A pediatric case of tubulointerstitial nephritis and uveitis syndrome

Um caso pediátrico de síndrome de nefrite tubulo-intersticial e uveíte

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ABSTRACT

Tubulointerstitial Nephritis and Uveitis Syndrome (TINU Syndrome) is a rare entity of unknown origin. Most cases described affect adolescents and women. It often implies a renal biopsy and is established upon the presence of uveitis and tubulointerstitial nephritis in the same patient, after all possible causes are excluded. The authors report the case of a 12-year-old teenage boy with nausea, vomiting, and weight loss lasting two weeks, taken to his local hospital with acute kidney injury, oliguria, and high blood pressure. After transfer to a specialized centre and exclusion of infectious, toxic, and autoimmune causes, intravenous and oral corticosteroid therapy was started. Renal biopsy confirmed interstitial nephritis of undetermined aetiology and the patient was discharged after favourable restauration of renal function, with a course of 4 weeks of steroids and progressive decrements over 10 weeks. Four

months after the onset of the condition, the teenager was taken to the hospital with eye redness and tenderness. Bilateral anterior uveitis was described, which established the diagnosis of TINU Syndrome. After two years of joint follow-up by Paediatric Nephrology and Ophthalmology, the patient remains stable, without relapses, or ocular or renal sequelae.

Keywords: TINU syndrome, nephritis, uveitis, paediatrics.

RESUMO
A Síndrome de Nefrite Túbulo-Intersticial e Uveíte (Síndrome TINU) é uma entidade rara cuja patogénese não é ainda totalmente compreendida. A maioria dos casos descritos afetam adolescentes e mulheres. No diagnóstico, feito frequentemente com recurso a biópsia renal, estabelece-se aquando da presença de uveíte e nefrite túbulo-intersticial, na ausência de outras causas identificáveis. Os autores relatam o caso de um adolescente de 12 anos com náuseas, vómitos, e perda ponderal com duas semanas de evolução, observado no hospital da sua área de residência com lesão renal aguda, oligúria e hipertensão arterial. Após transferência para centro especializado e exclusão de causas infeciosas, tóxicas e auto-imunes, inicia esquema de corticoterapia endovenosa e oral. A biópsia renal revela nefrite intersticial de etiologia indeterminada e o doente tem alta após evolução favorável da função renal, com esquema de corticoterapia oral durante 4 semanas e redução progressiva ao longo de 10 semanas. Quatro meses após o início do quadro, o adolescente recorre ao hospital por olho vermelho doloroso, observando-se uveíte anterior bilateral, estabelecendo-se o diagnóstico de Síndrome TINU. Passados dois anos de seguimento conjunto por Nefrologia Pediátrica e Oftalmologia, o doente mantém-se estável, sem recorrências ou sequelas oculares ou renais.

Palavras-chave: síndrome TINU, nefrite, uveíte, pediatria.

1 INTRODUCTION

A new syndrome consisting of bilateral anterior uveitis and interstitial nephritis was first reported in two adolescent girls in 1975(1). Almost five decades later, more than 250 cases of tubulointerstitial nephritis and uveitis (TINU) syndrome have been reported in ophthalmology, nephrology and pediatric literature(2).

Diagnostic criteria for TINU syndrome cases have been proposed(3). It is considered an exclusion diagnosis characterized by the combination of biopsy-proven tubulointerstitial nephritis (TIN) and uveitis, in the absence of other identifiable causes, such as systemic infectious, auto-inflammatory or other autoimmune etiologies(4–8).

In 2001, Mandeville et al. reported 133 cases of TINU syndrome with a median age of onset of 15 years (range 9–74 years), a 3:1 female-to-male predominance and no association to specific racial or ethnic groups(3). Recent studies have challenged this ratio as more cases in males have been reported in the last decades(9).

It is thought that TINU syndrome accounts for up to 28% of all TIN and 0,1-2% of all uveitis(2,8–10). In children with sudden-onset bilateral anterior uveitis, the prevalence may be

as high as 32%(9,11). Although its true prevalence is unknown, approximately 60% of all cases seem to occur in children and adolescents(2).

2 CASE PRESENTATION

An otherwise healthy twelve-year-old boy is admitted in his local emergency department with complaints of nausea and vomiting for the last two weeks. On the first day of illness, and after an uneventful physical examination, a general practitioner prescribed a week's course of 10mg domperidone, three times daily. Although the frequency of vomiting diminished, the nausea and anorexia became increasingly debilitating. Fever, diarrhoea, localized pain, recent infections, aphthae, rashes or any other signs and symptoms were denied. No other medications or under-the-counter supplements were taken.

Upon arrival to the hospital, he was afebrile with preserved general condition. The initial evaluation showed a 7.3% weight loss in 4 weeks and hypertension.

Blood and urine were drawn, urine output was monitored, and an intravenous saline solution was started. Preliminary results revealed diuresis of 0.6ml/kg/hour with serum creatinine of 3.1mg/dL and blood urea nitrogen of 20,4mmol/L, significant proteinuria 113.7mg/mmol and glycosuria. At this point, the teenager was transferred to our tertiary hospital to undergo complementary etiological investigation.

Infectious causes were excluded, as serologic tests for Epstein-Barr virus, cytomegalovirus, hepatitis B and C, HIV, *Chlamydophila pneumoniae, Legionella, Mycoplasma pneumoniae*, *Toxoplasma*, PCR for Human herpesvirus 6, SARS-CoV-2, interferon-gamma release assay, blood and urine cultures were all negative. Stool samples tested negative for *Salmonella, Shigella, Campylobacter, Clostridium, Yersinia*, *E. coli*, rotavirus, adenovirus, and norovirus. Autoimmunity panel showed normal complement and immunoglobulin levels, as well as and negative anti-streptolysin O, anti-DNase B, anti-double stranded DNA, and antineutrophil cytoplasmic antibodies. Chest X-ray, transthoracic echocardiogram and electrocardiogram were unremarkable. Abdominal and renal ultrasound showed globose kidneys with increased echogenicity, with no other changes. Ophthalmologic examination was normal, with no signs of uveitis.

A hyposaline diet was instituted from the start, as well as furosemide 20mg as needed for hypertension control and ondansetron 8mg for nausea. Upon deterioration of renal function, with increase of serum creatinine to 3.5mg/dL, urinary beta2-microglobulin of 49.9mg/L, urinary protein/creatinine ratio of 71.6 mg/mmol, protein electrophoresis showing mainly tubular proteinuria, and urine output of 0.9ml/kg/h. Intravenous methylprednisolone 250mg

daily was instituted from day 2 to 5 of admission, followed by oral prednisolone 60mg/day. Renal biopsy revealed tubulointerstitial nephritis and acute tubular necrosis, without vascular abnormalities. There was normalization of diuresis on day 3 of admission, and blood pressure values on day 7. The patient was discharged after 10 days, with a serum creatinine of 1.5 mg/dL, blood urea nitrogen of 38.6 mg/dL, no electrolyte imbalances, and a urinary protein/creatinine ratio of 30.7 mg/mmol. A diagnosis of tubulointerstitial nephritis of unknown origin was established at his point.

Ambulatory follow-up in the Paediatric Nephrology outpatient clinic started with close monitoring of renal function and autoimmunity with weekly to monthly check-ups. On the first consult there was normalization of proteinuria and glycosuria and of the remaining renal function on the subsequent week, with a serum creatinine of 0.74mg/dL.

The patient completed 4 weeks of 60mg/day prednisolone with progressive decrements along 10 weeks before complete suspension. He resumed his normal activities without limitations, attending school and after-school programs.

Twenty-five days after steroid suspension, and 4 months after the onset of his condition, the patient progressively developed eye redness, photophobia, pain, and blurred vision. Ophthalmological evaluation revealed bilateral anterior uveitis and contacted the Nephrology team. Thorough investigation showed no changes in renal function, or immunologic markers. The diagnosis of TINU Syndrome was established.

Topical therapy with a beta-blocker and dexamethasone was started, for the duration of one and three months respectively, with great clinical response.

Frequent follow-up by the Nephrology and Ophthalmology teams showed no recurrent episodes of uveitis nor tubulointerstitial nephritis. Two years later the patient remains stable, with normal ocular and renal function, without any medication.

3 DISCUSSION

Although believed to be the result of a humoral and cellular immune-mediated process, the precise mechanisms behind the disease's pathogenesis are poorly understood(7,8). The role of infections and drugs, specially non-steroidal anti-inflammatory drugs and antibiotics, as immunological triggers, has been suggested(4,8). We did not find such associations in our case. The presence of common or closely related antigens shared by both uvea and kidney leading to cross-reactivity seems to be the most commonly accepted theory(4–8).

Clinically, TIN may present concurrently (15%), follow (20%) or precede (65%) uveitis(2–4,6,8,12). Renal involvement may be of acute or subacute onset, often presenting with

fever, weight loss, fatigue, malaise, anorexia, abdominal or flank pain, nausea, vomiting and oliguria(4,10). Elevated sedimentation rate, serum creatinine and blood urea nitrogen, anemia, proteinuria, microscopic hematuria and normoglycemia glycosuria are the most common laboratory findings. Ocular involvement in TINU syndrome seems to be very uniform(9). Most frequently the uveitis is of sudden onset, bilateral and anterior, presenting with eye redness, decreased vision, pain and photophobia(3,6,9–12). To a lesser extent, posterior and panuveitis, have been reported(3,8,9,11,13). Onset of uveitis is variable, and has been described as early as 3 months prior to TIN(14) and up to 14 months after renal involvement(3). This has led to recommendations for ophthalmology observation in all cases of idiopathic TIN on presentation and every 3 months thereafter(11). Additionally, in some cases, uveitis can be accompanied by a relapse in renal function(3).

Our patient presented many of the classic symptoms and analytical findings, and TIN was supported by findings in the renal biopsy. As our hospital's Nephology and Ophthalmology teams have worked in collaboration in previous TINU syndrome cases, it has been established that all TIN patients are to be screened for uveitis. Furthermore, as uveitis was later detected, the teams promptly proceeded to reevaluate renal function and established a follow-up plan.

As various pathologies can present renal and ocular involvement, Sarcoidosis, Sjogren's syndrome, Systemic Lupus Erythematosus, Wegener's granulomatosis and Behçet disease(15) are to be ruled out before assuming TINU syndrome as a definitive diagnosis. Upon admission, we proceeded to exclude various possible infectious(16) and auto-immune causes of TIN and continued to monitor autoantibodies as part of our outpatient follow-up.

In general, children with TINU syndrome have a favorable outcome and renal disease often resolves spontaneously(17,18). In the cases where it progresses, there is usually a positive response to systemic steroid therapy, as was our patient's case, and very few cases need dialytic support. Recurrence of uveitis is well characterized in TINU syndrome, but topical steroids and cycloplegics, sometimes in association with systemic steroids, are often sufficient.

Rare diseases of unknown cause will always portray themselves as a diagnostic challenge. Underdiagnosis is a difficult barrier to overcome, especially in children, the most affected age group, considering that to definitively diagnose TINU syndrome, a renal biopsy is required. This invasive procedure can be debatable whether a child with minor renal disfunction should be submitted to such a procedure. Additionally, both failure to screen for uveitis in TIN patients without ocular symptoms or renal function in uveitis patients, further contributes to underdiagnosis(8,11,12). An elevation in urinary beta2-microglobulin, a sensitive marker for TIN, has proven to be particularly helpful in screening for TIN in uveitis patients(13).

TINU syndrome can present in a multitude of degrees of severity, from mildly blurred vision to renal failure and children are often oligosymptomatic. Our goal is to expand our community's knowledge on this disease and highlight the need for international pediatric guidelines for case definitions, follow-up, and management of both renal and ocular complications.

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