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□ Case Report □

A Case of Behcet's Disease Complicated by IgA Nephropathy

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Behcet's disease (BD) is a rare, multisystemic disorder characterized by vasculitis. Although renal involvement rarely coexists with BD, several types of renal involvements have been reported: amyloidosis, glomerulonephritis and vascular involvement. Herein, we report a rare case of BD complicated with IgA nephropathy (IgAN). A 42-year-old woman visited the hospital due to joint pains and painful subcutaneous nodules. Based on her medical history of recurrent orogenital ulcers, arthritis, enteral ulcers, erythema nodosum-like skin lesions, and a positive pathergy test, we diagnosed her with BD. To evaluate proteinuria, we performed a renal biopsy. The patient was diagnosed with BD complicated with IgAN, and treated with a low dosage of steroid, colchicine, as well as angiotensin II type I receptor blockers. Although renal involvement in BD is rare, it is important to periodically perform renal function assessments in patients with BD involving abnormal urine results.

Key Words. **Behcet's disease, Proteinuria, IgA nephropathy**

Introduction

BD is a rare, multisystemic disorder characterized by ocular, mucocutaneous, articular, gastrointestinal, neurological and vascular abnormalities (1). The primary pathologic changes in BD are vasculitis-related; renal involvement in BD is less frequent and often less severe than in other types of vasculitis (2). The frequency of renal problems among BD patients has been reported to vary between 0% and 55% (3). Several types of renal involvement in BD have been reported. Amyloidosis (AA type), glomerulonephritis (GN), and vascular involvement are the main causes of renal BD. The clinical spectrum of renal BD varies from asymptomatic hematuria and/or proteinuria to end-stage renal disease (ESRD) (4). The two kinds of IgAN associated with BD cases have been reported in Korea. Reported cases were represented nephrotic range proteinuria, and other report recommended all patients with BD perform the urine test, especially 1g more than one day, renal biopsy is proposed (5). We report here a case of BD complicated with IgAN showing less than nephrotic range proteinuria diagnosed by biopsy and perform a review of the relevant medical literatures.

Case Report

A 42-year-old woman presented with joint pain and painful subcutaneous nodules. Five months prior, she reported developing pain and swelling over the left elbow and both ankles insidiously. Simultaneously, multiple tender nodules appeared on both her forearms and legs. She had a history of recurrent oral and genital ulcers over the past few years. She was also diagnosed with proteinuria of unknown origin in a prior periodic health examination, but did not undergo further evaluations. She had no specific familial history. She had taken a low dose steroid prescribed to her by her local clinic for the prior 3 months but at the time of her examination, was no longer taking this steroid. There was no history of alcohol or smoking or evidence of infection, such as a chilling sensation, diarrhea, cough, or sputum. On physical examination, her vital signs were stable. There were multiple apthous ulcers ranging

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in size from 5 mm to 8 mm on her lower lip and soft palate. Swelling and tenderness of lt. ankle and lt. wrist were observed. There was no pretibial pitting edema. Laboratory studies revealed the following: WBC 9,600/mm^3 (neutrophils 63.3%, lymphocytes 29.6%), hemoglobin 13.7 g/dL, hematocrit 41%, ESR 44 mm/hr, CRP 0.34 mg/dL, fasting blood glucose 80 mg/dL, BUN/Cr 14/1.0 mg/dL, AST/ALT 17/12 IU/L, and a positive pathergy test. In a radiologic study of her hands, no evidence of articular erosion was found. Urinalysis revealed an urine RBC 1.6/HPF, albumin+, protein: creatinine ratio of 825, with a creatinine clearance rate of 99.3 mL/min. Analysis of a 24 hr urine sample revealed a daily urinary protein excretion rate of 718 mg/day. Serological tests for rheumatoid factor, antinuclear and antineutrophil cytoplasmic antibodies, complement, syphilis, gonorrhea, hepatitis B, and HIV were negative. The patient underwent upper and lower gastrointestinal endoscopy for general health check-up. Exudate was noted on the ileocecal valve area. The microscopic findings of the endoscopic biopsy showed chronic nonspecific inflammation with necrotic inflammatory exudate.

Based on the patient's history of recurrent orogenital ulcers, arthritis, enteral ulcers, erythema nodosum-like skin lesions, and a positive pathergy test, we diagnosed the patient with BD.

The patient's proteinuria made us suspect renal involvement, and we therefore performed a renal biopsy. On one section of the biopsied kidney, 3 out of 20 glomeruli were globally sclerotic. Each glomerulus was mildly increased in size and focally increased in mesangial cellularity (Figure 1). The mesangial region showed mild focal segmental expansion due to mesangial hypercellularity. Capillary lumens were focally segmentally collapsed with Bowman's adhesion, resulting in sclerosis in glomeruli. There were mild tubulointerstitial changes with intraluminal red blood cell casts (Figure 2). A direct immunofluorescence study revealed strong mesangial staining of IgA, and C3 was seen with focal segmental involvement of the peripheral capillary loops (Figure 3). Ultrastructural examination demonstrated moderate mesangial expansion with multiple mesangial electron-dense deposits and focal subendothelial interposition (Figure 4). All these findings were consistent with IgA nephropathy, Haas subclass III and the M0S1E0T0 Oxford classification (6,7).

The patient was diagnosed BD accompanied by IgA nephropathy. She was treated with a prednisolone at 5 mg/day,

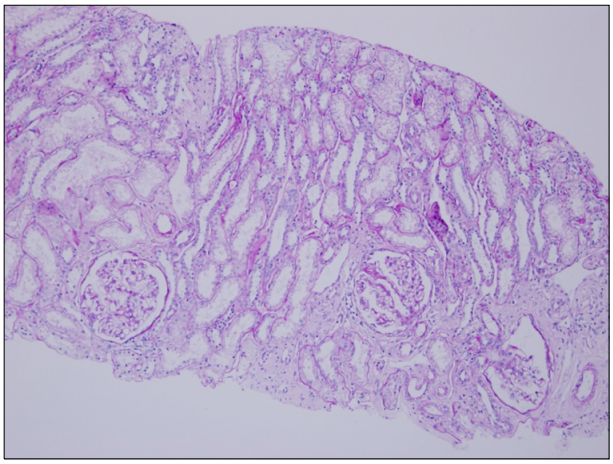

Figure 1. Each glomerulus was mildly increased in size and focally increased in mesangial cellularity (PAS, ×100).

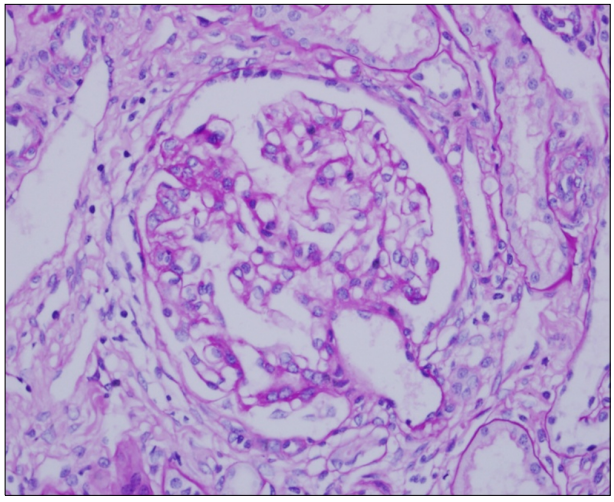

Figure 2. Light microscopic finding of renal biopsy. A focus of segmental mesangial expansion by mild mesangial hypercellularity is seen with Bowman's adhesion (PAS, ×400).

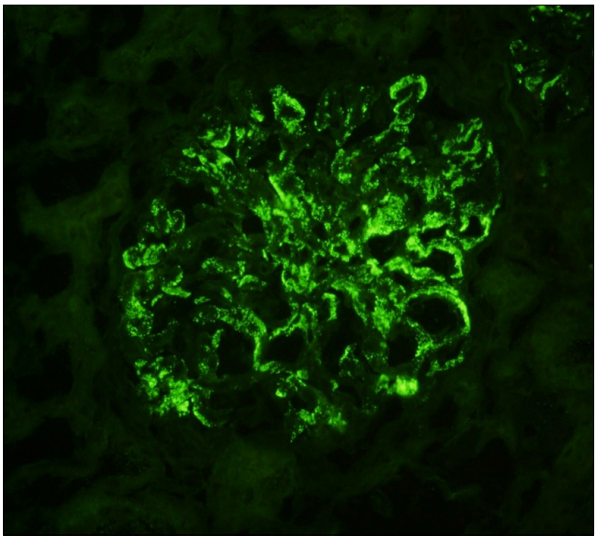

Figure 3. Immunofluorescent finding. Strong positive staining of IgA is noted in the mesangium and focal peripheral capillary loops (DIF for IgA, ×400).

colchicine at 0.6 mg/day, angiotensin II type I receptor blockers, and was told to limit the amounts of protein and sodium in her diet. At the 3 year follow-up, the patient's protein: creatinine ratio had decreased to 102.

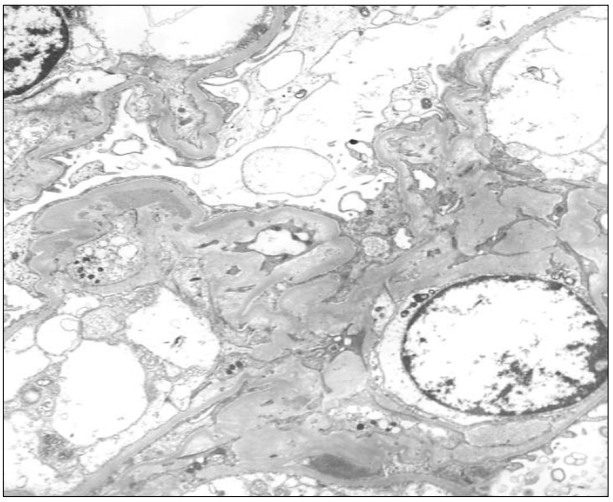

Figure 4. Ultrastructural finding. Multiple mesangial electron dense deposits are presentedin the mesangial region with subendothelial mesangial interposition (original magnification, ×2,500).

Discussion

BD is a chronic, relapsing, multisystemic, autoinflammatory condition characterized by vasculitis involving both arteries and veins of any size. This disease can be recognized by the triad of recurrent ulcers of the oral and genital mucosa and relapsing uveitis (5). Renal complications are not commonly associated with BD, and few studies have evaluated the histopathologic findings of renal problems in BD. The renal problems that have been associated with BD can be divided into five groups: 1) GN, 2) amyloidosis, 3) renal vascular involvement, 4) interstitial nephritis (IN), and 5) other problems, such as complications due to drug therapy or genitourinary system abnormalities (3). Analysis of published papers, including this paper, revealed that 254 patients with BD and a specific renal disease have been described (amyloidosis 108, GN 89, renal vascular disease 55, and IN 5) (3,4). A list of patients diagnosed with BD accompanied by IgAN is provided in Table 1. The co-occurrence of IgAN with BD has only been reported a few times to date (8). IgAN is classified with primary and secondary associated with systemic disease. The presence of mesangial IgA deposits is also associated with many other diseases. The IgA deposits are often incidentical findings with unclear pathogenesis or clinical significance. The many secondary conditions are dis-

Table 1. Reported cases of IgA nephropathy associated with Behcet's disease

Silent glomerular disease	Treatment	Outcome/Remarks
Diffuse proliferative GN (IgA) (13)	None	Proteinuria and hematuria persisted
Diffuse proliferative GN (IgA) (14)	Colchicine 0.5 mg/d orally Dipyridamole 2～4 mg/kg/d Cyclosporine 5 to 2.5 mg/kg/d orally (for ocular problems)	Improvement
Diffuse proliferative GN (IgA) (3)	None Prednisolone 7.5～60 mg/d orally (after elevation of serum creatinine)	Serum creatinine increased 4 years later Serum creatinine levels stabilized
Diffuse proliferative GN (IgA) (3)	Cepharanthin 20 mg/d orally	No change
Diffuse proliferative GN (IgA) (3)	Methylprednisolone 24 mg/d	Improvement
Focal proliferative GN (IgA) (present)	Prednisolone 5 mg/d Colchicine 1.2 mg/d, Losartan 50 mg/d	Improvement after 3 years
Focal proliferative GN (IgA) (3)	Prednisolone 10～60 mg orally every other day	Improvement
Nephrotic syndrome		
Diffuse proliferative GN (IgA) (3)	Prednisolone 10～30 mg/d Azathioprine 50 mg/d	Improvement
Diffuse proliferative GN (IgA) (2)	Candesartan 4 mg/d, Atorvastatin 10 mg/d	Improvement
Acute GN/Rapidly progressive GN		
Focal segmental necrotizing GN (IgA) (15)	None	Disappearance of proteinuria at 2 months, but hematuria persisted Patient also had Henoch-Schönlein purpura

tinguished from primary IgAN by their distinctive clinical expressions. Because IgAN is a prevalent disease, it may be found in association with other glomerular diseases. A recent report, BD is also considered the secondary cause of IgAN, but the function of increased circulating IgA and IgA immune complexes have not been identified. And BD patients without kidney disease, increased serum IgA and secretary IgA have been reported (9). Therefore possible that expressed simply as two diseases cannot be ruled out. The clinical course of IgAN with BD varied from silent to acute. The clinical course of the disease was generally mild when patients were treated with low dose steroids and/or immunosuppressants, and all reported cases showed improvement. Although the etiology of renal involvement in BD is unknown, vasculitis and vessel wall inflammation may be important contributing factors; regulation of the activity of vasculitis could therefore be helpful. Vasculitis can lead to the enhancement of platelet aggregation and the impairment of fibrinolysis, resulting in thrombosis (10). Immune complexes, IgA deposition, and ANCA have also been implicated in the pathogenesis of GN (3), but the etiology remains elusive.

Angiotensin II type I receptor blockers and angiotensin converting enzyme inhibitors are effective at slowing the progression of IgAN. The ability of other therapeutic options such as steroids, cytotoxic drugs, tonsillectomy, anti-platelet drugs, fish oil, and vitamin E to modulate the rate of progression has been evaluated (11). The routine prescription of colchicine to all BD patients to prevent amyloidosis requires further investigation. Corticosteroids, colchicine, azathioprine, and cyclophosphamide have been used in the management of GN in BD. However, the beneficial effects of such treatments on the course of glomerular disease are unclear (3). Because the treatment for each type of renal involvement differs, ranging from conservative treatment to immuosuppressants, it is necessary to perform regular renal function assessments and consider performing a renal biopsy in patients with BD even if the urine analysis results are only mildly abnormal. In general, we treat a BD patient with renal involvement in a similar manner to a non-BD patient that has the same renal manifestations. Routine urine analysis and measurement of serum creatinine levels are needed for the early diagnosis of renal BD. Renal BD has some special, but nonspecific, features. In most cases of BD complicated with IgAN due to GN, the disease status is active. There seems to be a positive relationship between the activity of BD and IgAN. Furthermore, two recent studies reported that BD could be one potential cause of secondary IgAN (5,12). The cause of the mild nature of renal disease, the rarity of GN in BD, and factors predisposing to progressive and overt glomerular disease require further investigation.

Summary

Although renal BD is very rare, if present, it may potentially progress and ultimately result in ESRD. It is therefore important to periodically perform renal function assessment to enable BD patients with renal involvement to be treated appropriately.

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