CASE REPORT

A child with tubulointerstitial nephritis and uveitis (TINU) syndrome

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SUMMARY

Tubulointerstitial nephritis and uveitis syndrome is an uncommon disease, probably underdiagnosed in clinical practice. Its aetiology and pathogenesis remain unknown. This syndrome is defined by an association of uveitis and tubulointerstitial nephritis, with no evidence of systemic disease or infection that might cause both ocular and renal inflammation. Renal and ocular manifestations may not occur simultaneously, making the diagnosis even more challenging. Treatment includes topical and oral corticosteroids. Renal involvement usually resolves spontaneously with full recovery of kidney function, however uveitis can persist or recur years after its initial presentation. We report a case of a 13-year-old girl with tubulointerstitial nephritis and uveitis syndrome.

BACKGROUND

Tubulointerstitial nephritis and uveitis (TINU) syndrome is a rare condition, probably under-recognised.^{1–3} Establishing this diagnosis may be particularly difficult because the ocular and renal manifestations may not occur concurrently.^{1,2} It is essential to identify this syndrome in order to correctly follow this group of patients.

CASE PRESENTATION

A 13-year-old previously healthy girl presented with a 3-week history of blurred vision, redness and pain in the right eye. She also referred an intentional weight loss following a hypocaloric diet (20% of body weight). Patient denied fever, anorexia, asthenia, arthralgia, myalgia, oral or genital ulcers, abdominal or flank pain, polyuria, nocturia and changes of the normal aspect of urine.

On physical examination, she was afebrile and in good general condition. Blood pressure was 135/90 mmHg (above the 99th percentile for systolic and diastolic blood pressure).

Bilateral anterior non-granulomatous uveitis was diagnosed by an ophthalmologist. There was no involvement of the intermediate or posterior segment, and intraocular pressure was normal.

INVESTIGATIONS

Laboratory analysis showed increased inflammatory markers (erythrocyte sedimentation rate of 96 mm and C reactive protein of 2.6 mg/dL), deterioration in renal function (serum creatinine level of 1.4 mg/dL and glomerular filtration rate of 48 mL/min/1.73 m²) and hypokalaemia (potassium of

3.0 mmol/L) (table 1). Urinalysis showed a normal pH level (6.5) and urine specific gravity (1.010), leucocyturia (125/μL), glycosuria (250 mg/dL), proteinuria (100 mg/dL) and haematuria (10/μL). Urine protein excretion collected 24 hours was 366 mg/m² and urinary excretion of β2-microglobulin was raised (19.83 mg/L; reference range: 0.03–0.10 mg/L).

Serological tests for hepatitis B and C, *Toxoplasma gondii* and *Brucella* were negative, as well as Epstein-Barr virus and cytomegalovirus detection by PCR.

Level of ACE was normal. Antinuclear antibodies and antineutrophil cytoplasmic antibodies were negative.

Chest X-ray was unremarkable.

Renal ultrasound showed kidneys of dimensions slightly above the upper limit of normal. A percutaneous kidney biopsy revealed histological findings consistent with tubulointerstitial nephritis with a diffuse lymphocytic infiltrate. Immunofluorescence was negative.

Considering the clinical features and laboratorial results, TINU syndrome was diagnosed.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of TINU syndrome includes infections (tuberculosis, toxoplasmosis, brucellosis, histoplasmosis and cytomegalovirus) and systemic diseases (sarcoidosis, Sjögren's syndrome, systemic lupus erythematosus, granulomatosis with polyangiitis and Behçet's disease).

TREATMENT

Treatment consisted of ocular dexamethasone and mydriatics and oral prednisolone 5 mg/m²/day, as well as amlodipine and potassium citrate.

OUTCOME AND FOLLOW-UP

The patient improved with normalisation of blood pressure, serum creatinine and tubular function. After 3 months of treatment, the uveitis was in remission and renal function was normal. A relapse of uveitis was detected 2 months later and oral therapy with methotrexate 9 mg/m²/week was started. The patient experienced two additional relapses under therapy with methotrexate 1 and 3 years after diagnosis. The first one required methotrexate dose adjustment to 12 mg/m²/week and the second resolved with ocular steroids. Currently, 5 years after diagnosis, the patient is asymptomatic under therapy with methotrexate.

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Table 1 Laboratory data at presentation

	Values	Reference range
Haemoglobin	12.9 g/dL	12–15.3 g/dL
White cell count	14.89×10 ⁹ /μL	4.0–11.0×10 ⁹ /μL
Neutrophils	77.7% (11.5×10 ⁹ /μL)	1.9–7.5×10 ⁹ /μL
Eosinophils	2.7% (0.40×10 ⁹ /μL)	0.0–0.5×10 ⁹ /μL
Basophils	0.3% (0.04×10 ⁹ /μL)	0.0–0.2×10 ⁹ /μL
Monocytes	3.6% (0.54×10 ⁹ /μL)	0.1–1.0×10 ⁹ /μL
Lymphocytes	15.7% (234.0×10 ⁹ /μL)	1.0–4.8×10 ⁹ /μL
Platelet count	513×10 ⁹ /μL	150–450×10 ⁹ /μL
C reactive protein	2.6 mg/dL	<0.5 mg/dL
Erythrocyte sedimentation rate	96 mm	
Blood urea nitrogen	41 mg/dL	10–50 mg/dL
Serum creatinine	1.4 mg/dL	0.5–1.1 mg/dL
Total serum protein	8.7 g/dL	6.4–8.2 g/dL
Serum albumin	3.9 g/dL	3.2–4.9 g/dL
Aspartate aminotransferase	14 U/L	<34 U/L
Alanine aminotransferase	11 U/L	10–49 U/L
Sodium	138 mmol/L	135–145 mmol/L
Potassium	3.0 mmol/L	3.5–5.1 mmol/L
Calcium	9.3 mg/dL	8.6–10 mg/dL
Phosphorus	3.1 mg/dL	2.4–5.1 mg/dL

The patient is being followed by a paediatric nephrologist, an ophthalmologist and a rheumatologist.

DISCUSSION

TINU syndrome was first described by Dobrin and collaborators in 1975.^{1 4–9} It affects mostly young females,^{3–5} with a median age at diagnosis of 15 years¹⁰ and a 3:1 female-to-male ratio.^{3 6 8 9}

The aetiology and pathogenesis of the disease remain unknown.^{2 3 7–9} Risk factors such as infections (chlamydia and Epstein-Barr virus) and drugs (antibiotics and non-steroidal anti-inflammatory drugs) have been implicated.^{1–3 6} We found no such associations in our case. Recently, autoantibodies against modified C reactive protein were found in the uvea and renal tubular cells of the patients with the disease.^{1 11} More studies, however, are needed to prove the involvement of these autoantibodies in the pathogenesis of TINU syndrome.¹

TINU syndrome is characterised by renal and ocular involvement.^{1 2 4 12} Patients with TINU may present with systemic findings including fever, general malaise, fatigue, anorexia, asthenia, weight loss, headache, arthralgia and myalgia.^{1 2} Renal manifestations include abdominal and flank pain, polyuria and nocturia, sterile pyuria, subnephrotic proteinuria, haematuria, acute kidney injury and multiple proximal and distal tubular defects resulting in aminoaciduria, acidification defects, glycosuria and phosphaturia.^{1 3 7} The urinary excretion of β2-microglobulin was raised in our case, which suggested a tubular defect. Simultaneous elevated creatinine serum and β2-microglobulin urinary levels seem to be the most sensitive marker for the diagnosis.^{1 3} Other laboratory findings may include anaemia, eosinophilia, abnormal liver function tests, an elevated erythrocyte sedimentation rate and C reactive protein.^{1 3}

Eye involvement includes pain, redness, blurred vision, photophobia, foreign body sensation, itching and dry eyes, superficial keratitis and decreased visual acuity.⁷ Ocular involvement usually presents with bilateral anterior uveitis.^{3 5} Unilateral and alternating uveitis can also occur.² Our patient presented with

unilateral eye pain, redness and blurred vision, but the ophthalmological evaluation revealed a bilateral anterior uveitis. Uveitis occurs after the onset of the interstitial nephritis in 65% of the patients, but it may also precede or occur simultaneously with the renal disease.^{1 2 9 12} Uveitis has been described to happen from 2 months before up to 14 months after the onset of the renal disease. Patients diagnosed with tubulointerstitial nephritis should be therefore monitored by an ophthalmologist for at least 12 months after the diagnosis.¹⁴

Diagnosis of this entity is suggested by the combination of uveitis and tubulointerstitial nephritis, after exclusion of other causes, namely infections and systemic diseases.^{3 7}

The prognosis of TINU is usually favourable.⁴ Tubulointerstitial nephritis can resolve spontaneously or after treatment with systemic corticosteroids.^{2 7} Patients with progressive renal insufficiency are treated with prednisone for 3–6 months and most of them fully recover renal function.⁶ In the case described blood pressure, serum creatinine and tubular function normalised 3 months later. Topical and systemic corticosteroids have been used to treat uveitis.⁶ Uveitis persists or recurs at least once in half of the patients even after 10 years.^{2 5} In these patients immunosuppressive agents can be used, such as methotrexate, mycophenolate mofetil and ciclosporin.⁶ Methotrexate is used as first-line immunosuppressive therapy in paediatric population, because of its efficacy and safety.¹⁵ Our patient was initially treated with ocular mydriatics and dexamethasone and oral prednisolone. The uveitis, however, relapsed several times and treatment with methotrexate was needed.

Learning points

- ▶ When acute anterior uveitis is diagnosed in paediatric population, it is strongly recommended to evaluate for concomitant interstitial nephritis with a urinalysis, serum creatinine and urinary 2-microglobulin.
- ▶ An interdisciplinary effort is necessary to properly diagnose and treat patients with tubulointerstitial nephritis and uveitis syndrome.
- ▶ A long-term follow-up is important to guarantee the correct identification of relapses.

Contributors CP, PC-R, JEdS and RS conducted the analysis of the described case. CP drafted the manuscript. PC-R, JES and RS critically reviewed the manuscript. All the authors read and approved the final version.

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