Case Report

Tubulo-interstitial nephritis with Fanconi syndrome in Behçet disease

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Keywords: acute interstitial nephritis; Behçet disease; proximal tubular dysfunction; tubulitis

Introduction

Behçet disease (BD) is a chronic and inflammatory systemic disorder of unknown aetiology, with an estimated prevalence of 1/500,000 in Europe and the United States. BD, which typically affects young adult males, is characterized by recurrent oral and genital ulcerations, with anterior or posterior uveitis. Skin, joint, nervous system, lung and gastrointestinal tract manifestations are common, along with small and large vessel vasculitis that may involve veins and arteries [1]. Renal complications in BD are less frequent and are mostly related to the development of AA amyloidosis due to chronic systemic inflammation. Various and non-specific glomerular diseases have been described in BD, including focal or diffuse proliferative glomerulonephritis, membranous nephropathy, crescentic glomerulonephritis, or anti-immunoglobulin (Ig) A nephritis [2]. Other causes of renal failure are exceptional, including vascular disease related to arterial aneurysms and venous or arterial occlusions, and acute interstitial nephritis which has been reported in only 4 cases [3–6].

Fanconi syndrome (FS) is a proximal tubular (PT) dysfunction including renal glucosuria, generalized aminoaciduria, phosphaturia, uricosuria, low-molecular weight protein and PT (type II) acidosis. FS is often acquired in adults, secondary to the administration of certain drugs, heavy metal poisoning, or to the urinary secretion and reabsorption of a monoclonal immunoglobulin light chain in proximal tubules. PT dysfunction has been also described in rare patients with auto-immune interstitial nephritis, such as Sjögren’s syndrome [7], TINU syndrome [8], or primary biliary cirrhosis [9].

We report here the first case of BD with acute tubulo-interstitial nephritis (TIN) and FS probably related to PT infiltration by CD8(+) T cells. Classical causes of TIN and PT dysfunction were ruled out by careful investigations. Renal and PT function recovered completely after low-dose corticosteroids and long-term colchicine treatment.

Case report

A 46-year-old North African woman, with no significant medical history, was admitted with complaints of recurrent oral ulcers (every 3 weeks), headaches, asthenia, anorexia, diffuse arthralgia, weight loss and abdominal pain for the last 3 months. She had been diagnosed as having bilateral acute anterior uveitis 20 days prior to admission and was treated by local corticosteroids. The patient had no history of renal disease, diabetes mellitus or hypertension and she had no current medication. Physical examination was unremarkable except for bilateral Raynaud phenomenon and oral ulcers. Temperature was 37.2°C, body weight 53 kg, blood pressure 100/60 mmHg and daily urine output ranged between 1.6 and 2.2 l. Abdominal ultrasonographic and chest radiographic examinations were normal.

Laboratory data showed acute renal failure with hypophosphataemia, hypokalaemia, hypouricaemia, orthoglycaemic glucosuria, metabolic acidosis and hyperchloraemia (Table 1). Other results were: total proteins 73 g/l, albumin 42 g/l, γ-globulins 12 g/l, aspartate aminotransferase 13 U/l, alanine aminotransferase 22 U/l, alkaline phosphatase 75 U/l. Full blood count was normal, except for anaemia. Urinalysis showed pH 5.5, proteinuria 0.35 g/day with slight microscopic haematuria and aseptic leukocyturia. Plasma and 24 hour urine osmolality were 290 and 269 mOsm/kg, respectively. Increased fractional excretion of phosphate and uric acid confirmed urine leak. Urine chromatography disclosed generalized amino-aciduria with prominent excretion of lysine,
tyrosine, cystine, leucine, arginine and phenylalanine. Urine levels of β2 microglobulin were high (20.49 mg/g creatinine, normal <0.3). Plasma anion gap was +10 mmol/l, with urine net charge (Na+K-Cl) of +46 mmol/l, suggestive of renal tubular acidosis. An intravenous sodium bicarbonate loading test showed normal fractional excretion of HCO3 (1.6%, normal value <15%) for a serum bicarbonate concentration of 25 mmol/l.

Tests for antinuclear, anti-DNA, antineutrophilic cytoplasmic, anti-SSA and anti-SSB antibodies were negative. Levels of C3, C4, CH50 and angiotensin convertase were normal. Serologic tests for HIV, hepatitis B and hepatitis C infections were negative. Serum and urine immunoelectrophoresis revealed no monoclonal component. Serum levels of heavy metals including lead, copper, cadmium and mercury were normal. HLA phenotyping revealed the presence of B51 antigen. Pathergy test was negative.

A minor salivary gland biopsy showed mild infiltration of capillary walls by lymphocytes and plasma cells, without amyloid deposits. Multiple ulcers were seen on colonoscopy. Colon biopsies revealed moderate interstitial lymphocytic inflammatory infiltrates. A left kidney biopsy was performed. Light microscopic examination showed interstitial fibrosis and acute granulomatous TIN with polymorph inflammatory cells (neutrophils, lymphocytes, histiocytes, eosinophils and plasma cells) infiltrating the interstitium, peritubular capillary lumens and PT epithelium with tubulorrhexis (Figure 1A–1D). Additionally, tubular micro abscess and foci of peri-tubular capillaritis were observed. Tubular basement membrane were wrinkled (Figure 1B). Glomeruli showed moderate segmental mesangial expansion with slight thickening of capillary walls. Congo red and thioflavine staining was negative. Immunofluorescence study with anti-immunoglobulin (Ig) light and heavy chains, C3 and C1q complement components conjugates, was negative. Electron microscopic examination demonstrated severe PT lesions, including atrophy of the apical brush border and focal lymphocytic tubulitis (Figures 1E and 1F). By immuno-histochemistry, cellular infiltrates appeared to be predominantly composed of CD3(+) and CD8(+) T lymphocytes with few CD3(+) and CD4(+) lymphocytes and CD68(+) macrophages. Paraffin-embedded normal human kidney sections were incubated with two different samples of the patient's serum (collected on admission and at last follow-up) and examined using fluoresceine isothiocyanate conjugated anti-human IgG goat antibody. No significant staining of proximal tubules was observed (Data not shown).

Initial treatment consisted of intravenous methylprednisolone pulses (1000 mg/day, 3 days), followed by oral prednisolone (1 mg/kg/day), and colchicine (1.5 mg/day). Two weeks later, serum creatinine level was 0.9 mg/dl and symptoms of PT dysfunction disappeared. Corticosteroids were progressively tapered and stopped after 2 years. No other therapy, including ciclosporin, was initiated. On last follow-up, 76 months after initial admission, the patient was asymptomatic, except for scarce, recurrent oral ulcers and renal parameters were normal (Table 1). Urinary aminoacids were within the normal range.

### Discussion

As there is no pathognomonic laboratory test or characteristic histology, the diagnosis of BD relies on the presence of suggestive clinical findings according to the criteria of the International Study Group For Behçet Disease [10]. In the present case, only two of these criteria were present (recurrent oral ulcers and bilateral anterior uveitis). However, association with focal bowel ulcerations, efficacy of long-term colchicine therapy with lack of evidence for another systemic disease despite prolonged follow-up, and the presence of HLA B51 antigen, strongly supported the diagnosis.
Strikingly, clinical presentation was dominated by renal failure with features of PT dysfunction including renal glucosuria, generalized aminoaciduria, phosphaturia and uricosuria and low-molecular weight proteinuria, consistent with FS. The mechanism of metabolic acidosis was not clear, as PT acidosis was not confirmed by bicarbonate loading test. Elevated urine net charge was suggestive of defective urine NH4+ excretion, supporting the hypothesis of renal distal (type I) tubular acidosis. The association of renal distal tubular acidosis with PT dysfunction, featuring or not PT leak of bicarbonate, has been shown in patients with Sjögren’s syndrome and severe acute interstitial nephritis [7]. However, specific tests were not performed to confirm or not this hypothesis. Kidney biopsy revealed the presence of severe acute TIN with significant infiltration of interstitium and PT epithelium by inflammatory cells, neutrophils and T lymphocytes.

Renal involvement in BD is probably underestimated. Large retrospective studies have shown that urine abnormalities (proteinuria and/or haematuria) are detected in 10.8% to 20% of the patients [11,12]. Whereas various glomerular diseases have been clearly described, particularly in patients with severe disease, whether TIN is a manifestation of BD remains...
uncertain. To our knowledge, only 4 cases of biopsy-proven TIN have been reported, which were recently reviewed by Akpolat et al. [2]. The first case was a 48-year-old female who presented initially with acute renal failure, followed by severe ulcerations of the tongue and acute uveitis. Renal biopsy revealed interstitial nephritis without glomerular involvement [3]. In the three other cases, clinical data were insufficient to firmly establish the role of BD in the development of TIN. Nagata et al. reported a 50-year-old man, with a past history of hypertension and diagnosed with BD, who developed a cerebral haemorrhage and died 65 days after admission, from bronchopneumonia and severe gastrointestinal bleeding. Post mortem kidney examination showed marked arteriosclerotic changes, and ‘benign nephrosclerosis with interstitial nephritis’ [4]. In a collaborative study of children who fulfilled the international criteria for BD, Koné-Paut et al. found that 2 out of 65 patients had urinary sediment abnormalities. In one of those with haematuria, TIN was diagnosed on kidney biopsy examination [5]. Finally, the patient reported by Jo et al. had biopsy-proven megalocytic interstitial nephritis, responsible for acute renal failure in the context of Escherichia-coli urinary tract infection with septicaemia. Renal function progressively recovered with antibiotics [6].

We report here the first case of TIN with FS syndrome in BD. Extensive investigations failed to demonstrate any of the diseases responsible for both PT dysfunction and acute interstitial nephritis, such as drug-induced TIN or systemic disorders including Sjögren’s syndrome, TINU syndrome, or primary biliary cirrhosis [7,9]. That TIN represents a specific complication of BD was strongly suggested by the simultaneous development of renal manifestations with oral and ocular symptoms, and their parallel improvement with steroid and colchicine therapy.

BD is generally considered as a form of systemic vasculitis, of which the pathogenesis remains unclear. The disease may result from an aberrant immune reactivity triggered by exposure to an infectious agent, in patients with enhanced innate immune reactivity. A genetic disposition to BD is also suggested by its common association with certain HLA antigens, particularly HLA B51, as in the present case. Cellular and humoral immunity against self antigens, with subsequent increased cytokine production and endothelial activation have been shown in BD. Recent studies have suggested that TH1 polarization of the immune response is a key mechanism in the development of BD [13]. In our case, immunopathological and electron microscopic studies demonstrated predominant T cell infiltration of the renal interstitium with severe proximal tubulitis. These findings were very similar to those we previously described in a patient with primary Sjögren’s syndrome, TIN and complete PT dysfunction [7]. Similarly, both renal function and metabolic abnormalities completely recovered with steroid therapy. We hypothesized that lymphocytic infiltration of the tubular epithelium is likely to be involved in the inhibition of PT function in TIN-associated auto-immune disorders. Autoantibodies targeting distal tubular cells have been demonstrated in renal distal tubular acidosis in various systemic diseases, including Sjögren syndrome, lupus nephritis, Biermer anaemia, Basedow disease and autoimmune thyroiditis [14]. Whether humoral immunity is involved in the pathogenesis of PT dysfunction in autoimmune diseases is not established. Lino et al. [9] recently reported two patients with primary biliary cirrhosis and renal involvement characterized by TIN and FS. In one case, they showed that serum had an inhibitory effect on pyruvate deshydrogenase and α-ketoglutarate. They proposed that anti-mitochondrial antibodies could interfere with intrarenal mitochondrial machinery, leading to TIN and FS, two typical renal features of mitochondrial cytopathies [9]. In our patient, the lack of serum reactivity towards normal proximal tubules by indirect immunofluorescence did not support a role for auto antibodies in PT dysfunction in BD and reinforced the probable role of proximal tubulitis. The mechanisms by which infiltrating lymphocytes affect sodium, uric acid, glucose, phosphorus and amino-acid apical transports across the PT cells remain unknown. In summary, TIN and FS should be added to the spectrum of renal manifestations in BD. Kidney biopsy should be performed in patients with BD and renal disease for early diagnosis and appropriate therapy.

Conflict of interest statement. None declared.

References


Received for publication: 8.9.06
Accepted in revised form: 9.3.07