CASE REPORT

When Kidney Mirrors the Eye: Tubulointerstitial Nephritis and Uveitis Syndrome - Case Report

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Abstract

Tubulointerstitial nephritis and uveitis syndrome is an underdiagnosed condition, characterized by the involvement of the kidney and the eye that affects mostly young people. Its pathophysiology remains poorly understood; however, pediatric morbidity is mostly associated with recurrences of uveitis. This article aimed to describe two clinical cases of tubulointerstitial nephritis and uveitis syndrome, with distinct presentations and clinical courses, illustrative of the diversity of this entity. Case 1: An 11-year-old male was admitted to the hospital due to a non-oliguric acute kidney injury. A 24-hour urine examination revealed a tubular lesion, and two months later, he was diagnosed with bilateral anterior uveitis. He was started on steroids, with a favorable response. After six weeks, renal function and urine parameters returned to normal. Case 2: A 12-year-old male was admitted to the hospital with complaints of bilateral red eyes. He was diagnosed with bilateral anterior uveitis and treated with topical steroids with transient improvement. At the same time, the clinical investigation detected a tubular lesion. Four months later, due to a uveitis hypertensive flare with macular edema, methotrexate was added to his treatment, which had a favorable response. Six months later, the urinary abnormalities disappeared. The tubulointerstitial nephritis and uveitis syndrome should be actively searched in the presence of tubular renal abnormalities or uveitis in pediatric patients.

Keywords: Child; Nephritis, Interstitial/diagnosis; Nephritis, Interstitial/drug therapy; Uveitis/diagnosis; Uveitis/drug therapy; Case Report

Keypoints

What is known:

- Tubulointerstitial nephritis and uveitis syndrome is an underdiagnosed condition, characterized by the involvement of the kidney (with acute tubulointerstitial nephritis) and the eye (with uveitis).
- Kidney disease and uveitis tend to evolve independently; however, pediatric morbidity is mostly associated with recurrences of uveitis.
- Although acute interstitial nephritis in the setting of tubulointerstitial nephritis and uveitis syndrome may resolve spontaneously, some studies have reported that kidney injury can be persistent in 10% of cases.

What is added:

- Systemic glucocorticoids were effective in the treatment of acute interstitial nephritis, with complete resolution and prevention of progression to chronic kidney disease.
- Although renal biopsy is the gold standard for the diagnosis of tubulointerstitial nephritis, its performance should be considered individually, especially when there is mild renal involvement, to avoid the risks associated with the procedure.
- The tubulointerstitial nephritis and uveitis syndrome should be actively searched in the presence of tubular renal abnormalities or uveitis in pediatric patients.

Introduction

Tubulointerstitial nephritis and uveitis (TINU) syndrome is a rare condition described for the first time by Dobrin in 1975. It is characterized by the involvement of the kidney (with acute tubulointerstitial nephritis) and the eye (with uveitis), which may not be contemporary. In fact, uveitis may occur before, concurrent with, or posterior to the onset of the kidney disease. It mostly affects young people, including school-age children, adolescents, and young adults. A female preponderance is reported, although the proportion of male adolescents reported has increased over time.[1-3] Its pathophysiology remains poorly understood; however, abnormalities in

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both humoral and cell-mediated immune responses are likely to play an important role.[1,4]

This paper aimed to describe two clinical cases of tubulointerstitial nephritis and uveitis syndrome, with distinct presentations and clinical courses, illustrative of the diversity of this entity.

Case Report

Case 1

An 11-year-old male, with unremarkable past medical and family history, was admitted to a pediatric nephrology clinic with non-oliguric acute kidney injury. Two weeks before the evaluation, he complained of weakness, anorexia, nausea, and sporadic vomiting. Herbal tea (including senna) had been used in the last month (~ 1 L/day) due to constipation, but no other drugs or medications had been used.

It should be mentioned that the physical examination was unremarkable. Moreover, laboratory tests revealed normal complete blood count, normal liver function, and acute kidney injury: serum creatinine 1.37 mg/dL (reference values 0.44-0.66 mg/dL), urea 48 mg/dL (reference values 10-40 mg/dL), and cystatin C 1.16 mg/L (reference values 0.53-0.95 mg/dL), with an estimated glomerular filtration rate of 57 mL/min/1.73 m^2. A 24-hour urine examination revealed glycosuria (1.81 g/L), proteinuria (0.9 g/L), protein / creatinine ratio of 0.71, and microalbuminuria (120 mg/L); the remaining urinary indices showed no abnormalities. Urinalysis did not show hematuria or leukocyturia.

Epstein-Barr virus, cytomegalovirus, parvovirus B19, herpes simplex virus, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* acute infections were excluded, and immunological workup was normal (immunoglobulins, complement, antinuclear antibodies, antineutrophil cytoplasmic antibodies, anti-dsDNA, anti-extractable nuclear antigen, anti-glomerular basement membrane, and antiphospholipid antibodies). Renal ultrasound showed normal-sized and well-differentiated kidneys with increased parenchymal echogenicity. At this time, an expectant attitude was adopted, actively monitoring proteinuria and renal function.

Two months later, he developed redness in both eyes without visual impairment or pain. An ophthalmological evaluation diagnosed bilateral anterior uveitis, and he was started on topical steroids. A kidney biopsy was then performed under ultrasound guidance. Histopathological examination showed tubular necrosis and atrophy, lymphocytic inflammatory infiltrate of the interstitium, interstitial fibrosis (20%), and mild mesangial proliferation; there were no deposits on immunofluorescence.

Oral prednisolone (1 mg/kg/day) was started, with a favorable response. After six weeks, his renal function and urine parameters returned to normal. The medication was progressively reduced and discontinued after three months. During follow-up, he maintained ocular remission without sequelae, as well as normal renal function and urinalysis. He was discharged three years later.

Case 2

A 12-year-old male was admitted to the emergency room with complaints of bilateral red eyes after three weeks of evolution. He was diagnosed with symptomatic bilateral anterior uveitis and was treated with topical steroids with transient improvement. At the same time, the clinical investigation detected urine abnormalities suggestive of the tubular lesion (glycosuria and urinary beta 2-microglobulin), and he was referred to pediatric nephrology clinic.

Personal and family history were unremarkable. Other than the ocular findings, his physical examination was normal and he had no other complaints. Moreover, the laboratory tests showed normal renal function. Viral serologies, *Mycoplasma pneumoniae*, *Chlamydia pneumonia* serologies, and immunological workup were negative. Urinalysis results revealed elevated glycosuria (without hyperglycemia) and elevated beta 2-microglobulin (1098 mg/L, reference values < 180 mg/dL); however, the remaining urinary indices were normal. It should be mentioned that the renal ultrasound was normal. Follow-up consisted of monitoring tubular changes and renal function, without any specific treatment. Four months later, due to a uveitis hypertensive flare with macular edema, methotrexate was added to his treatment, with a favorable response to monotherapy. Six months later, the urinary abnormalities disappeared. He remains asymptomatic with normal tubular renal function after four years. He maintains ocular remission with bilateral posterior synechiae, normal vision, and no other sequelae. Methotrexate treatment is currently being weaned.

Discussion

Tubulointerstitial nephritis and uveitis syndrome is probably an underdiagnosed condition. Nevertheless, its prevalence has been described in up to 2.3% of pediatric patients attending specialist uveitis services.[5] Furthermore, in pediatric patients diagnosed with tubulointerstitial nephritis, the prevalence is estimated to range from 5% to 28%.[6]

Pediatricians, nephrologists, and ophthalmologists must be aware of this entity to perform a correct diagnosis and treatment. Despite having a benign evolution in most cases, it can also cause permanent eye or kidney sequelae if left untreated.[6]

In the presence of uveitis in adolescents, especially in the case of symptomatic anterior (redness, pain, and photophobia) or bilateral uveitis, as manifested in these two cases, it is important to consider the possibility of tubulointerstitial nephritis and uveitis syndrome syndrome. Therefore, renal function evaluation and urinalysis should be performed to identify the abnormalities suggestive of the tubular lesion: glycosuria, proteinuria (predominantly tubular proteinuria with elevated beta 2-microglobulin), and hematuria.[7,8]

Uveitis in the setting of tubulointerstitial nephritis and uveitis syndrome syndrome is typically diagnosed between two months before and 12 months after the tubulointerstitial nephritis diagnosis, and sometimes can be asymptomatic.[6,9] Therefore, ophthalmologic evaluation is essential in pediatric patients diagnosed with tubulointerstitial nephritis of unknown origin.[2]

As observed in the first case, tubulointerstitial nephritis may present with systemic symptoms (*eg*, fever, weight loss, and asthenia). However, it is asymptomatic in most cases, and the failure to identify these changes may hamper diagnosis indefinitely.[8] The concurrent onset of tubulointerstitial nephritis and uveitis, as observed in the second patient, occurs only in a minority of cases (15%). Given the time discordance between ocular and renal diseases, a high degree of awareness is indeed imperative.[4]

The TINU syndrome requires both the presence of acute tubulointerstitial nephritis and uveitis and the exclusion of any other systemic disease (*eg*, infections or systemic immune-mediated disorders). It has also been reported as the causative agent of interstitial nephritis or uveitis.[2,5] Some triggers have been identified, such as the use of certain medications or previous infections.[3] Moreover, several studies have reported associations with certain human leukocyte antigen phenotypes, with the possibility that tubulointerstitial nephritis and uveitis syndrome could be an autoimmune disease involving a common antigen to the eye and the kidney.[4]

Renal biopsy is considered the gold standard for the diagnosis of acute tubulointerstitial nephritis. However, the diagnosis can also be made in its absence, based only on clinical criteria (abnormal kidney function, systemic symptoms, and abnormal urinalysis), especially if initial kidney involvement appears to be limited.[6,8,9]

In the first case presented in this study, it was the presence of significant and persistent renal dysfunction that motivated the performance of a kidney biopsy for better clarification. After the histopathological examination, the definitive diagnosis of tubulointerstitial nephritis and uveitis syndrome was obtained and treatment with glucocorticoids was started, which resulted in complete resolution.

In the second patient, considering the history of typical uveitis associated with clinical criteria of acute tubulointerstitial nephritis, the kidney biopsy was not performed. The kidney involvement was not significant and the risk / benefit of performing a renal biopsy was taken into account.

The course of the renal disease appears to be independent of the ocular disease.[4] In children, complete resolution of renal abnormalities is common, and morbidity is usually associated with frequent recurrences of uveitis.[10] In addition, increased age and greater severity of symptoms at diagnosis seem to be linked to a worse prognosis at 12 months of follow-up.[11] Although acute interstitial nephritis in the setting of tubulointerstitial nephritis and uveitis syndrome syndrome may resolve spontaneously, some studies have reported that kidney injury can be persistent in 10% of cases.[12] However, acute kidney injury and chronic kidney disease seem to be more frequent in adult patients, compared to children.[10]

As there are no evidence-based protocols for the treatment of tubulointerstitial nephritis and uveitis syndrome, management relies on case reports and case series. Systemic glucocorticoids may be considered in progressive or significant renal disease, to prevent chronic kidney disease. In fact, some clinical reports have demonstrated rapid improvement of renal function after the initiation of therapy, as happened in the first case. Nevertheless, the uveitis of tubulointerstitial nephritis and uveitis syndrome appears to be more persistent,[4] and responds well to topical and systemic corticosteroids.[2] For severe, refractory, or recurrent uveitis, steroid-sparing agents may be required.[4]

There are no specific tubulointerstitial nephritis and uveitis syndrome biomarkers. Elevation of urinary beta 2-microglobulin has emerged as a sensitive, but non-specific test for the diagnosis of tubulointerstitial nephritis and uveitis syndrome. Its reabsorption by the renal tubular epithelium is reduced in cases of acute interstitial nephritis and may persist after normalization of the renal function, which makes it a useful test to detect previous renal dysfunction. However, it can be elevated in any cause of acute interstitial nephritis and is not specific to tubulointerstitial nephritis and uveitis syndrome. Some degree of correlation with the

histopathological grade of acute interstitial nephritis has been shown.[3,8,11]

In conclusion, this study aimed to emphasize that tubulointerstitial nephritis and uveitis syndrome syndrome should be actively searched in the presence of tubular renal abnormalities or uveitis in pediatric patients.

Author Contribuitions

SMG and SHF participated in acquisition of data. SMG, SHF, MR, JLB and HP participated in the drafting of the manuscript. MR, JLB and HP participated in the critical revision of the manuscript. All authors approved the final manuscript and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this study.

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The authors declare that they have followed the protocols of their work center on the publication of patient data.

Consent for publication

Consent for publication was obtained.

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