Clin J Gastroenterol (2009) 2:380–383
DOI 10.1007/s12328-009-0112-x

CASE REPORT

Infliximab treatment for Crohn's disease in a patient with IgA nephropathy

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Received: 8 June 2009 / Accepted: 18 August 2009 / Published online: 3 October 2009

Abstract We describe herein a case of IgA nephropathy in a 34-year-old woman with Crohn's disease (CD) treated with infliximab. CD first appeared at the age of 15 years. An elemental diet was started for remission maintenance. Ten years later, the patient suffered from a recto-vaginal fistula and subtotal colectomy with stoma formation was performed. At the age of 33 years, the patient was investigated for painless macroscopic hematuria and proteinuria. Renal biopsy revealed IgA nephropathy. Mizoribine was started but proteinuria persisted. Due to diarrhea she was admitted to our hospital, and scheduled maintenance therapy with infliximab was initiated. After the first infliximab infusion, the patient presented significant clinical improvement in both diarrhea and proteinuria with concomitant decrease of C-reactive protein to normal levels and proteinuria $\sim$1 g/day. This represents the first report of infliximab treatment in a patient with IgA nephropathy associated with CD and clarifies the importance of tumor necrosis factor-alpha (TNFα) in immunity to renal disease. Further studies are needed to draw firm conclusions for the safety of infliximab in patients with IgA nephropathy.

Keywords Crohn's disease · Infliximab · IgA nephropathy

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Introduction

Infliximab, a chimeric anti-tumor necrosis factor-α (TNFα) monoclonal antibody, has proven to be an effective treatment for Crohn's disease (CD). However, the safety of infliximab has not been evaluated in patients with complicated renal disease. We describe herein the case of a 34-year-old woman who suffered from IgA nephropathy associated with CD whose proteinuria successfully improved with infliximab.

Case report

In 1988, a 15-year-old female presented with abdominal pain and diarrhea and was diagnosed with CD (ileocolic type). She was started on an elemental diet (1200 kcal/day). She did not take standard mesalamine therapy because she had an allergy to the drug. At several points during the 9-year period after her initial diagnosis, her symptoms were poorly controlled with regular exacerbations. She was treated with prednisolone during this period and the symptoms recurred when the dose of prednisolone was reduced. She suffered from osteoporosis in 1997 and the prednisolone was stopped. In January 2001, she presented with fever, diarrhea, and abdominal pain. Colonoscopy demonstrated severe stenotic lesions at the transverse colon and anal ring. Computed tomography (CT) scan showed focal wall thickening on the terminal ileum. She underwent ileal resection at the length of 40 cm and subcolectomy with stoma formation. The stoma was made by residual ascending colon. In July 2004, she was diagnosed with perianal abscess and recto-vaginal fistula, and underwent rectal resection. She was treated only with elemental diet because she did not want to take

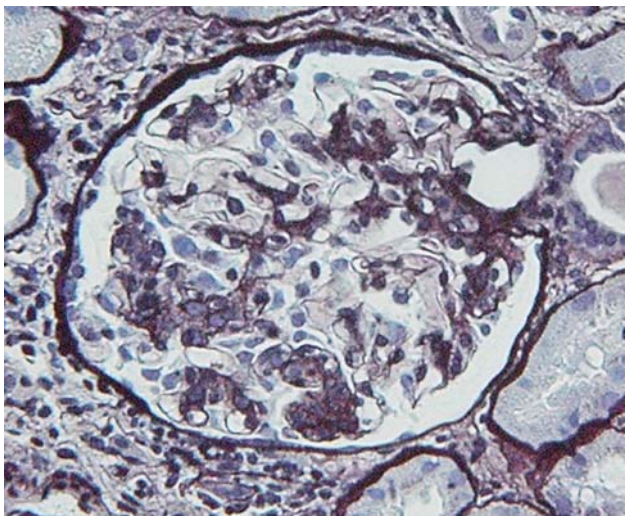

Fig. 1 Renal biopsy shows mesangial proliferative glomerulonephritis; periodic acid silver-methenamine (PAM) staining, ×100

immunomodulators. In October 2007, a routine serum and urine analysis showed high serum creatinine level (1.82 mg/dl), microscopic hematuria, and proteinuria. Urinalysis demonstrated numerous erythrocytes and heme-pigmented granulocytes, with heavy proteinuria by dipstick. Serum IgA was selectively high (858 mg/dl) with normal IgG level. Creatinine clearance was mildly decreased (33.9 ml/min per 1.26 m^2). Renal ultrasound showed two normal-sized, nonobstructed kidneys and urine culture showed no infection. A renal biopsy was done, which revealed mesangial proliferative glomerulonephritis and diagnosed IgA nephropathy (Fig. 1). Mizoribine was started for the nephropathy, which resulted in no improvement of serum creatinine and proteinuria. In January 2008, due to severe diarrhea and dehydration, she was admitted to our hospital. Relapse of CD was confirmed by colonoscopy from the stoma, which showed longitudinal ulcers with cobblestone appearance (Fig. 2a, b). Her serum creatinine and blood urea nitrogen (BUN) on admission were 3.24 and 36 mg/dl, respectively. Although the dehydration was improved by total parenteral nutrition, severe abdominal pain persisted. Because of her history of steroid-induced osteoporosis, the patient was started with a scheduled maintenance infusion of infliximab (5 mg/kg) (Remicade, Centocor, Malvern, PA) from March 2008. Before the initiation of infliximab treatment, her International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) score [1] was 7, and serum CRP level was 0.8 mg/dl. The patient showed moderate proteinuria (1922 mg/day) with high BUN (28 mg/dl) and serum creatinine (1.6 mg/dl).

A few days after the infliximab infusion, the diarrhea improved dramatically. Two weeks after the infusion, the IOIBD score was improved to 1 and serum CRP level was

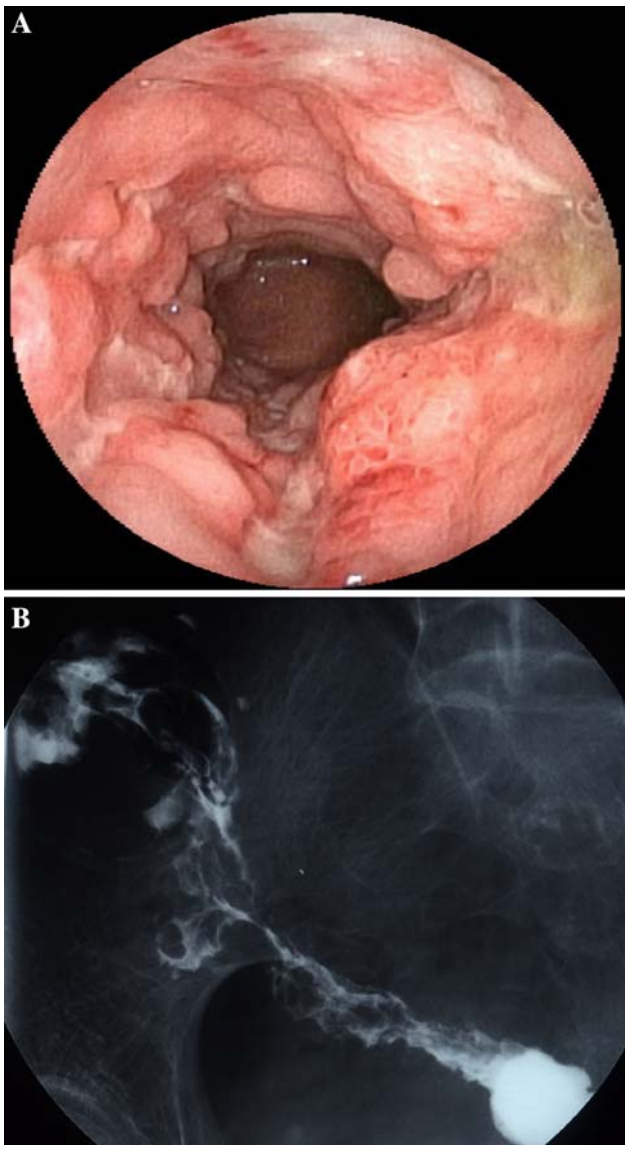

Fig. 2 **a** Colonoscopy reveals cobblestone appearance with longitudinal ulcers on the ascending colon. **b** Barium follow-through from stoma showing longitudinal ulcers suggestive of active Crohn's disease

decreased to 0.2 mg/dl. Ten weeks after the first infusion, 24-h urinary protein decreased to 451 mg. Creatinine levels later decreased to 1.28 mg/dl 22 weeks after the first infusion. Quantitative urine analysis showed no proteinuria but hematuria still persisted. Serum IgA level decreased mildly to 706 mg/dl. The course of proteinuria, serum creatinine, and serum albumin is shown in Fig. 3.

Discussion

To our knowledge, this is the first documented use of infliximab therapy in a patient with both IgA nephropathy

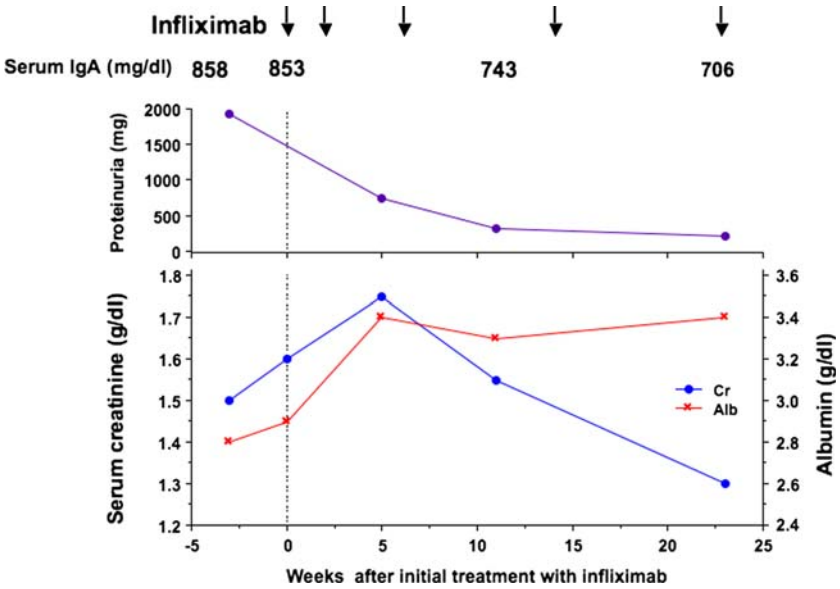

Fig. 3 The course of proteinuria, serum creatinine, albumin level, and infliximab management of this patient. *Arrows* indicate times of infliximab dosage

and CD. Infliximab is an effective treatment for refractory or fistulizing CD [2, 3]. Infliximab is also effective in some extraintestinal manifestations such as psoriasis, arthritis, and pyoderma gangrenosum [4]. However, no reports so far have demonstrated the effectiveness of infliximab in renal diseases complicated with CD. Here, we have demonstrated that infliximab also improves proteinuria associated with IgA nephropathy.

Because she suffered from active longitudinal ulcers on the ascending colon and steroid-induced osteoporosis, we considered using infliximab in this case, which induced clinical remission. It has been reported that repeated infusions of infliximab are effective for steroid-refractory CD [2].

There are several reports about patients with inflammatory bowel diseases associated with IgA nephropathy [5–7]. Although the relationship between CD and IgA nephropathy remains unclear, mucosal inflammation in the intestine may promote exposure of immune cells to various antigens in food or bacteria, which provokes increases in IgA, with the development of immune complexes that accumulate in the glomerulus.

The precise mechanism by which proteinuria was improved with infliximab is not known. Data from animal models indicate that inhibition of TNFα decreases urinary albumin excretion in experimental diabetic rats [8]. Raveh et al. reported the case of a 13-year-old boy with refractory nephrotic syndrome treated with infliximab [9]. They showed suppression of proteinuria with infliximab with tapering of steroids, and recommended that anti-TNFα antibodies may be potential treatment strategies in idiopathic nephrotic syndrome.

In our case, there has been concomitant improvement of proteinuria with good control of CD. Several reports suggest that there is a causal relationship between severity of intestinal inflammation in CD and IgA nephropathy. Forshaw et al. reported the case of a 29-year-old man with CD who had previously been diagnosed with IgA nephropathy, whose proteinuria improved following hemicolectomy and resection of 30 cm of terminal ileum [10]. Takemura et al. described the case of a 13-year-old boy with CD and IgA nephropathy. The patient was treated with an elemental diet combined with oral prednisolone, followed by maintenance therapy with salazosulfapyridine, resulting in clinical improvement of both CD and proteinuria [11]. Sakellariou et al. describe two cases of patients with psoriatic arthritis and secondary IgA nephropathy who were treated with infliximab [12]. In both cases, proteinuria improved promptly after infusion of infliximab. However, one of these cases had deterioration of proteinuria with relapse of psoriasis. Therefore, when the primary disease has been controlled, IgA nephropathy appears to subside.

TNFα plays a pivotal role in the pathogenesis of IgA nephropathy. The levels of intrarenal TNFα gene transcripts are related to the severity of clinicopathological findings, especially with the amount of proteinuria and the degree of glomerular sclerosis and mesangial matrix expansion [13]. When the IgA binds to its receptors on the mesangial cells they produce TNFα, which induces apoptosis of podocytes and tubular epithelial cell damage [14]. No specific treatments exist for IgA nephropathy. Although immunomodulators such as corticosteroids, cyclophosphamide, and mycophenolate mofetil, have been used for inhibition of progression of the disease, about 15–30% of patients will ultimately develop end-stage renal failure [15]. Therefore, TNFα may be a potential target for the treatment of proteinuria induced by IgA nephropathy.

TNFα plays a pivotal role in the pathogenesis of both CD and IgA nephropathy. Although IgA nephropathy is primary or secondary, anti-TNFα therapy could be considered as one of the potential treatments for IgA nephropathy.

Scheduled maintenance treatment with infliximab is reported to have improved clinical symptoms by inducing mucosal healing in CD [16]. Could infliximab also induce complete healing in IgA nephropathy? In our case, infliximab improved proteinuria but not hematuria. This suggests that infliximab is not sufficient to completely improve the function of the glomerulus in IgA nephropathy. Urinalysis and creatinine clearance should be closely monitored; and larger and longer-term studies are still required. However, our experience in this case suggests that infliximab can be used as a potent therapeutic option in refractory cases of CD, even in the presence of IgA nephropathy.

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