Behcet’s disease and IgA nephropathy: report of this association in a patient from Brazil and literature review.

Paula FCBC Fernandes¹, Geraldo B. Silveira Júnior², Fernando AS Barros¹, Daniela C. Sousa¹, Luciano M Franco² and Régia MSV Patrocínio².

¹Serviços de Nefrologia e Reumatologia do Hospital Universitário Walter Cantídio and ²Departamento de Patologia e Medicina Legal, Faculdade de Medicina, Universidade Federal do Ceará. Fortaleza, CE, Brasil. E-mail: paulafcbfernandes@yahoo.com

Key words: Behcet’s disease, IgA nephropathy, acute renal failure, glomerulonephritis.

Abstract. Behcet’s disease (BD) is associated with renal involvement in about one-third of the cases and a variety of renal lesions have been reported. A 27-year-old man presented a history of recurrent oral and genital ulcers, associated with pseudofolliculitis and arthritis in his left knee. The first laboratory tests revealed: urea = 53mg/dL, creatinine = 1.8mg/dL. The urinalysis showed leukocyturia. Initial treatment with ceftriaxone, thalidomide and prednisone was instituted. He became clinically stable, with normal renal function, but presenting hematuria and proteinuria. One year later the patient presented dark urine. The new laboratory tests showed urea = 58mg/dL, creatinine = 1.4mg/dL, and mild proteinuria (500-1000mg/24h). Two years later the proteinuria was 2230mg/day. The renal biopsy showed one glomerulus with severe glomerular sclerosis, mild tubular atrophy, mild interstitial fibrosis and thickening of arterial walls. Treatment with captopril was started to decrease proteinuria. Two years later, the patient presented creatinine = 1.7mg/dL and proteinuria = 2509mg/day. A new renal biopsy evidenced proliferative crescentic glomerulonephritis, with diffuse granulary deposits of IgA, IgM and C3. It was instituted pulsotherapy with metilprednisolone, monthly endovenous cyclophosphamide and maintenance prednisone. The patient became clinically stable, with creatinine of 1.3mg/dL and proteinuria of 500mg/day. BD could be one of the various causes of secondary IgA nephritis. It is important to periodically perform renal function evaluation in patients with BD, through urinalysis and measurement of serum creatinine and its clearance, in order to detect any abnormality and provide an early adequate treatment.
Enfermedad de Behcet y nefropatía por IgA: reporte de tal asociación en un paciente de Brasil y revisión de literatura.

Invert Clín 2006; 47(4): 405 - 411

Palabras clave: Enfermedad de Behcet, Nefropatía por IgA, Insuficiencia renal aguda, glomerulonefritis.

Resumen. La enfermedad de Behcet (EB) está asociada a daño renal en cerca de un tercio de los casos y una variedad de lesiones renales han sido descritas. Un hombre de 27 años presentaba historia de ulceraciones orales y genitales, en asociación con pseudofoliculitis y artritis en su rodilla izquierda. Los primeros exámenes evidenciaban urea = 53mg/dL, creatinina = 1,8mg/dL. El análisis de orina presentaba leucocituria. El tratamiento inicial fue ceftiraxone, talidomida y prednisona. El enfermo se quedó clínicamente estable, con función renal normal, pero presentando hematuria y proteinuria. Pasado un año, su orina resultó oscura. Nuevos exámenes mostraban urea = 58mg/dL, creatinina = 1,4mg/dL y proteinuria (500-1000mg/día). Dos años después la proteinuria aumentó para 2230mg/día. La biopsia renal mostraba un glomérulo con esclerosis severa, atrofia tubular blanda, fibrosis intersticial blanda y espesamiento de las paredes arteriales. Tratamiento con captopril fue iniciado para reducir la proteinuria. Dos años después el paciente presentaba creatinina = 1,7mg/dL y proteinuria = 2509mg/día. Una nueva biopsia renal fue realizada e identificó glomerulonefritis creciente proliferativa, con depósitos granulares de IgA, IgM y C3. Fue ministrada pulso terapia con metilprednisolone, ciclofosfamida endovenosa mensual y prednisone de manutención. El paciente se quedó estable, con creatinina de 1,3mg/dL y proteinuria de 500mg/día. La EB puede ser una de las muchas causas de nefritis secundaria por IgA. Es importante realizar periódicamente exámenes de función renal en los pacientes con EB, a través del análisis de orina y medidas de creatinina sérica y su clearance, para detectar cualquier anormalidad y providenciar un tratamiento precoz.

Received: 07-01-2006. Accepted: 11-05-2006.

INTRODUCTION

Behcet’s disease (BD) is a multisystem recurrent inflammatory disease, characterized by aphthous stomatitis, iritis and genital ulcers (1-4). BD frequently comprises lesions in skin, joints, kidneys, lungs, gastrointestinal organs and nervous system. The disease is known to be associated with renal involvement in about one-third of cases and a variety of renal lesions have been reported (1, 2).

The diagnosis is based on the International Study Group for Behcet’s Disease diagnostic criteria (major criteria: recurrent oral and genital ulcerations, eye lesions, skin lesions, positive pathergy test; minor criteria: arthritis/artralgia, deep vein thrombosis, subcutaneous thrombophlebitis, epididymitis, family history, gastrointestinal lesions, CNS symptoms and vascular lesions) (5, 6). It is believed that circulating immune complexes and deposition in glo-
merular and arteriolar tissue can cause immune mediated nephropathy in Behcet’s disease (3). IgA nephropathy associated with Behcet’s disease has been reported before and it is still not known if this association is a mere coincidence or if there is some link in the pathophysiology of these two entities (1, 2, 7).

After the patient’s informed consent we report the case of a young man with Behcet’s disease who presented acute renal failure, which was found to be due to IgA nephropathy.

CASE REPORT

In July 1998, a 27-year-old man presented purulent tonsillitis, associated to high degree fever, aqueous diarrhea, without mucus or blood, adynamia and weight loss. He also presented mouth and scrotal region’s ulcerations. He reported to have frequent previous episodes of oral ulcerations. At hospital admission he was febrile (axillary temperature = 39.3°C), dehydrated (1+/4+), with arterial blood pressure of 100 x 60 mmHg. The oropharynx presented purulent exudate in tonsils and ulcerations in jugal and lingual mucosa. The genital organs revealed the presence of three ulceral lesions, some with necrosis and elevated borders, associated with inguinal lymphadenopathy.

The laboratory tests revealed: hemoglobin = 12.3g/dL, hematocrit = 38.6%, white blood cells = 15000/mm³ (80% neutrophils, 16% lymphocytes, 3% monocytes), platelets = 410000/mm³, erythrocyte sedimentation rate (ESR) = 60mm/h, urea = 53mg/dL, creatinine = 1.8mg/dL, serum sodium = 133mEq/L, serum potassium = 4.5mEq/L, ASO = 400UI/mL, negative VDRL. The urinalysis showed 25-30 leukocytes/high power field and pyocitary blocks. The bacteriology of the genital ulceral lesion found the presence of Gram-positive agents and Gram-negative bacilli. The biopsy of the lesions showed signals of vasculitis, intense lymphohistiocytary inflammatory exudate along the vessels, with prominent endothelial cells.

Based on these findings it was raised the hypothesis of Behcet’s disease and treatment with ceftriaxone, thalidomide 200mg/day and prednisone 40mg/day was instituted for five days, with gradual decrease in the dose of prednisone for 5mg/day and thalidomide for 100mg/day. It occurred a significant improvement, with regression of the lesions and recovery of renal function.

The patient became clinically stable for seven months, after which he presented ocular hyperemia, with partial loss of the left vision. The fundoscopy showed a mild papillary edema in the left eye. The patient was also presenting episodes of ulceral lesions in the oral mucosa. It was noted the presence of pseudofoliculitis in his dorsum and arthritis in his left knee. These findings reinforced the diagnosis of Behcet’s disease. He was on treatment with thalidomide 100mg/day and prednisone 5mg/day. A new laboratory evaluation found no alteration in the total blood count, normal renal function, ESR = 52mm/h, non-reagent antinuclear antibodies (ANA), non-reagent ANCA antibodies, serum complement within normal values and urinalysis that showed hematuria (2+) and proteinuria (1+). The urine culture and bacilloscopy for Mycobacterium tuberculosis were negative.

After two years of these initial manifestations (in year 2000) the patient was still presenting recurrent oral ulcerations. He was submitted to another urinalysis that showed an increase in hematuria (3+) and proteinuria (2+). The urine culture was negative. The abdominal ultrasound and urethrocytoscopie found no abnormalities. One year later (2001) the patient presented dark urine. The new laboratory tests showed
urea = 58mg/dL, creatinine = 1.4mg/dL, hematuria (3+) and proteinuria (2+). Two months later the 24h proteinuria was 2230mg/dL. A renal biopsy was done, which showed 18 glomeruli, with mesangial hypercellularity, one glomerulus with severe sclerosis, two glomeruli with pericapsular fibrosis and the other with thin loops and a mild increase in cellularity and mesangial matrix. It was also observed tubular atrophy, interstitial fibrosis, thickening of arterial walls, with subintimal fibrosis (Fig. 1). On that occasion, immunofluorescence was not performed.

Treatment with captopril 25mg/day was instituted to decrease the proteinuria. In the subsequent follow-up it was observed a recovery in his renal function and a decrease in the 24h proteinuria to 594mg/dL. During this period the patient presented an elevation in his arterial blood pressure, and the dose of captopril was gradually increased to 100mg/day.

Two years later (2003) the patient presented serum creatinine = 1.1mg/dL, creatinine clearance = 94mL/min and 24h proteinuria = 1262mg/dL. He was on conservative treatment with captopril and thalidomide. Four months later, during one of the follow-up visits, the serum creatinine increased to 1.7mg/dL and the 24h proteinuria to 2509mg, it increased later to 3990 mg/24h. A new renal biopsy was performed, which showed crescentic proliferative glomerulonephritis (Fig. 2). The tissue had eight glomeruli, four of them with fibroepithelial crescents (50%), segmental and global sclerosis, thickness of arterial loops, increase in mesangial matrix and lymphomononuclear interstitial infiltrate. There was no vasculitis. The direct immunofluorescence showed diffuse granulillary deposits, mainly in the mesangium, with irregular extension to the capillary loops, with IgA (2+), IgM and C3 (+); IgG deposits were not observed.

Immunosuppressive treatment was instituted: intravenous pulsotherapy with methylprednisolone for three days, intravenous cyclophosphamide 1g monthly for six months and maintenance oral prednisone 120mg/day every other day (1 mg/kg per day). After 60 days the prednisone was tapered progressively (decrease of 10 mg every month until the maintenance dosis of 10 mg/day). The patient became clinically stable, with improvement of renal and non-renal manifestations. His serum creatinine decreased to 1.3mg/dL. After six months of this treatment the urinalysis showed proteinuria (+), hemoglobinuria (+) and 3 erythrocytes/high power field. The 24h proteinuria seen in the last follow-up visit was 500mg/day. The patient is currently using Mycophenolate Mofetil 2 g/day, prednisone 5mg/day, captopril 25 mg twice a day and thalidomide 100 mg/day.

**DISCUSSION**

This is probably the first report of renal involvement in a Brazilian patient with Behcet’s disease (BD), which is not common in our region. We did not find in the medical literature any reference to the occurrence of this association in Brazil. The disease is more frequent in Oriental countries, near the Mediterranean sea, but since our continent has a known mixture of races it is not surprising to find a patient with BD in our country. The present patient was born in Carábas town, Rio Grande do Norte State (Northeast Brazil), he has blue eyes and blond hair. Mother, father, two sisters and grandparents are white. They are also from Brazil.

Renal involvement in BD was believed to be very rare in the past, but since some reports from the end of the last century showing renal lesions in patients with this syndrome have been published it seems to be a relatively frequent complication of BD.
Behcet’s disease and IgA nephropathy

Fig 1. First Renal Biopsy (Mesangial Glomerulonephritis). A - Section of kidney showing mesangial hypercellularity and epithelial crescents. H&E, 200x. B - Section of kidney showing mild increase in cellularity and mesangial matrix. H&E, 400x. C - Section of kidney showing thickness of arterial walls, with subintimal fibrosis, and glomerular sclerosis. Masson staining, 200x.

Fig 2. Second Renal Biopsy (Crescentic Proliferative Glomerulonephritis). A - Section of kidney showing fibroepithelial crescents. H&E, 400x. B - Section of kidney showing mild increase in cellularity and mesangial matrix. H&E, 400x. C - Immunofluorescence showing IgA deposits in kidney.
The spectrum of renal involvement in BD ranges from mild urinary abnormalities to glomerulonephritis with persistent renal failure (2). Different renal lesions have been reported in patients with BD, including focal glomerulonephritis, diffuse proliferative glomerulonephritis, membranous nephropathy, glomerulonephritis and renal amyloidosis (1). Amyloidosis seems to be the most common type of renal lesion in BD (8). The present cases illustrates a case of a patient with BD in which renal involvement was observed. His serum creatinine was increased when BD diagnosis was made (1.8mg/dL). Before the initiation of renal disease the patient was suffering from recurrent oral ulcers, a known manifestation of incomplete forms of BD that frequently precedes full-blown cases. Seven months after the diagnosis he presented hematuria and proteinuria, but he spent some years with normal renal function after the diagnosis of BD. The diagnosis of IgA nephropathy, however, was achieved only some years later, when an analysis of renal tissue through immunofluorescence was performed.

El Ramahi et al. (3) described nine cases of renal involvement in BD. These patients represented 7.5% of 120 patients studied with BD. Eight of these patients presented proteinuria and one presented hematuria. Renal biopsy was performed in 4 cases, in which it was found glomerulopathy with mild to moderate mesangial proliferation. IgA deposits were not seen in these cases.

Akutsu et al. (1) reported the case of a young girl with BD who presented hematuria and proteinuria. The renal biopsy was compatible with IgA nephritis. Differently from our case her renal function was normal. Hemmen et al. (2) described a case of mesangioapillary glomerulonephritis, with IgA deposits, in a patient with BD who presented proteinuria of unknown origin. Proteinuria and hematuria are the most frequent manifestations of IgA nephropathy associated with BD (1, 2, 7, 9-11). The occurrence of urinary abnormalities in BD varies from 7.5% to 32%. In the present case the patient developed crescentic proliferative IgA nephropathy, with an important loss of renal function. Renal failure in BD is not common, with some reported patients presenting high levels of serum creatinine (10, 11).

BD is a systemic vasculitis associated to an inflammatory process in mucosal sites, that can cause elevation of serum IgA. A defect in the mucosal barrier in BD could lead to enhanced antigen exposure of the focal IgA producing cells, which could result in increased production of IgA, that could be an stimuli to the development of nephritis (1).

The treatment of our patient was done with immunosuppressive agents, with successful recovery of renal function and reduction of proteinuria to non-nephrotic range (500 mg/day). In patients with BD and renal involvement the treatment depends on the severity of the disease and in the findings of the renal biopsy. These is a general agreement that immunosuppressive agents must be used, with steroids alone or in combination with cyclophosphamide (9, 12, 13). Recently, have been reported some cases of renal transplantation in patients with BD (12, 14).

The development of primary IgA nephropathy in a patient of BD cannot be ruled out, including our case. IgA nephritis is one of the most common types of glomerulonephritis all over the world and can incidentally occur in patients with BD (15). In Brazil, IgA nephropathy is found in approximately 10% of kidney biopsies and this frequency can be higher (up to 29%) among patients with hematuria and proteinuria without nephritic syndrome (16). However BD could be one of the vari-
ous causes of secondary IgA nephritis. It is important to perform renal function evaluation periodically in patients with BD, through urinalysis and measurement of serum creatinine and its clearance, in order to detect any abnormality and provide an early adequate treatment in order to prevent the progression to end-stage renal disease.

ACKNOWLEDGMENTS

We thank Professor Luiz A. R. Moura, from the Department of Pathology and Citopathology of the Universidade Federal de São Paulo – Escola Paulista de Medicina for providing the renal biopsies to our patient, and physicians, nurses and residents from the Hospital Universitário Walter Cantídio, Universidade Federal do Ceará for the assistance provided to the patient.

REFERENCES


