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CASE BASED REVIEWS

Renal involvement in Behcet's Disease: a rare clinical challenge

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ABSTRACT

Although Behçet´s disease (BD) is a systemic inflammatory disease, renal involvement is uncommon and ranges from mild asymptomatic urinary abnormalities to severe disease with progressive renal failure.

We describe the case of a 30 years-old woman with multiorgan BD, under ustekinumab, who presented with proteinuria, hematuria and impaired renal function. Kidney biopsy revealed histological findings of active renal vasculitis in the context of IgA nephropathy and tubulointerstitial nephritis and the patient was treated with corticosteroids and cyclophosphamide with excellent response.

Our case highlights the importance of recognizing a possible renal involvement in BD patients, reinforcing the need for monitoring renal function and urinalysis in these patients.

Keywords: Behçet's disease; Renal involvement; IgA nephropathy.

INTRODUCTION

Behçet´s disease (BD) is a rare systemic inflammatory disease typically characterized by recurrent oral and genital ulcers and uveitis[1]. Is it more frequent along the "silk road", with a higher incidence in males in the third decade of life[2]. The involvement of major organs – the nervous, gastrointestinal, cardiac and pulmonary systems - is less frequent, leads to significant morbidity and mortality, and represents a more challenging diagnostic and therapeutic approach[3]. There are conflicting reports in the literature about the renal involvement in BD[4].

CASE REPORT

We report the case of a 30 years-old female patient with BD diagnosed 12 years earlier, with mucocutaneous (recurrent oral ulcers, positive pathergy test), neurologic (optic neuritis and white matter lesions) and gastrointestinal (proctocolitis) involvement. The gastrointestinal disease was corticodependent and refractory to multiple therapies (azathioprine, methotrexate, infliximab, vedolizumab and adalimumab). Initial colonoscopy showed diffusely inflamed mucosa with a large amount of edema and erythema and histology was negative for cytomegalovirus and showed a non-specific inflammation. Gastrointestinal involvement required a segmental colectomy (sigmoid colon and distal descending colon) at ten years of illness. After surgery, due to persistently active gastrointestinal disease, the patient started off-label therapy with ustekinumab (subcutaneous, 90mg every 8 weeks) and prednisolone (oral, 7.5 mg daily).

Three months later, she reported macroscopic hematuria, with no other genitourinary symptoms. Renal/pelvic ultrasound and abdominopelvic computed tomography angiography revealed no abnormalities and the urine cytology ruled out high-grade urothelial carcinoma. The initial blood tests revealed leukocytosis (16.42x10^9/L) and neutrophilia (12.74x10^9/L), high levels of c-reactive protein (84.3 mg/L [normal<3.0]), increased erythrocyte sedimentation rate (67mm/h) and a first-time raised in serum creatinine (1.58mg/dL, normal<0.95), with an estimated glomerular filtration rate (EGFR) of 49mL/min. Proteinuria (0.28g/24h) and erythrocyturia (52.1/uL) were noticed in the urine sediment.

Two weeks later, she already reported asthenia. The analytical study confirmed the abnormal renal function (creatinine 1.5 mg/dL; EGFR: 50 mL/min) and the urine sediment, although maintaining the same level of proteinuria and erythrocyturia, revealed a new finding of dysmorphic erythrocytes. No immunological abnormalities were found in the blood tests, as would be expected in BD, and it was decided to perform a renal biopsy.

Histological analysis revealed a mesangioproliferative glomerulonephritis with focal endocapillary prolif-

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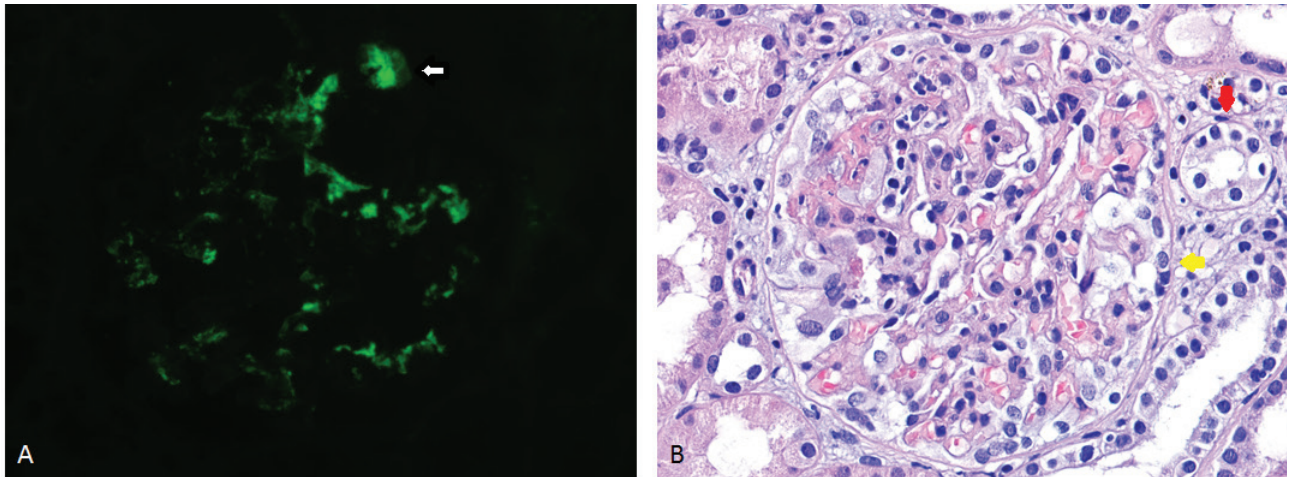

Figure 1. (A) Granular mesangial immune deposits (white arrow) [IgA, 200x]. (B) Glomerular mesangial (yellow arrow) and endocapillary (red arrow) hypercellularity and fibrinoid necrosis [HE, 400x]. The kidney biopsy with 27 glomeruli in light microscopy revealed a mesangioproliferative glomerulonephritis with focal endocapillary proliferation. There was two fibrocellular crescents and one cellular crescent with fibrinoid necrosis. In the interstitium there was moderate lymphocytic inflammatory infiltrate with coexisting lesions of tubulointerstitial nephritis. Tubular atrophy and interstitial fibrosis was unremarkable. In direct immunofluorescence study granular deposition of IgA and C3c immune complexes was observed.

eration with two fibrocellular crescents and one cellular crescent with fibrinoid necrosis, moderate lymphocytic inflammatory infiltrate and lesions of tubulointerstitial nephritis, findings compatible with an active renal vasculitis in the context of an IgA nephropathy and tubulointerstitial nephritis (Figure 1). IgA associated conditions - as HIV infection, liver disease and celiac disease - were excluded.

In view of these findings and the impaired renal function - suggesting an initial phase of severe renal involvement - it was decided to initiate intravenous corticosteroids (3 daily pulses of methylprednisolone 1g) and cyclophosphamide (CYC). The patient started monthly intravenous CYC associated with progressive tapering of oral prednisolone (starting with 1mg/kg/day). Additionally, enalapril 5mg was prescribed and blood pressure was monitored. At 5 months of CYC, due to diarrhea, a colonoscopy was performed and revealed chronic colitis with signs of activity. The biopsy was positive for cytomegalovirus and she was treated with valacyclovir.

She fulfilled 6 months of CYC with an excellent response: creatinine decreased to 0.83 mg/dL (EGFR: 91 mL/min) and no more hematuria or proteinuria was found. Then, azathioprine was started in increasing doses and up to 150mg daily. One year later, the patient maintains normal renal function and urine sediment.

DISCUSSION

Renal involvement in BD is less frequent and mostly less severe in comparison with other vasculitis. In BD urinary abnormalities such as proteinuria and hematuria (mostly asymptomatic) can be observed in around 10% of patients[5]. There is a large spectrum of renal involvement in BD ranging from glomerulonephritis, arterial aneurysms and interstitial nephritis[6,7]. Amyloidosis may be one of the most common type of renal involvement leading to renal failure in BD[8].

Renal macro or microvascular – occlusions/stenosis - involvement is another rare but possible renal involvement in patients with BD that carries a higher mortality[9]. However, renal vasculitis, with evidence of fibrinoid necrosis is even more exceptionally described in the literature[10].

As in our case, IgA nephropathy is one of the glomerular diseases reported in patients with BD[11,12]; presentation may vary between proteinuria[13,14], hematuria and proteinuria[15] and even crescentic proliferative nephropathy with progressive loss of renal function[16]. Also of note, IgA nephropathy is the most commonly diagnosed glomerulonephritis worldwide[17,18] and that is why it is not possible to exclude the possibility thar it´s coexistence with BD could happen by chance. More knowledge about the pathophysiology of both conditions would help to clarify if they could represent a common entity.

Besides, it should be kept in mind the possible association of IgA nephropathy with some drugs: there are some reports in the literature of IgA nephropathy - mostly with mild disease - associated with TNF inhibitors (adalimumab[19], infliximab[20] and golimumab[21])

and also with ustekinumab[22].

Other important aspect is the mimicry between gastrointestinal involvement in BD and inflammatory bowel disease (IBD). Our patient had a severe and refractory gastrointestinal disease and the colonoscopy showed diffusely inflamed mucosa with a large amount of edema and erythema. Histology showed a non-specific inflammation with cryptic micro-abscesses, which may be explained by the severe and possibly longstanding gastrointestinal disease. Moreover, the fact that the patient was already under corticosteroids and immunosuppressant drugs by the time of the colonoscopy could have change the endoscopic appearance and preclude a precise attribution of the gastrointestinal disease. Thus, despite the lack of histologic definitive proofs of gastrointestinal BD, gastrointestinal findings were supported by other organ manifestations and allowed the diagnosis of BD. The difficult differential diagnosis between IBD and gastrointestinal BD and the association described in the literature between IBD and IgA nephropathy[23] imposes that we cannot fully exclude that the renal disease in this patient could have been related to a possible IBD diagnosis. However, the association between BD and IBD is rare, which makes that an unlikely hypothesis.

The uniqueness and the importance of our case relies on the extreme and refractory multiorgan involvement of BD, the rare and severe renal disease and the excellent but not early response to aggressive imunossupressive therapy. Two aspects favour a major role for CYC in the clinical response: the patient was already under corticosteroids before renal flare and the renal function only improved months after this treatment regimen and not soon after the initial methylprednisolone pulses.

This case, in line with other cases described in the literature, highlights the importance of routine assessment of renal function and urinalysis in order to detect early abnormalities, providing the best treatment to prevent the possible progression to end-stage renal disease. The best management of renal involvement in BD is not yet known, but it may well be the one that is tailored to the specific type of kidney disease.

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