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Tubulo-interstitial nephritis and uveitis with Fanconi syndrome

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To the Editor,

Tubulointerstitial nephritis (TIN) with uveitis (TINU) is a rare disease whose pathogenesis is unknown.

We present the case of a boy 9 years of age examined for glycosuria. The patient had asthenia, anorexia and had lost more than 5kg body weight in the course of 1 month. No prior infections. The patient experienced nocturnal enuresis which was treated with desmopressin; that treatment was suspended 2 months before onset of the listed symptoms.

Examination revealed high blood pressure (maximum 135/97mm Hg), with other values being normal.

Blood analysis revealed renal dysfunction: creatinine (Cr) 1.2mg/dl; creatinine clearance 54ml/min/1.73 m²; urea 51mg/dl; uric acid 2.1mg/dl; phosphorus 4.4mg/dl; mild metabolic acidosis with C-reactive protein 29mg/l and globular sedimentation velocity 62mm (Table 1).

Table 1. Laboratory blood and urine analyses at onset of symptoms and during syndrome progression

Patient evaluation	On admission	Day 10	Day 20	Day 60	Day 120	Day 210	Reference values
Biochemical tests							
Cr (mg/dl)	1.2	1.1	1.1	1	0.8	0.7	0.2-0.7
CrCl (ml/min/1.73m ²)	54	51	66	67	78	116	89-165
Urea (mg/dl)	51	36	62	44	38	33	21-50
Uric acid (mg/dl)	2.1	1.9	2	2.4	3.2	3.4	3.4-7
Glucose (mg/dl)	71	90	82	84	82	93	60-100
Phosphorus (mg/dl)	4.4	3.3	3.9	4.3	4.5	4.5	4.5-5.5
Calcium (mg/dl)	9.1	9.7	10	10.3	9.9	10.4	8.8-10.8
Proteins (g/dl)	7.5	8.5	8.3	7.8	7.2	7.2	6-8
Sodium (mEq/l)	136	141	139	139	142	142	135-145
Potassium (mEq/l)	4.3	4.6	4.4	4.8	4.8	4.8	3.5-5
Cl (mEq/l)	102	115	111	107	107	108	101-111
pH	7.3	7.26	7.3			7.33	7.36-7.4
pCO ₂	36	43	39			40.3	40-45
Bicarbonate (mmol/l)	17.5	19	19			21.1	22-26
EB	-6.1	-7.2	-6			-3.9	-2-3
Urine							
pH	6	6.5	7		6.5		5-7.5
Proteins (g/l)	1.2	0.7	0.3	0.12	0.06	0.05	0.01-0.14
Prot/Cr	0.94	0.7	0.63	0.27	0.12	0.08	<0.2
µalb/Cr (mg/g Cr)	148	107	99	42	<6	<6	0-30
Glucose (g/l)	0.8	1	1	0.3	0	0	0-0.5
TPR (%)	78	85	87	88	89	92	90-95
FEUA (%)	48	31	33	17			<10%
UrEI (mg/100 GF)	0.63	0.60	0.67	0.56	0.42	0.41	0.2-0.42
Proteinuria (mg/kg/day)	13	9.7	11	4.4	2.3	1.1	<4

µalb: microalbuminuria; CrCl: creatinine clearance; Cr: creatinine; EB: excess of bases; FEUA: fractional excretion of uric acid; UrEI: Uric acid excretion index; Prot/Cr: protein/creatinine index; TPR: tubular phosphate reabsorption.

The urine analysis showed glycosuria (0.8g/l); non-nephrotic range proteinuria (13mg/kg/day, microalbuminuria 148mg/g Cr); hyperphosphaturia with low tubular phosphate reabsorption (78%); hyperuricosuria with a high uric acid index (0.78/100ml glomerular filtration); normal glomerular filtration and calcium levels (1.1mg/kg/day); fractional excretion of sodium 0.3%, and fractional excretion of potassium 19%. Urinary sediment showed granular and hyaline casts, leukocyturia without eosinophils and a negative urine culture.

These findings are compatible with multiple dysfunctions of the proximal tubule (PT), or Fanconi syndrome.

Liver, thyroid and parathyroid functions were normal. The immunological study revealed low-level positivity for antinuclear antibodies (1/80). The anti-streptolysin O (ASLO) titre was high (2175IU/ml) with a negative oropharyngeal culture. Immunoglobulin levels were normal, but IgG was high 1 week later (1820mg/dl). An IgM test was run for Epstein-Barr, cytomegalovirus, parvovirus B19, toxoplasmosis and hepatitis B and C. All were negative. Renal ultrasound was normal.

Given the PT dysfunction and mild renal failure, we suspected a case of TIN. We adopted a watchful waiting approach and kidney function and blood

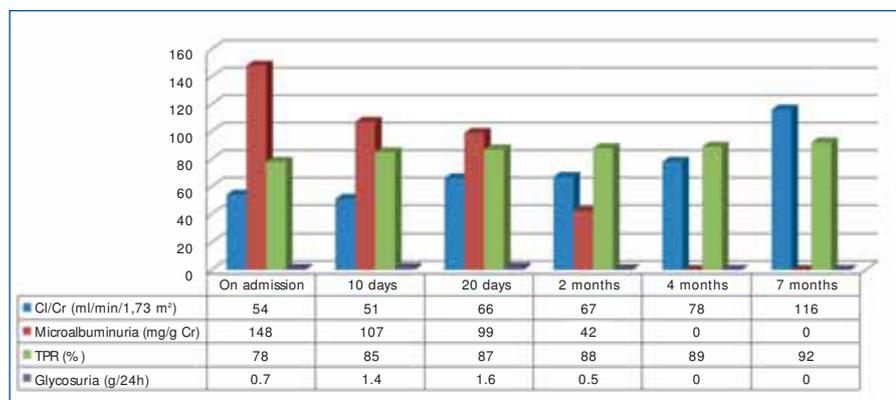


Figure 1. Creatinine clearance, microalbuminuria, tubular reabsorption of phosphate and glycosuria

Changes in creatinine clearance levels in ml/min adjusted for body surface area; in microalbuminuria expressed in mg/g of creatinine; in glycosuria expressed in g/day and in tubular reabsorption of phosphate as a percentage.

CrCl: creatinine clearance; Cr: creatinine; TPR: tubular phosphate reabsorption.

pressure normalised in less than 4 weeks. No kidney biopsy was performed (Figure 1).

One month after renal symptoms began, he presented with acute anterior uveitis, which evolved favourably under treatment with topical steroids and cycloplegic agents.

According to Mandeville's criteria,¹ we diagnosed tubulointerstitial nephritis associated with uveitis (TINU). After 18 months, renal function remains normal, although there have been various relapses of uveitis.

DISCUSSION

The aetiology and pathogenesis of this disease are unknown, but hypotheses suggest mechanisms mediated by cellular immunity. It has been linked to infections, systemic diseases and previous use of medications.²

In our case, the high ASLO titres suggested a streptococcus infection, but there were no associated symptoms and the oropharyngeal culture was negative. It seems unlikely to have originated with the desmopressin as no causal relationship has been established. We have not found any cases linking TIN to the use of that drug.

Clinical manifestations are variable, with non-specific systemic symptoms and renal symptoms that include flank pain, sterile pyuria, haematuria, non-nephrotic range proteinuria and different stages of renal failure. Proximal and distal tubular defects may also be associated.

Our patient presented glycosuria with general PT dysfunction, moderate renal dysfunction and mild hypertension.

We diagnosed TINU syndrome according to Mandeville's criteria.¹ Differential diagnosis was performed to rule out other entities involving both renal and ocular disease,² such as sarcoidosis, Sjögren's syndrome, Wegener's granulomatosis, Behçet's disease, toxoplasmosis, tuberculosis, histoplasmosis and brucellosis.

Renal dysfunction tends to be self-limiting,³ but becomes persistent in some 10% of patients. Oral steroids are the treatment of choice,⁴ although immunomodulators may also be used in patient with a poor response.²

Uveitis may develop prior to (in 20%) or after (in 65%) renal symptoms, and is rarely concomitant. Cases of uveitis presenting as much as 2 months before or 14 months after renal symptoms

have been observed.² Uveitis generally has a favourable prognosis, but some articles report complications in up to 20% of patients² and relapses are frequent.

Since the manifestations of TINU syndrome are non-specific, its true incidence rate may be underestimated. Both nephrologists and ophthalmologists must be aware of this entity and check renal function in patients with uveitis (and vice versa).

Conflicts of interest

The authors affirm that they have no conflicts of interest related to the content of this article.

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