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CASE REPORT

Tubulointerstitial Nephritis and Uveitis Syndrome (TINU) after use of Isotretinoin - case report

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Abstract

TINU syndrome (tubulointerstitial nephritis and uveitis) is characterized by the presence of acute tubulointerstitial nephritis associated with uveitis. It is a rare syndrome and an immune-mediated condition that can be triggered mainly by infections and medications. The authors describe a case of a teenager who developed tubulointerstitial nephritis and uveitis after using Isotretinoin. The main objective of this description is to alert to the possibility of renal adverse effects in patients using this medication, aiming to assist in early diagnosis and treatment if renal involvement occurs. The Isotretinoin is an effective and safe medication, but this case highlights the importance of monitoring renal function with urinalysis and creatinine in patients using Isotretinoin.

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INTRODUCTION

Isotretinoin is an effective treatment for severe acne and some types of cancer, and is a common medication of significant clinical importance. It has adverse effects, the most widely studied being liver damage and teratogenicity. However, some studies highlight the risks of renal impairment secondary to isotretinoin, including interstitial nephritis[1]. We draw attention to the case described here because the patient presented, in addition to interstitial nephritis, uveitis, characterizing TINU syndrome.

TINU syndrome is described as tubulointerstitial nephritis associated with uveitis, with uveitis occurring before, during, or, more frequently, after the nephritis[2]. It is a rare condition, estimated to account for 0.1% to 2% of uveitis cases. However, its diagnosis is crucial, as it can lead to renal failure, cataracts, and glaucoma[3]. The main objective of this report is to raise awareness of the association between isotretinoin and adverse renal effects, including TINU syndrome, aiming at early diagnosis and treatment of these complications. This case report was submitted to the Institution's Research Ethics Committee and approved under CAAE 81020324.2.0000.5335.

CASE REPORT

A 13-year-old girl presented with symptoms of fatigue and malaise. Her medical history indicated she was being seen by a neurologist due to migraines with photophobia, requiring occasional use of paracetamol and dipyrone. She also had acne and had been treated with isotretinoin for two months.

On physical examination, she weighed 42.5 kg, was 160 cm tall, and had a blood pressure of 90/50 mmHg. She was in good general condition, well perfused, with a depressed and painless abdomen on palpation, and no masses or enlargement . She had no edema and maintained normal diuresis . He brought exams: urine summary with glycosuria and proteinuria (with other normal aspects), hemoglobin 10.1 g/dL, hematocrit 30.7%, transferrin saturation 20%, glucose 107 mg/dL, albumin 4.1 g/dL, total cholesterol 186 mg/dL, triglycerides 140 mg/dL, HDL 33 mg/dL, AST 18 u/L, ALT 10 u/L, creatinine 1.76 mg/dL (enzymatic method, estimated glomerular filtration rate, eGFR, of 37.5 ml/min/1.73 m²), urea 56 mg/dL, potassium 4.6 mEq/L, sodium 136 mEq/L, alkaline reserve 16 mEq/L, chlorine 110 mEq/L. From a previous history, the patient was born at term, with a birth weight of 3100 g, with no history of comorbidities.

Further investigation required: a urinary tract Doppler ultrasound, which revealed increased bilateral kidney echogenicity, no other abnormalities, and kidneys of appropriate size for her age; a urinary protein/creatinine ratio of 1.27; and microalbuminuria of 143 mg of albumin per gram of creatinine. The parathyroid hormone level was 23 pg/mL, and screening for infections was negative. The increase in creatinine was considered acute, as the patient had kidneys of appropriate size for her age, normal height, no significant anemia, and a normal bone assessment.

The differential diagnosis of acute kidney injury (AKI) considered the main causes of this condition. The patient had no history of diarrhea or vomiting and showed no signs of hypovolemia on physical examination. There were no symptoms or tests suggestive of glomerulopathy or urinary tract obstruction. Renal Doppler revealed good arterial flow, with no signs of ischemia. Infectious causes were ruled out based on clinical history and laboratory tests.

Due to signs of proximal tubular damage (renal glycosuria and albuminuria, suggestive of Fanconi syndrome), the diagnoses of interstitial nephritis and cystinosis were considered. Cystinosis was considered because the patient had photophobia, but it was ruled out after an ophthalmological evaluation with a slit lamp and due to the acute nature of the condition . Because the patient continued to have elevated creatinine, a renal biopsy was performed (Figures 1 and 2), which revealed significant eosinophil deposition and negative immunofluorescence, confirming tubulointerstitial nephritis.

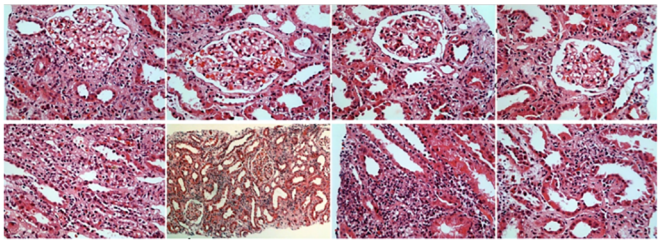


Figure 1. Image of the glomerular and tubulointerstitial compartment in the pathological anatomy of the patient's renal sample.

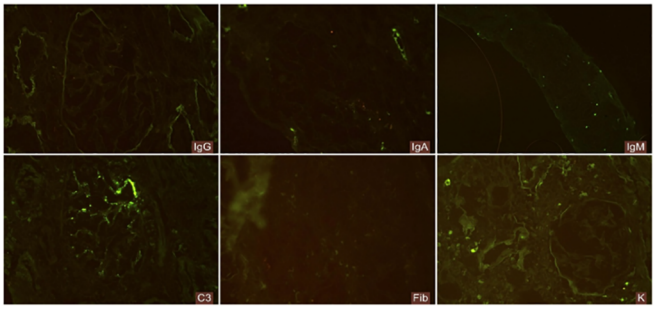


Figure 2. Immunofluorescence image of the patient's renal sample.

Caption: Mesangial matrix and cellularity are within normal limits. The glomerular basement membrane is unremarkable. No fibrous capsular adhesion, tubulization, crescents, fibrin, or necrosis are observed in Bowman's spaces. No segmental sclerosis, hyalinosis, fibrin, or signs of endocapillary proliferation of the glomerular tufts were detected. Several trophic tubules separated by edema and numerous granulomononuclear inflammatory cells permeated the interstitium and tubules, along with neutrophils, lymphocytes, and some plasma cells, in addition to numerous eosinophils. No signs of amorphous deposits, crystals, or polarizable material were observed in the multiple sections and stains examined.

Considering that isotretinoin was the main change in the patient's routine and that the predominant diagnosis was drug-induced interstitial nephritis, isotretinoin was associated as the cause of this condition. The medication was discontinued, and treatment was initiated with three doses of methylprednisolone 500 mg, followed by prednisone 40 mg (1 mg/kg/day), with a gradual reduction until discontinuation over four weeks. The patient showed significant improvement in creatinine levels, reaching 0.75 mg/dL (filtration rate, eGFR, 88 ml/min/1.73 m²) after one month of treatment.

Two months after the onset of symptoms, due to a new episode of photophobia, reduced visual acuity, periocular pain, and eyelid edema, the patient returned for an ophthalmologist appointment. A 4+/4 anterior chamber cellular reaction (anterior uveitis), ciliary injection, reduced acuity, corneal edema, and fine endothelial kerotic precipitates were identified during the examination, without involvement of the posterior uvea. Complementary rheumatological tests, including antinuclear factor, anti-DNA antibody, rheumatoid factor, pANCA, and cANCA, were normal.

Given the recent onset of tubulointerstitial nephritis and uveitis, a diagnosis of TINU syndrome was established. The patient continued taking oral corticosteroids, and topical corticosteroids were added, improving her ophthalmological complaints. Three months later, the patient returned with ophthalmological symptoms, which became recurrent. She required azathioprine to control the recurrence of ophthalmological symptoms.

DISCUSSION

Despite the therapeutic effects of isotretinoin, this medication has adverse effects, including kidney damage. In the literature, isotretinoin has been attributed as a cause of hematuria[4] and nephrotic syndrome[5]. Experimental studies in rats have associated the use of this medication with urinary tract obstruction, membranoproliferative glomerulopathy, and allograft nephropathy[1]. There are similar reports to the case described in which adolescents developed interstitial nephritis after using this medication. Some of these cases were treated only with fluid therapy and discontinuation of isotretinoin[6], while others also required corticosteroids[7].

After the nephritis, the patient also developed anterior uveitis, leading to the diagnosis of TINU syndrome. Renal and ocular manifestations of this disease often occur at different times, usually affecting the kidneys first rather than the eyes. The disease is more prevalent in adolescents and in females. Symptoms of nephritis are nonspecific and may include malaise, weakness, fever, anorexia, and abdominal pain. Interstitial nephritis can lead to renal failure. Uveitis usually presents as an anterior, acute form, initially unilateral and non-granulomatous, and can progress to a chronic, bilateral form. Complications associated with uveitis include cataracts and glaucoma[8].

The pathophysiology of TINU syndrome is still poorly understood, but genetic, immunological, and environmental components are suggested. The syndrome is believed to be related to certain specific types of human leukocyte antigen (HLA)[9]. In renal biopsy, the presence of inflammatory cells such as monocytes and lymphocytes suggests the involvement of cellular immunity. There is evidence of triggering factors for the disease manifestations, including medications, infections, and systemic conditions, although TINU syndrome can also be idiopathic. Among the medications most associated with TINU syndrome are nonsteroidal anti-inflammatory drugs (NSAIDs) and antibiotics. Infectious agents that can trigger TINU syndrome include *Epstein-Barr, Varicella zoster, Chlamydia trachomatis, Mycobacterium tuberculosis, Toxoplasma gondii, and Treponema pallidum* . Furthermore, some systemic diseases are related to the syndrome, such as hypothyroidism, hyperthyroidism, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus, Sjogren's syndrome and Wegener's granulomatosis[8].

The diagnosis of TINU syndrome is one of exclusion and requires a renal biopsy, as there is no non-invasive diagnostic test. A renal biopsy typically reveals edema, interstitial infiltration of T lymphocytes, neutrophils, and plasma cells, as well as tubular damage. However, the glomeruli, mesangium, and blood vessels are usually preserved. Other tests that may reveal abnormalities include anemia, elevated C-reactive protein, deterioration of renal function, metabolic acidosis, Fanconi syndrome, and increased α2-microglobulin levels[8].

The first-line therapy for TINU syndrome is corticosteroids, which preserve renal function in the long term[10]. In cases of corticosteroid resistance, therapeutic options such as azathioprine and mycophenolate mofetil may be considered[8,11]. Uveitis associated with TINU syndrome is also treated with corticosteroids, often requiring a systemic approach in addition to topical treatment. It is important to note that recurrence of uveitis is common[8,12].

The use of isotretinoin, although effective and safe in the treatment of severe acne, may be associated with the development of TINU syndrome. This condition should be closely monitored during isotretinoin treatment, through urinalysis and creatinine measurement. Early diagnosis and appropriate treatment are crucial to preserving renal and ocular function, preventing more serious complications, such as chronic renal failure and visual loss. The case presented highlights the importance of including TINU syndrome as an adverse effect of isotretinoin, which is rarely reported in the literature, emphasizing the need for monitoring renal function during the use of this medication. In cases of interstitial nephritis, ophthalmological evaluation should not be neglected.

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