Fanconi Syndrome as Initial Presentation of Tubulointerstitial Nephritis with Uveitis

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Introduction

Fanconi syndrome is characterized by global dysfunction of the proximal tubule, resulting in excessive urinary excretion of amino acids, glucose, phosphate, and bicarbonate. The causes often include drug/toxin exposure, metabolic syndromes, or renal disease. Here, we present that case of Fanconi syndrome due to diffuse tubular damage secondary to Tubulointerstitial Nephritis with Uveitis (TINU). TINU is an increasingly recognized autoimmune disorder that results in inflammation of both the renal interstitium and uveal tissue. TINU should be a differential consideration in adolescent patients presenting with elevated creatinine and signs of tubular dysfunction.

Presentation of Case

- 14 yo M presents with 2 weeks of fatigue, generalized abdominal pain, N/V, poor appetite, associated weight loss of 15-20lbs.
- ROS: regular BM, denies fevers, night sweats, rashes, or joint pain.
- SH: plays high-school football, denies drug use, took OTC ibuprofen x 3 tabs, denies metal exposure or recent travel.
- Significant labs:
  - Normocytic anemia (Hgb 10.8)
  - Elevated ESR 94 and CRP 4.6.
  - Elevated BUN 36, and Cr: 4.63.
  - Hypokalemia (3.1), hyperchloremia (111), non-anion gap metabolic acidosis (Bicarb 17)
  - Urine: glucosuria and proteinuria.
- Diagnosed with proximal RTA with Fanconi Syndrome. Further work-up included:
  - Protein/Cr: 1,289 mg/g
  - Cystatin C: 3.0, estimated GFR 25.
  - Urinary β2-macroglobulin: 21,041 mcg/L (normal <190)
- Renal biopsy: acute diffuse tubulointerstitial nephritis, concerning for TINU.
- Metabolic, toxin, and infectious work-up negative for underlying cause of TINU.
- Slit lamp exam: negative for uveitis.

Pathophysiology

TINU involves both humoral and cellular immunity leading to granuloma formation and acute kidney injury. The renal interstitium is infiltrated by T cells, monocytes and macrophages which may initially help repair acute injury but eventually results in further inflammation and production of fibrogenic cytokines. The high metabolic demand of the tubulointerstitium makes it particularly susceptible to this type of injury. If prolonged, this process may lead to irreversible damage such as fibrosis and tubular atrophy. Thus, the primary renal derangements in TINU are related to tubular dysfunction with sparing of glomeruli architecture. The uveitis component is classically described as bilateral non-granulomatous anterior uveitis. Researchers have attempted to further understand TINU as it pertains to both renal and uveal tissue. Humoral immunity has been emphasized for its important role in this unique cross reactivity. Renal tubular and ciliary body epithelia share several functions including those pertaining to electrolyte transporters and carbonic anhydrase inhibitors. It has therefore been postulated that they also share closely related antigens that account for this cross reactivity[2,6]

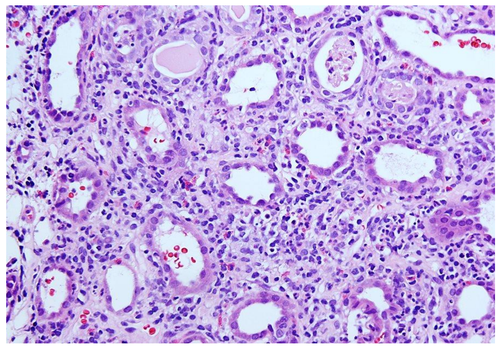
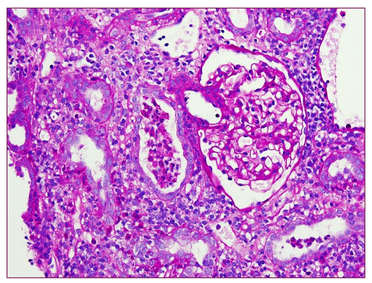


Figure 1: Renal tissue. Dense, diffuse mixed tubulointerstitial inflammatory infiltrate (lymphocytes, plasma cells, eosinophils, neutrophils, and histiocytes).



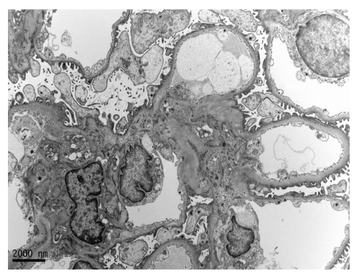


Figure 2 & 3:
Renal tissue. No immune deposits on both immunofluorescence and electron microscopy. Glomeruli unremarkable.

Discussion

-TINU is a rare, under-reported disorder that causes severe renal and ocular disease and may occur in response to various environmental triggers (ie drug-exposures or pathogens). Cause can also be undetermined (idiopathic), such as in our case.

-Epidemiology: 0.2 cases/million/year [2]. Median age of onset 15 years (range 9-74 yrs). 3:1 female predominance.

-Initial presentation: fatigue, fever, weight loss, abdominal pain, N/V, eye-redness and pain. Lab findings consistent with anemia, renal failure, tubular proteinuria (elevated β2-macroglobulin), and elevated inflammatory markers. Renal dysfunction often presents first. Uveitis can present 1 month prior to, concurrently, or up to 14 months after renal presentation. Renal disease will often self-resolve without recurrence, but uveitis may persist and become chronic.

-Diagnosis: given rarity, there is no standardized diagnostic criteria. Renal biopsy is the gold standard, but a recent study revealed 100% PPV for TINU in patients presenting with a combination of elevated β2-microglobulin and elevated creatinine[3].There is a reported HLA antigen-related genetic predisposition: specifically HLA-DQ and HLA-DR alleles[4].

-Treatment: standard approach is initiating steroids, but data indicates that kidney function generally resolves in 3-6 months without treatment[5]. Prolonged disease course or progressively increasing creatinine can be treated with steroid taper. Uveitis is often the more persistent and recurrent component of TINU. Steroid-refractory uveitis can be treated with immunomodulators such as adalimumab and mycophenolate mofetil[6]. Additionally, mycophenolate mofetil has shown to improve renal function in steroid-refractory renal disease.

Conflict of interest: the authors declared that they have no conflict of interest

Case Resolution

-Patient's creatinine increased shortly after discharge and he was started on a steroid course.
-Renal function initially improved with steroids, but experienced worsening function with taper, so steroid dose increased again. Normalization of renal function achieved at 9 month post-diagnosis.
-Developed uveitis 2 months after diagnosis. Uveitis was refractory to steroid treatment and he was started on adalimumab and mycophenolate mofetil 6 months after diagnosis. Continues to follow with ophthalmology and rheumatology for chronic uveitis.

Conclusion

-TINU should be on the differential for adolescent patients presenting with elevated creatinine, especially when signs of tubular dysfunction are present (ie Fanconi syndrome)
-Elevated urinary β2-macroglobulin in combination with elevated Cr has 100% PPV for TINU and should be considered in the work-up for elevated creatinine of unclear etiology. Renal biopsy is the gold standard.
-Uveitis can present up to 14 months after renal symptoms and patient should be given anticipatory guidance and ophthalmology follow-up.
-Although often self-resolving, refractory cases of TINU, particularly for the uveitis component, can be treated with steroids or with immunomodulators if steroid-resistant.

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