Renal involvement in Adamantiades-Behcet's disease. Case report and review of the literature

V.G. Kaklamani,
N. Nikolopoulou,
F. Sotsiou, A. Billis,
P. Kaklamanis

McGaw Medical Center, Northwestern University, Chicago, USA; Evangelismos Hospital and Athens Medical Center, Athens, Greece.

Please address orrespondence and reprint requests to: Phaedon Kaklamanis, MD, 61 Ipsilantou Street, 115 21 Athens, Greece. E-mail: virginia @hol.gr

Received on January 8, 2001; accepted in revised form on April 6, 2001.

Key words: Behçet's disease, kidney involvement.

ABSTRACT

A patient with Adamantiades-Behçet's disease with renal involvement is reported. This patient fulfilled the International Study Group criteria for the disease. Kidney biopsy was performed and proliferative glomerulonephritis with deposition of IgA and IgM immunoglobulins were demonstrated.

Review of the literature demonstrates that renal involvement in this disease is not so rare as it was believed. Crescent formation and IgA nephropathy are infrequently observed. Treatment of renal involvement may require immunosuppressive drugs.

Introduction

Adamantiades-Behçet's disease (ABD) is a chronic multisystem vasculitis (1). The etiopathogenesis of the disease remains to be elucidated. The international Study Group for BD published the classification criteria for the disease, (2) which are widely used as diagnostic criteria for clinical studies. However, some investigators apply their own diagnostic criteria (3).

We present here a case of ABD-associated glomerulonephritis and we review the literature on renal involvement.

Case report

A 31 year-old male at the age of 19 (February, 1988) developed recurrent oral aphthous ulcers. Two years later he had recurrent genital ulcers and pseudofolliculitis, which lasted for 2 weeks. Laboratory investigation gave normal or negative results. In April 1995 anterior uveitis was found and the diagnosis of ABD was made. Laboratory investigations showed normal ESR, haemoglobin and white blood cell count. However, for the first time proteinuria (600 mg/24 hours) and microscopic heamaturia with red cell casts were found and therefore renal involvement was documented. Renal function studies were normal.

The patient was admitted to Evangelismos hospital and the 3rd of May 1995 kidney biopsy was performed. On light microscope a moderate degree of proliferative glomerulonephritis with a mild increase in the amount of mesangial matrix and in the number of mesangial and endothelial cells were found (Fig. 1a, b). Focal interstitial infiltration by lymphocytes and plasma cells was also demonstrated, as well as inflammatory cells. On immunofluorescence granular deposits of IgA and IgM in the mesangium and scattered C3 in the capillaries were found (Fig. 2). Laboratory investigations were repeated: ESR, C-RP, liver function studies, autoantibodies and biochemical studies were normal or negative. Haematological examinations: haemoglobin, haematocrit, white blood cells and platelets were also normal. He carried HLA A2, Ax, B7, Bx, Cw7, DR5(11), B(12), DRB*1 alleles 1104/1201. Pathergy test was negative.

Treatment with 60 mg of prednisolone with 750 mg of cyclophospshamide followed by 50-100 mg *per os* daily for four years was given. In December 1995 his previous symptoms were recorded in a prestructured questionnaire and the patient was follow up every four to five months. The dose of prednisolone was tapered on to 7.5 mg of prednisolone every other day. Oral aphthous ulcers recurred frequently and genital ulcers developed 6 times. In 1995 another eye attack developed which lasted for 2-3 days. However, eye examination including fluorangiography did not show any abnormalities. In December 1998 he stopped the treatment for a few weeks and recurrence of oral aphthae and genital ulcers were observed.

Telephone contact with the patient in December 2000 established that he is free of any symptoms and the results of the laboratory investigations, including renal function, were either normal or negative except for a few red cells in the urine without proteinuria. He is still taking 7.5 mg of prednisolone every other day.

Review of the literature

Renal involvement in ABD was reported for the first time in 1963 (4) . Twelve years later it was claimed that ABD does not affect the kidney (5). In recent reviews of the subject as well as in classical rheumatology text books renal involvement in this disease is reported to

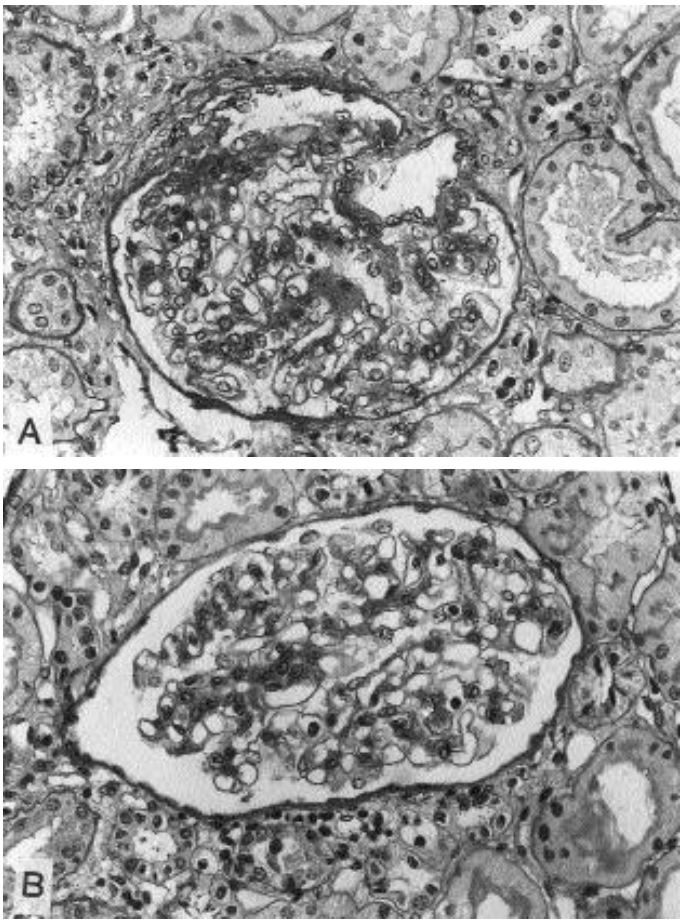

Fig. 1. A. Mild mesangial and endothelial hyperplasiawith small segmental adhesion to Bowman's capsule; **B.** Some glomerular infiltration by monocytes. Also obvious is the periglomerular interstitial monocytic inflammation. (Paraffin sections, A & B: P.A.S., x 100).

be infrequent (6). Nevertheless, from recent kidney biopsies or *postmortem* studies renal involvement in ABD has been documented and it is not so rare. The mild nature and the not very frequent involvement of the kidneys and also the lack of awareness of this process constitute the reasons for the relative lack of interest in this complication in ABD. Renal involvement in ABD was considered and case reports have been published (3, 7-12). The exact prevalence of renal involvement in ABD has not yet been clearly reported, although in some clinical studies it ranges from 0 to 10% (13). In our material of 115 patients proteinuria and / or haematuria was found in three and renal biopsy was performed only in the reported case.

Amyloidosis in ABD was first reported in 1964 (14) followed by other cases (15). Although amyloidosis in this disease is rare it has a poor outcome (16). In this review, however, we report on non amyloid renal involvement in ABD.

Urinary and other laboratory and clinical findings

In 1963 Oshima *et al*. (4) reported that in 13 out of 65 patients traces of proteinuria or microhaematuria were found. However, the histological examination of renal tissue in 4 of them did not show any abnormalities. Since that time, urinary findings (haematuria and various amounts of proteins in the urine) have been reported. Our patient presented with haematuria and proteinuria 7 years after the initial symptoms of the disease. The mild nature of renal involvement and the late appearance of this are interesting points. In the literature severe proteinuria has only been seen in few patients (12, 17-19) and nephrotic syndrome has been reported (7, 10, 11, 20, 21). Acute focal necrotizing glomerulonephritis was also observed (9). In some cases, the renal involvement was considered severe and end-stage renal failure developed (10). In 1977 a patient with significant microhaematuria, but without proteinuria was reported (22). A year later, proteinuria, haematuria or both were found in 25 out of a group of 77 patients (23). Two years later, another patient with haematuria and proteinuria was described (24). In a series of 316 patients only 4 developed proteinuria or nephrotic syndrome (25).

ANCA positivity in patients with ABD was reported (26, 27). In one case ABD was suspected, but Wegener's granulomatosis was the final diagnosis (7). Schonlein-Henoch purpura was also reported in a patient with ABD (28).

Histological findings

1. Light microscope findings

Biopsy specimens of the kidney in four cases of ABD revealed no pathological changes (4). In a *postmortem* examination florid fibrinoid necrosis of the glomeruli was demonstrated. However, in more recent studies microscopic findings of the kidney were reported. Acute glomerulonephritis, diffuse proliferation of mesangial cells, diffuse proliferative glomerulonephritis (3, 12, 19, 29-32) and focal glomerulonephritis have been described (17, 33). The biopsy of the kidney in our patient showed moderate degree of proliferative glomerulonephritis with focal interstitial infiltration of lymphocytes and plasma cells. Membranous nephropathy has also been reported (34). Diffuse mesangial expansion (35) and minimal change glomerulonephritis (21) have been demonstrated. Crescentic glomerulonephritis has been described in several cases and involvement up to 80% of the glomeruli have been reported (7, 10, 11, 32, 36).

Crescentic formations may be focal or diffuse, active or non active and their prognostic role in ABD is not recognized. This severe reaction of the kidney may be explained by the lytic damage of the capillary loops *i.e.* necrosis, lysis and rupture of the capillary basement membrane with leakage of plasma, red blood cells and fibrin-fibrinogen into the capsular space (37).

In a patient with ABD the renal cortex was diffusely infiltrated by some neutrophils, lymphocytes and many macrophages containing PAS-positive material in their expanded cytoplasm (38). Therefore, the kidney biopsy is indicat-

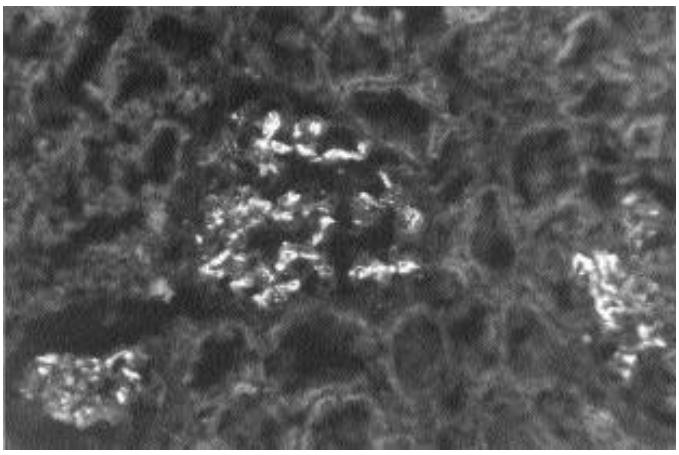

Fig. 2. Mesangial granular deposits of IgA (Cryostat section, direct immunofluorescence, x 80).

ed in patients with ABD when proteinuria of haematuria is documented.

2. Immunofluorescence studies

Deposits of IgG, IgA and IgM immunoglobulins and C3, C4 complement components in the kidney of patients with ABD have been reported (10, 18, 20, 30, 31, 33, 36) as well as fibrinogen (32, 36). In our patient granular deposits of IgA and IgM and diffuse capillary depositions of C3 were demonstrated. Particularly the IgA immunoglobulin deposition in the kidney of our patient is of interest because of its possible pathogenetic significance. Immune complex deposition in the glomeruli has been reported by several investigators (3, 29, 33, 40, 41) . Deposition of IgA is of particular interest. However, the criteria for IgA nephropathy include immunoglolulins staining for IgA as a prominent immunoglobulin, early classical pathway complement components (C1q, C4) and minor relative to C3 and electron dense deposits intrastructurally (42). Therefore, according to this definition only a few patients with ABD have real IgA nephropathy (32, 43). It is possible that IgA nephropathy in ABD may be coincidental simply by chance alone, since it is the most common glomerulonephritis occurring among young males (43). However, the deposition of IgA immunoglobulin in the kidney is not frequent (3,43). The demonstration of the IgA nephropathy in the renal biopsies may signify the entrance of an antigen through the diseased mucosae with consequent IgA production, formation of antigen-antibody complexes which are consecutively deposited at the renal basal membrane (43). However this hypothesis has remained unproven so far (43).

3. Election microscopic studies

Ultrastructural findings from renal biopsies in ABD patients are not specific and have been found in many other immune complex-mediated glomerulonephritides. Electron dense deposits in various parts of the kidney (mesangium, subepithelium, subendothelium) have been reported (10, 20, 35, 36). In a recent paper many phagolysosomes in the cytoplasm of macrophages were demonstrated (38). Although in some vasculitides ANCA has a pathogenetic significance, in ABD its role has not been determined. However the possibility of immune complex-mediated and ANCA-associated vasculites in the pathogenesis of ABD cannot been excluded (26).

In short, renal involvement in ABD includes (43): Glomerulonephritis (diffuse crescentic, focal and segmental necrotizing), renal vein thrombosis and amyloidosis. The symptomatology of renal involvement consists of proteinuria 20-55%, haematuria 20-31% and occasionally elevated creatinine (43).

Management

The treatment of patients with renal involvement in ABD depends on the severity of the disease in general and in particular the renal findings including the biopsy results. In patients with crescentic or focal sclerosing glomerulonephritis, particularly if renal function is deteriorated, immunosuppressive therapy with steroids alone or in combination with cyclophosphamide has to beconsidered(43).However other combinations may be used (45). In severe renal involvement the effectiveness of this regimen remains to be established (27). When the patient develops end-stage renal failure maintenance haemodialysis is indicated. Recently the first successful renal transplantation in a patient with BD who had end- stage renal failure secondary to glomerulonephritis was reported (30).

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