagnosis, and sarcoidosis, which is one of the etiologic factors, was not found. Levels of C3 and C4, antibodies used in the autoimmune (antinuclear antibodies [ANA], a*nti-neutrophil cytoplasmic antibodies* [ANCA], and anti-dsDNA, etc.) and extractable nuclear antigens (ENA) test panels were within normal limits. Serologic tests for *Mycoplasma pneumoniae*, chlamydia, hepatitis, *Toxoplasma gondii*, cytomegalovirus (CMV), and Epstein-Barr virus (EBV) did not show any evidence of acute infection. On day 5 of the follow-up period, redness and photosensitivity of both eyes, but more prominent in the left, became apparent. Ophthalmological examination was compatible with bilateral anterior uveitis, and the patient was evaluated to have acute interstitial nephritis associated with uveitis (TINU). At the first week of the follow-up period, his renal functions had improved without receiving systemic steroid therapy. Topical steroid (dexamethasone) therapy was maintained for three weeks for the uveitis. The patient is monitored periodically with nephrologic and opthalmologic tests.

Case 2

A 14-year–old female patient was consulted with complaints of abdominal pain, malaise, and weight loss (5 kg in 3 months) starting four months ago. No associated high fever, joint pain, or headache was observed. It was learned from her family that she had been hospitalized in another medical center upon detection of pyuria, higher ESR (107 mm/min), lack of bacterial growth in urine culture media, and malaise, with the presumptive diagnosis of iron deficiency anemia, for which she received treatment with iron preparations for one month. The patient indicated that she had been using drugs containing paracetamol and codeine phosphate every time she felt fatigue and flu-like symptoms, and had received these medications again one month ago, consisting of 500 mg paracetamol and 10 mg codeine phosphate two or three times a day for four days. Her personal and familial medical history was unremarkable. Her weight was 47 kg (50th percentile) and height 161 cm (60th percentile), and pale conjunctivas were determined. She was not hypertensive or febrile and had normal systemic physical examination findings. Her biochemical test results were as follows: BUN, 17 mg/dl and creatinine, 0.9 mg/dl (estimated glomerular filtration rate (eGFR),

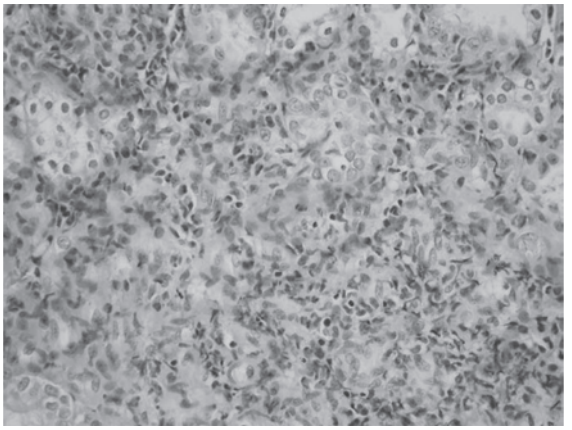

Fig. 1. Renal biopsy with hematoxylin and eosin (H&E) stain. Diffuse interstitial nephritis with eosinophils.

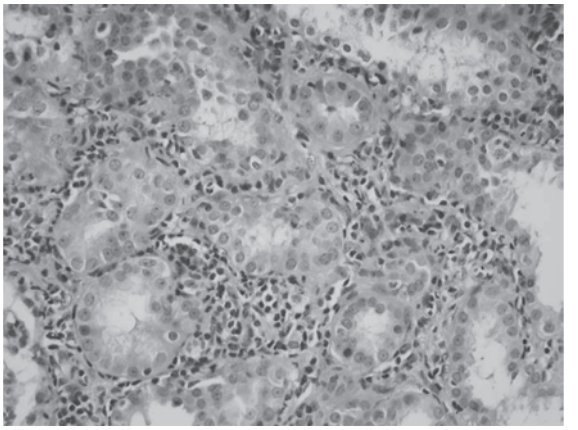

Fig. 2. Diffuse interstitial nephritis with neutrophils and mainly lymphocytes.

98.3 ml/min/1.73 m^2). Furthermore, levels of serum electrolytes, calcium, phosphorus, blood gases, and parathyroid hormone (PTH) were within normal limits. Liver function test results were unremarkable. ESR (47 mm/h) and C-reactive protein (8.8 mg/L) values were also determined. Whole blood cell counts revealed microcytic normochromic anemia (hemoglobin, 11.3 mg/dl; mean red blood cell volume [MCV]= 78 fL). Leukocytosis was not detected; however, eosinophilia (10.5%) was noted. Urine density and pH were within normal ranges with normoglycemic glucosuria, proteinuria (0.5 g/L), and absence of any morphologically abnormal cells in the urine sediment. During urinalysis with 24-hour samples, a creatinine clearance of 99 ml/min/1.73 m^2, nonnephrotic proteinuria (22 mg/m^2/h), and microalbuminuria (162 mg) were detected. Tubular phosphorus resorption and fractionated Na excretion were unremarkable without any evidence of calciuria or uricosuria. Urinary tests of her parents were unremarkable with respect to familial glucosuria. Renal ultrasound (US) demonstrated increasing echogenicity of both kidneys. Levels of IgE, C3 and C4 were within normal limits. Increase in creatinine levels, eosinophilia, specific symptoms at admission, tubular dysfunction, and renal US findings led us to consider the diagnosis of acute interstitial nephritis. Kidney biopsy was not performed. Results of serologic tests performed in terms of EBV, CMV, and hepatitis to exhibit etiologic factors were not compatible with acute infection. Serologic tests aimed to identify autoimmune diseases could not detect the presence of abnormal antibodies (ANA, ANCA, anti-dsDNA, ENA). Thyroid function test results were unremarkable. Drug use (paracetamol, codeine phosphate) was thought to be the etiological factor for the acute interstitial nephritis. Ophthalmological examination done to determine any evidence of uveitis was unremarkable. Two weeks later, levels of urine creatinine and protein regressed spontaneously to 0.8 mg/dl and 16 mg/m^2/h, respectively. Glucosuria disappeared. The patient continues to attend follow-up visits.

Discussion

In accordance with the definition of TIN/TINU, both cases had nonspecific symptoms (e.g., nonoliguric acute renal failure in the first case and mild azotemia in the second case). Especially in drug-induced TIN, fever, rash, and arthralgia were detected to various extents[1]. Drug-induced TIN was assumed to be present in both cases; however, while fever was identified in the first case, the other two symptoms were not observed in either case. In a study conducted on 128 adults with a diagnosis of TIN, 70% of the cases were considered to be induced by drugs, and rash, fever, and eosinophilia were determined in only 10% of the cases[3]. Diagnostic laboratory test results are increased serum creatinine levels and increased ESR, normochromic normocytic anemia, leukocytosis, and peripheral eosinophilia. Additional laboratory findings were abnormal urinary sediment findings, as well as proteinuria, glucosuria, impaired phosphorus intake, and renal tubular acidosis, which vary based on the affected segment of the

nephron. Although not diagnostic, increased IgE levels are seen in drug-induced TIN. Increased IgE levels associated with leukocytosis and peripheral eosinophilia were present in the first case, but only peripheral eosinophilia in the second case. The definitive diagnosis is established during examination of biopsy specimens. However, since renal functions improve upon elimination of the causative agent presumably responsible for the acute TIN, there is no need for biopsy[1]. Biopsy in the first case was carried out due to the presence of more prominent signs of renal failure. Biopsy in the second case was not carried out due to the mild renal dysfunction and rapid functional improvement. Typical light microscopic findings demonstrated tubulointerstitial cell infiltration with lymphocytic dominance. Vascular or glomerular structures are not affected. A moderate degree of mesangial cellularity or periglomerular inflammation can be detected. Especially in drug-induced TIN, eosinophils are more prominent[1]. Histopathological findings of the first case were also similar to those described above.

Tubulointerstitial nephritis and uveitis (TINU) syndrome is accompanied by uveal inflammation. Since renal and ocular symptoms do not appear together, some cases present diagnostic difficulties[4]. TINU syndrome is observed at a median age of 15 years (9-74 years) with a female/male ratio of 3/1[5]. Since drug-related TIN is an idiosyncratic reaction, it is very difficult to identify the patient who might develop TIN. OTC drugs are mostly utilized, especially with the intention to relieve pain, fever and symptoms. Potential development of TIN after use of analgesic was reported. Both of our cases used paracetamol and codeine phosphate-containing drugs for their malaise and flu-like symptoms. The purpose of this report is to emphasize TIN/TINU, which developed based on the use of paracetamol and codeine phosphate. Paracetamol is essentially metabolized in the liver by conjugation with glucuronic acid (55%) and sulfuric acid (35%). In the therapeutic plasma concentration range, this metabolite is detoxified by conjugation with glutathione. In case of intoxication, the amount of this toxic metabolite increases and outweighs the amount of available glutathione, which can lead to hepatic failure and renal tubular necrosis. Codeine is metabolized by O- and N-demethylation in the liver (via the cytochrome P450 system) to morphine (about 10% of a codeine dose is demethylated to morphine), norcodeine, and other metabolites, including normorphine and hydrocodone. Codeine and its metabolites are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid. Approximately 3%-16% of a dose is eliminated unchanged in the urine. TINU syndrome might present with symptoms of fever, weight loss, malaise, abdominal pain, flank pain, arthralgia, myalgia, polyuria, and nocturia. Accordingly, the first case had symptoms of weight loss, malaise and fatigue. TINU is also associated with granulomatous hepatitis, hyperthyroidism, and autoimmune diseases such as EBV infection, Sjögren's syndrome, and rheumatic arthritis. Presence of renal failure and hypocomplementemia has been also reported in cases with TINU. These diseases were ruled out in both of our cases. Uveitis appears on average one month after renal disease, but it might delay 14 months following its onset[5]. Renal disease generally spontaneously recovers; however, uveitis may persist or recur within 10 years[6]. In the first case, uveitis was detected one month after the emergence of renal findings. In the second case, ophthalmologic findings were unremarkable, and the patient remains under follow-up for the presence of uveitis. Since subtle symptoms of uveitis are seen in children, its diagnosis and treatment during the early stage present difficulties. In 50% of the patients, uveitis persists or recurs[2]. The treatment consists of topical corticosteroids and cycloplegic agents. In cases refractory to topical therapy, oral corticosteroids equivalent to systemic prednisolone should be instituted as soon as possible. In the first case, uveitis responded to local treatment within a week, and there was no need for systemic steroids. Renal findings in TINU are usually self-limiting, and many cases recover spontaneously or after steroid therapy. Clarkson et al.[7] demonstrated comparatively similar follow-up results for patients with TIN who received or did not receive steroid therapy. On the contrary, Gonzales et al.[8] reported favorable impact of steroid therapy on interstitial fibrinogenesis especially during the early stage of drug-related TIN. Kodner and Kudrimoti[9] published an algorithm for the treatment of TIN, and

recommended initiation of prednisolone therapy at a daily dose of 1 mg/kg in cases with persistent symptoms despite elimination of the etiological factor and existing renal failure. Persistent cases with renal dysfunction have been reported in 10% of the cases[2]. Both of our cases recovered spontaneously without any requirement of systemic steroid therapy.

In conclusion, the prognosis is relatively improved in TIN associated with renal failure. The onset of uveitis associated with TIN can delay with an asymptomatic course. Patients with diagnoses of TIN/TINU should remain under long-term follow-up. Many drug-induced cases of TIN/TINU have been reported. Herein, we aimed to emphasize the importance of OTC drugs such as paracetamol and codeine phosphate in the etiopathogenesis of TIN/TINU.

REFERENCES

1. Alon US. Tubulointerstitial nephritis. In: Avner ED, Harmon WE, Niaduet P, Yoshikowa N (eds). Pediatric Nephrology (6th ed). Berlin, Heidelberg, Germany: Springer-Verlag; 2009: 1081-1098.
2. Jahnukainen T, Ala-Houhala M, Karikoski R, et al. Clinical outcome and occurrence of uveitis in children with idiopathic tubulointerstitial nephritis. Pediatr Nephrol 2011; 26: 291–299.
3. Baker RJ, Pusey CD. The changing profile of acute tubulointerstitial nephritis. Nephrol Dial Transplant 2004; 19: 8–11.
4. Thomassen VH, Ring T, Thaarup J, et al. Tubulointerstitial nephritis and uveitis (TINU) syndrome: a case report and review of the literature. Acta Ophthalmol 2009; 87: 676–679.
5. Mandeville JT, Levinson RD, Holland GN. The tubulointerstitial nephritis and uveitis syndrome. Surv Ophthalmol 2001; 46: 195–208.
6. Vohra S, Eddy A, Levin AV, et al. Tubulointerstitial nephritis and uveitis in children and adolescents. Pediatr Nephrol 1999; 13: 426–432.
7. Clarkson MR, Giblin L, O'Connell FP, et al. Acute interstitial nephritis: clinical features and response to corticosteroid therapy. Nephrol Dial Transplant 2004; 19: 2778–2783.
8. Gonzáles E, Gutiérrez E, Galeano C, et al. Early steroid treatment improves the recovery of renal function in patients with drug-induced acute interstitial nephritis. Kidney Int 2008; 73: 940–946.
9. Kodner CM, Kudrimoti A. Diagnosis and management of acute interstitial nephritis. Am Fam Physician 2003; 67: 2527–2534.