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TINU syndrome – Two clinical cases of tubulo-interstitial nephritis and uveitis

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ABSTRACT

TINU (Tubulo-Interstitial Nephritis and Uveitis) syndrome is a rare disease of unknown aetiology characterised by the association between interstitial nephritis and uveitis. The authors present the cases of two young children whose symptoms began with anorexia and weight loss, associated with renal failure and proteinuria of tubular origin. One child also presented anaemia, glycosuria without hyperglycaemia and microhaematuria. A few months later both developed uveitis. In both cases the renal biopsy showed changes compatible with interstitial nephritis. As interstitial nephritis and uveitis aetiologies were not identified, TINU syndrome was suggested as a possible diagnosis. In both children there was a complete resolution, with one needing systemic steroids and immunosuppressive treatment.

TINU syndrome should always be considered in the differential diagnosis of patients with renal and ophthalmologic changes.

Key-Words:
Interstitial nephritis; TINU syndrome; uveitis.

INTRODUCTION

The association between tubulointerstitial nephritis and uveitis (TINU syndrome) is a rare clinical entity, described for the first time in 1975 by Dobrin *et al*.[1-3]. Since then approximately 140 cases have been reported[2-5].

It is more prevalent in females (3:1), most commonly in pubertal girls and young women. The aetiology is not yet known. Laboratory results suggest an immune mechanism mediated by T4 cells, but genetic markers (HLA alleles) are suggested risk factors for the development of the disease[6,7].

Fever, myalgias, asthenia, weight loss and abdominal pain are usually the first clinical findings, to which ocular pain, visual acuity reduction and photophobia are frequently associated[2,8,9]. Renal manifestations are dominated by the dysfunction of both the proximal and distal tubules. Renal failure develops during the course of the disease. Uveitis is generally anterior and bilateral, but all chambers may be affected. It might appear prior to, concurrent with, or posterior to renal disease[7].

Histologically, there is evidence of acute interstitial nephritis with tubular lesions, with or without eosinophilic infiltrate. Non-caseating granuloma can also be seen. Mononuclear cells compose the cellular infiltrate, mainly formed by T CD4+ cells.

More frequent laboratory findings are anaemia, increased erythrocyte sedimentation rate, reduced glomerular filtration rate (GFR) and increased beta 2 microglobulin in the urine.

Nephritis has a good prognosis in younger patients, and might respond well to corticosteroids or there could be a spontaneous remission without treatment[3,4]. Nevertheless, renal failure might persist in 10% of patients.

Uveitis generally responds to topic or systemic steroids, but can have a chronic or recurrent course.

CASE 1

A 9 year-old male, born and living in a rural area, was admitted to hospital with anaemia and renal failure. His past medical and family history were unremarkable. One month prior to hospitalisation he developed asthenia, adynamia and anorexia (with a 5 kg weight loss in 4 weeks). Two weeks after the beginning of symptoms, he was medicated with nimesulide and ofloxacine for odynophagia. As symptoms persisted, laboratory tests were performed, revealing microcytic/hypochromic anaemia (haemoglobin 9.1 g/dl); erythrocyte sedimentation rate 132 mm in the first hour; urea 86 mg/dl; serum creatinine 2.9 mg/dl and glycosuria without hyperglycaemia and proteinuria.

On examination, he had a slightly pale skin and mucosas, good general state, normal blood pressure, no oedema, jaundice, hepatosplenomegaly, exanthema, changes in articulations or in the eyes.

Laboratory findings were Hb 9 g/dl, GFR 27 ml/min/1.73 m^2, discrete compensated metabolic acidosis (pH 7.35; HCO_3 18.6 mEq/L; BE -6.0, anion gap 11.8), total proteins 8.5 g/dl with normal albumin and gammaglobulins, urine pH 5.0, proteinuria 45.5 mg/m^2/h, glycosuria (without hyperglycaemia), microscopic haematuria and reduction of the phosphorus reabsorption rate (60%). Blood electrolytes, lipid profile and liver tests were normal. Urine culture was negative.

Serology tests were negative for HAV, HBV, HCV, HIV, toxoplasmosis, EBV and CMV. He had normal C3, C4 and CH50 levels. Widal, Huddleson and Bengala Rose tests, ANA, anti-DNA, LE test, Mantoux test, TASO, direct Coombs and PHA direct were negative.

Renal echography showed kidneys normal in size and morphology. Chest X-ray and abdominal echography were also normal.

During hospital stay (12 days) patient remained asymptomatic with the above mentioned laboratory findings, except for the metabolic acidosis. He started enalapril for proteinuria and iron sulphate and folic acid for anaemia. He was discharged diagnosed with interstitial nephritis secondary to ofloxacine.

Two and a half months after the beginning of symptoms he developed photophobia and bilateral conjuntival hyperaemia, and was diagnosed with anterior bilateral uveitis. Topic atropine and prednisolone were prescribed, with oral prednisolone introduced two weeks later as symptoms persisted.

The association of uveitis and systemic disease with the involvement of the renal function led to a probable diagnosis of TINU syndrome. A renal biopsy was performed. The histological exam revealed interstitial nephritis with cellular atrophy of numerous tubes, cellular vacuolisation and thickening of some basal membranes; interstitium had generalised fibrosis and moderated infiltrations of lymphocytes and eosinophils; glomeruli were normal and there were no vascular changes. No immune deposits were seen (Fig. 1).

After two months of corticosteroids there was an improvement in renal function but the tubular proteinuria and uveitis remained. Due to persistent proteinuria and uveitis associated with the parameters of severity

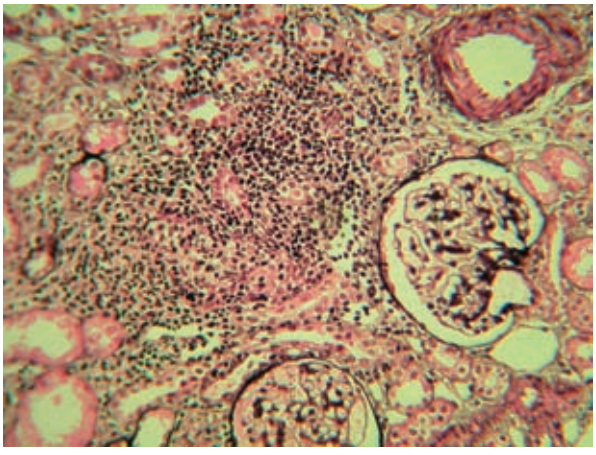

Fig. 1 – Renal biopsy with interstitial infiltrate and normal glomeruli

in the histological exam, it was decided to start chlorambucil (0.2 mg/kg/day). This was maintained for 3 months, with a rapid and complete recovery of renal function and ophthalmologic disease.

CASE 2

A ten year-old girl, born and living in a rural area, was referred to Hospital Dona Estefânia for renal failure and uveitis. Her medical history was unremarkable. Family background revealed an uncle with renal failure (caused by probable glomerular disease).

About one year prior to hospital admission she developed anorexia, asthenia and weight loss (about 3 kg). As these complaints persisted, complementary exams were performed, revealing haemoglobin 12.2 g/dl, erythrocyte sedimentation rate 36 mm in the first hour, urea 51 mg/dl and creatinine 1.48 mg/dl. She also presented proteinuria (12 mg/m^2/h) and a normal renal echography. About 10 months after the beginning of symptoms, she developed bilateral conjuntival hyperaemia and panuveitis was diagnosed and treated with topic steroids.

Her physical examination was normal on hospital evaluation. Laboratory findings were a GFR of 80.5 ml/min/1.73m^2, urea 39 mg/dl, creatinine 0.9 mg/dl, Beta-2-microglobulin 1472 UI, proteinuria 6.7 mg/m^2/h, and haemogram, serum electrolytes, total proteins and albumin, liver tests, rennin, aldosterone, TASO, arterial blood gas analysis, ANA, Anti-DNA, LE test, C3, C4, CH100, immunoglobulins and PTH normal.

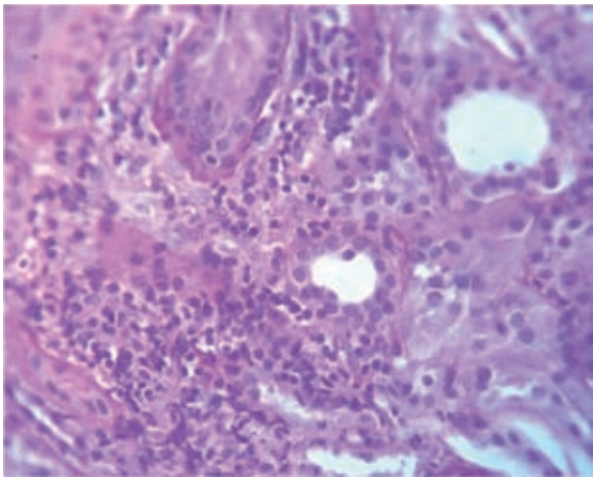

Fig. 2 – Renal biopsy with acute interstitial infiltrate

The clinical and laboratory findings led to a probable diagnosis of TINU syndrome and a renal biopsy was performed. Histology revealed interstitium with multifocal fibrosis and spots of inflammatory infiltration, made up of mononuclear cells, spots of tubular atrophy and hyaline cylinders and intratubular calcium depots (Fig. 2).

After 8 months of topic steroid therapy there was a meaningful improvement of the uveitis and treatment was suspended. Simultaneously, there was a slow increase of the GFR (last value of 110 ml/min/1,73m^2) and proteinuria values normalised.

DISCUSSION

Acute interstitial nephritis is usually associated to bacterial or virus infection, ingestion of medication (antibiotics, NSAIDs) and/or autoimmune diseases[1,10]. Clinically, in addition to renal failure, all patients present systemic symptoms, such as fever, anorexia, adynamia, headache and odynophagia.

TINU syndrome is a clinical entity characterised by the association between tubulointerstitial acute nephropathy and uveitis in which infectious, immunologic or toxic pathology must be ruled out. Definitive diagnosis of this syndrome is based on clinical, laboratory and renal biopsy findings and by the exclusion of other causes of nephritis and uveitis.

In the first clinical case, where a patient presented with systemic complaints associated to moderate renal failure, anaemia, glycosuria, microhaematuria and tubular proteinuria in a context of recent ofloxacin intake, it was initially felt that it could be a case of acute interstitial nephritis secondary to the antibiotic. In order to exclude infectious or immunological causes, complementary exams were performed. The presence of interstitial nephritis and uveitis with negative immunofluorescence, in the absence of other pathologies, suggested TINU syndrome.

In the second case, diagnosis was easier due to the fact that the child presented with complaints compatible with nephritis, uveitis and renal failure. Nevertheless it was important to exclude other possible causes.

As already stated, the pathogenesis of the TINU syndrome has not yet been defined. Treatment with systemic steroids is controversial, and spontaneous remission of the nephritis is frequent[3,4], as happened in case 2, where we observed a complete resolution of both uveitis and nephritis. Nevertheless, in cases of significant tubulo-interstitial lesion, responsible for the progression to chronic renal failure, steroids can improve or even resolve the nephropathy[2,4]. Uveitis should always be treated as it can be recurrent. If treatment with topic steroids is not enough, systemic steroids or even immunosuppressive therapy can be used.

The finding of transient nephrotic range proteinuria is not commonly seen and may indicate a glomerular compromise. Similar findings have been reported in the literature[5,11].

The authors report these clinical cases to draw attention to the fact that TINU syndrome should always be considered in the differential diagnosis of patients with renal and ophthalmologic changes.

Conflict of interest. None declared.

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