Case Report

AN ADOLESCENT GIRL WITH TUBULOINTERSTITIAL NEPHRITIS AND UVEITIS (TINU) SYNDROME

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Abstract: Tubulointerstitial nephritis and uveitis (TINU) syndrome is a rare and poorly understood condition that is likely underdiagnosed. The possibility that uveitis and acute tubulointerstitial nephritis do not occur simultaneously may make diagnosis more difficult. Treatment consists of systemic corticosteroids and potentially non-steroid immunosuppressants. Renal disease usually resolves spontaneously or with appropriate treatment; however, ocular manifestations may be chronic or relapsing. We report a case of tubulointerstitial nephritis and uveitis syndrome in a 12-year-old female.

Keywords: pediatric nephrology, tubulointerstitial nephritis, bilateral uveitis, acute on chronic renal failure

Abbreviations: TINU: Tubulointerstitial Nephritis and Uveitis

INTRODUCTION Tubulointerstitial nephritis and uveitis (TINU) syndrome is a rare cause of acute tubulointerstitial nephritis preceded by, accompanied with, or followed by uveitis [1]. Diagnosis is one of exclusion and may be difficult given the possibility of non-concurrent symptom manifestation. Approximately 5% of the cases of tubulointerstitial nephritis [2] and fewer than 2% of the cases of uveitis can be attributed to TINU syndrome; however, it has been estimated that it may account for up to a third of acute-onset bilateral anterior uveitis in patients under 20 years of age [3].

CASE PRESENTATION A 12-year-old female patient with no significant medical history presented to the hospital with elevated creatinine concerns on outside labs. For the two previous months, she experienced dull, non-radiating epigastric abdominal pain that occurred once or twice a week without any apparent aggravating factors. Additionally, she had 1-2 episodes of emesis per week that were not related to abdominal pain. The patient also reported headaches during that period but could not elaborate on their position, intensity, or duration. She had taken small quantities of both ibuprofen and bismuth subsalicylate in the previous two months. When her symptoms began, she was seen at a small community health center where she was found to be anemic (hemoglobin of 10.6 mg/dL and hematocrit of 32%), had elevated amylase (138 u/L) and lipase (164 u/L), elevated creatinine (11.58 mg/dL), and significant acidosis with a bicarbonate of 11 mmol/L. She was discharged on multivitamins.

On admission to our hospital, she denied sore throat, cough, arthralgia, joint swelling, lymphadenopathy, easy bruising, hematuria, or diarrhea, although she did report anorexia and an 11 kg weight loss in the past two months. She also attested to fatigue and dizziness. On physical exam, she was afebrile, alert, and in no apparent distress. She had 2+ pallor. There was an erythematous macular rash in the malar region, 1+ pitting edema to just above the ankles bilaterally, and mild spooning of the fingernails. Laboratory data are presented in Table 1.

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INVESTIGATION Laboratory analysis on admission showed deterioration in renal function (serum creatinine level 15.2 mg/dL, eGFR of 4.14 mL/min/1.73 m2, BUN 84 mg/dL, BUN/Creatinine ratio 5.5), hypokalemia (potassium of 3.1 mmol/L), and anemia (hemoglobin of 8.2 mg/dL and hematocrit of 24%). The patient was in metabolic acidosis with bicarbonate of 14.0 mmol/L. Serum amylase and lipase were still elevated (130 u/L and 253 u/L, respectively). C3 was low at 72 mg/dL and C4 was normal at 33 mg/dL. Urinalysis revealed aciduria (urine pH 5), 2+

	Values	Reference range
Hemoglobin	8.2 g/dL	12–15.3 g/dL
White cell count	6.5×10^9/µL	$4.0–11.0\times10^9$/µL
Neutrophils	60.4% (3.9×10^9/µL)	$1.9–7.5\times10^9$/µL
Eosinophils	4.0% (0.3×10^9/µL)	$0.0–0.5\times10^9$/µL
Basophils	0.1% (0.0×10^9/µL)	$0.0–0.2\times10^9$/µL
Monocytes	10.7% (0.7×10^9/µL)	$0.1–1.0\times10^9$/µL
Lymphocytes	24.8% (1.6×10^9/µL)	$1.0–4.8\times10^9$/µL
Platelet count	214×10^9/µL	$150–450\times10^9$/µL
C reactive protein	1.22 mg/dL	<0.5 mg/dL
Erythrocyte sedimentation rate	<1 mm/hr	0-10 mm/hr
Blood urea nitrogen	84 mg/dL	10–50 mg/dL
Serum creatinine	15.2 mg/dL	0.5–1.1 mg/dL
eGFR (pediatric)	4.14 mL/min/1.73m^2	>90 mL/min/1.73m^2
Total serum protein	8.7 g/dL	6.4–8.2 g/dL
Serum albumin	4.0 g/dL	3.2–4.9 g/dL
Aspartate aminotransferase	11 U/L	<34 U/L
Alanine aminotransferase	20 U/L	10–49 U/L
Sodium	140 mmol/L	135–145 mmol/L
Potassium	3.1 mmol/L	3.5–5.1 mmol/L
Calcium	9.7 mg/dL	8.6–10 mg/dL
Phosphorus	4.7 mg/dL	2.4–5.1 mg/dL
Bicarbonate	14.0 mmol/L	22-29 mmol/L

Table 1: Laboratory findings on the admission (abnormal values are marked in red)

proteinuria, 3+ glucosuria, 1+ ketones, 1+ blood, 11-20 WBCs and few bacteria with a urine protein/creatinine ratio of 1.2.

Differential Diagnosis: The differential diagnosis of TINU syndrome includes systemic inflammatory diseases such as sarcoidosis, systemic lupus erythematosus, Sjögren's Syndrome, Behçet's syndrome, and granulomatosis with polyangiitis. Given that a chest X-ray was unremarkable and antinuclear antibodies, antineutrophil cytoplasmic antibodies, and anti-Ro and anti-La antibodies were negative, these diagnoses were ruled less likely.

Infectious causes, including tuberculosis, cytomegalovirus, brucellosis, histoplasmosis, and toxoplasmosis, were also on the differential. The hepatitis panel was negative, and the PPD skin test was normal. A lack of clinical findings ruled out other infectious processes. It is worth noting that Antistreptolysin O (ASO) antibody titer was high at 2573.8. While working up the abdominal pain and anorexia, the patient was found to have a positive fecal occult blood test and stool lactoferrin but a normal upper GI and small bowel series. *H. pylori* antibodies were normal. She was evaluated by a dietitian who did not think there was an eating disorder component to her weight loss.

Renal ultrasound showed nonspecific mild right hydronephrosis. Renal biopsy of the left kidney showed histological findings consistent with tubulointerstitial nephritis with interspersed inflammatory cells.
Considering the laboratory results and clinical features, an initial diagnosis of acute on chronic renal failure due to tubulointerstitial nephritis was made.

Management: The patient was prescribed 8mg of Cyproheptadine twice a day for appetite stimulation. Additionally, she was treated with sodium bicarbonate and potassium to correct the electrolyte abnormalities secondary to renal tubular acidosis and Fanconi syndrome. She required one transfusion of albumin. Intravenous methylprednisolone 30 mg BID was prescribed to reduce inflammation noted on kidney biopsy. The elevated ASO titer suggested a post-streptococcal glomerulonephritis component so a ten-day course of amoxicillin 20 mg/kg daily (renally adjusted dose) was started to cover for nephrogenic strains. For her anemia she received one transfusion of packed red blood cells.

Outcome and follow-up: The patient was discharged on day 15 after stabilizing renal function and improving creatinine (decreased to 2.9 mg/dL). While a dialysis catheter was inserted in preparation; she ultimately did not require dialysis. She was discharged on prednisone 30 mg BID for an additional two weeks and was appropriately weaned in outpatient clinic encounters. A renal ultrasound approximately two months post-discharge showed mild bilateral renal pelviectasis that may have been secondary to a distended urinary bladder. Approximately three months after her initial diagnosis of tubulointerstitial nephritis, her creatinine was stable at 1.02 mg/dL.

The patient gained 7kg during her hospital stay. At her outpatient follow up appointments, she complained of increased appetite and an additional 11kg weight gain (putting her BMI at the 97th percentile), likely secondary to prolonged steroid use. Her abdominal pain, however, had improved.

Approximately 12-14 weeks after hospital discharge, the patient began complaining of dry, itchy eyes and bilateral pain with eye movement that did not improve over the counter allergy medication. She was seen by an optometrist who diagnosed her with uveitis, prescribed prednisolone eye drops, and referred her to an ophthalmologist. The ophthalmologist prescribed a systemic course of prednisone at 20 mg TID with a scheduled taper. 4 weeks after starting prednisone, she was re-evaluated by her ophthalmologist, who confirmed the uveitis had completely resolved along with her symptoms.

Final Diagnosis: After evaluation by a pediatric nephrologist and an ophthalmologist, it was determined that the patient's presentation was consistent with TINU syndrome. She is currently asymptomatic and being followed by a pediatric nephrologist and an ophthalmologist.

DISCUSION This report describes a case of TINU syndrome in an adolescent female. She initially presented with acute on chronic renal failure due to tubulointerstitial nephritis of unknown etiology. It was not until 12-14 weeks after the initial presentation of renal failure that she developed bilateral uveitis. Since it was first described by Dobrin et al. in 1975 [4], approximately 250 cases of this rare syndrome have been reported [5]. As was seen in our case, TINU syndrome is more common in adolescents and young women [1].

While this disease's etiology remains unknown, TINU syndrome is thought to be immune-mediated with T-lymphocyte driven inflammation [6]. There have been

reports of antibodies against modified C reactive protein found in the renal tubular cells and uvea of the patient with TINU syndrome [6]. Additionally, there is an association with the use of nonsteroidal anti-inflammatory drugs or prior infection with chlamydia or Epstein-Barr virus in TINU syndrome [5,7]. In combination with bismuth subsalicylate in our patient, the use of ibuprofen may have played a role in her renal pathogenesis.

Appropriately named, TINU syndrome is characterized by both renal and ocular involvement. Initial presentation may be nonspecific with systemic findings, such as was seen in our patient. Findings such as fever, myalgia, arthralgia, abdominal pain, anorexia, and headache may be present. However, some patients have more specific manifestations of renal failures, such as flank pain, polyuria, hematuria, and proteinuria [8]. There are currently no specific laboratory findings unique to TINU syndrome; however, increased urinary excretion of ß2-microglobulin in combination with a decreased GFR may be the most predictive laboratory evidence for tubulointerstitial nephritis in TINU syndrome [3]. An elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), leukocyturia, eosinophilia, slightly abnormal liver function tests, and anemia (as was seen in our patient) may also be found [5]. Interestingly, the underlying cause of anemia, abdominal pain, and anorexia was never determined in our patient. It is possible that these symptoms were unrelated to TINU syndrome; however, given that these symptoms have been present in other cases of TINU syndrome [8], further understanding of the systemic manifestations of TINU syndrome is warranted.

Uveitis often presents with dryness, eye pain, and visual changes, as was seen in our patient [8]. It is most commonly bilateral non-granulomatous anterior uveitis, although alternating or unilateral uveitis may also occur [7]. While most cases (65%) of uveitis occur after the onset of tubulointerstitial nephritis, it may precede or occur simultaneously with renal disease [1]. Patients with tubulointerstitial nephritis with no underlying cause should have a slit lamp examination and be followed by an ophthalmologist for up to 12 months to monitor for uveitis [1]. Our patient's diagnosis of uveitis approximately three months after the renal disease is within the normal range of presentation, which has been reported to range from 2 months to 14 months after the onset of renal disease [1]. Diagnosis of TINU syndrome is made based on the combination of acute tubulointerstitial nephritis and uveitis and after exclusion of other potential causes, most notably systemic disease and infection [9].

Fortunately, TINU syndrome typically has a favorable prognosis [10]. Kidney disease appears to be self-limited, with most patients regaining normal kidney function within one year of diagnosis [11]. Our patient returned to normal kidney function within three months after a relatively short course of systemic prednisone. Uveitis may be chronic and tends to recur in at least half of patients with TINU syndrome, even up to 10 years after initial diagnosis [8]. In the more refractory cases, immunosuppressive agents such as methotrexate, mycophenolate mofetil, and cyclosporine may be used [12]. Our patient was treated with oral prednisone with a complete resolution in her uveitis. To date, she has not had any relapses of uveitis, and such has not required the use of immunosuppressive agents. She is being followed by a pediatric nephrologist and an ophthalmologist.

TINU syndrome is rare but should remain in the differential diagnosis of any patient with acute interstitial nephritis or uveitis of unknown cause. Collaboration between pediatricians and specialists such as ophthalmologists and nephrologists is imperative in diagnosing and treating TINU patients with the potential to prevent permanent renal and ocular injury.

CONCLUSION This study reports a pediatric case of TINU syndrome. Of interest, the patient presented with acute on chronic renal failure approximately three months prior to developing ocular symptoms.

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Disclosure:
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