CASE REPORT

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Nephrotic Syndrome after Infliximab Treatment in a Patient with Ulcerative Colitis

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ABSTRACT

Tumor necrosis factor (TNF)-targeted therapies are increasingly used to treat a variety of inflammatory and autoimmune diseases. They are now used worldwide, and this class of medication has revolutionized the treatment of these diseases and the quality of life for patients but it also poses risk of developing various side effects including infections, exacerbation of some neurological manifestations, cutaneous lesions or induces antibody production. Renal complications are uncommon and poorly recognized. This report describes a probable case of infliximab-induced focal segmental glomerulosclerosis clinically presented as a severe nephrotic syndrome in a patient with ulcerative colitis.

Key words: ulcerative colitis – infliximab – nephrotic syndrome.

Abbreviations: IBD: inflammatory bowel disease; IFX: infliximab; TNF-α: tumor necrosis factor-α; UC: ulcerative colitis.

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INTRODUCTION

Infliximab (IFX) is a chimeric monoclonal antibody against tumor necrosis factor alpha (TNF-α), which has been extensively used in patients with inflammatory bowel disease (IBD). Renal complications are uncommon and poorly recognized. This report describes a probable case of IFX-induced focal segmental glomerulosclerosis, which clinically presented as a severe nephrotic syndrome.

CASE REPORT

Our patient, a 61-year old man, had a history of arterial hypertension since 1978, treated with beta-blockers, and left-sided ulcerative colitis (UC) since 1985. Previous treatments for UC included salazopyrin, steroids and azathioprine. Between February 2007 and May 2010, the patient also received etidronate for steroid-induced osteoporosis. In April 2010, IFX was introduced to treat a severe UC flare-up, and the patient rapidly achieved clinical remission. In September 2010, 24 hours after the 5th infusion of IFX 5 mg/kg, the patient developed an important edematous syndrome (12-kg fluid retention in 24 hours), hypertension and severe acute renal failure. Cardiac failure was rapidly excluded and the patient was referred to the nephrology department.

The biological assessment confirmed the presence of acute renal failure and nephrotic syndrome (Table I). Serologic testing for syphilis, hepatitis B and C, and human immunodeficiency virus were negative. Total complement, C3 and C4 fractions were normal and anti-DNA and perinuclear anti-neutrophil cytoplasmic antibody were negative. Transjugular renal biopsy was taken. Light microscopy showed segmental and focal hyalinosis affecting three glomeruli, associated with diffuse acute tubular necrosis. The patient was admitted in the intensive care unit and he received extrarenal filtration every other day for one week, albumin infusions, anticoagulants and steroids (methylprednisolone 1 mg/kg/day). The general condition and biological findings partially improved after three months (proteinuria: 1.6 g/24 hours versus 13 g/24 hours at diagnosis, serum albumin: 23 g/L versus 12.7 g/L at diagnosis), with edema regression. As the proteinuria persisted for 12 weeks after steroid treatment, an immunosuppressive therapy was introduced (mycophenolate mofetil 2 g/day in January

Table I. Biological findings upon hospital admission (September 2010)

Variable	Normal range	Values in the patient
Creatinine (µmol/L)	60-120	359
Urea (mmol/L)	4-7	37
Serum calcium (mmol/L)	2.20- 2.55	1.98
Serum potassium (mmol/L)	3.5-4.5	4.8
Alkaline reserve (mmol/L)	22-29	23
Serum total protein (g/L)	65-80	45
Serum albumin (g/L)	37-53	12.7
Proteinuria (g/24h)	< 0.15	13

2011. The dose of mycophenolate mofetil was increased in May 2011 and an angiotensin-converting enzyme inhibitor treatment (ramipril 5 mg/day) was introduced, allowing achievement of a transient complete remission of the nephrotic syndrome (creatinine: 127 µmo/L, albumin: 42 g/L, proteinuria: 0.5 g/24h) in September 2011, that enabled steroid withdrawal.

In June 2011, the patient experienced a severe UC flare-up with abdominal pain, bloody stools and a colectomy was considered. However, due to a severe relapse of the nephrotic syndrome and acute renal failure with a creatinine at 200 µmol/L, a decrease in serum albumin (27 g/L) and an increase in proteinuria (3.5 g/24h), surgery was delayed and a new medical treatment was attempted. In October 2011, mycophenolate mofetil was discontinued for treatment failure on both the renal and UC diseases and rituximab 375 mg/m^2 was initiated in association with transient steroid treatment. Six weeks later, the nephrotic syndrome improved (creatinine: 114 µmol/L, proteinuria: 0.26 g/24h, albuminemia: 32 g/L) and steroids were tapered then withdrawn after 6 months. Interestingly, UC was quiescent with a good general condition without abdominal pain and normal intestinal transit.

The colonoscopy performed in January 2015 showed mucosal healing (Mayo score: 0/3).

DISCUSSION

We report the case of a patient with UC who developed a nephrotic syndrome after IFX infusion. Although the renal biopsy showed focal glomerulosclerosis and acute tubular necrosis, the clinical picture was compatible with a nephrotic syndrome. Renal amyloidosis or drug toxicity was discussed to explain this situation. The renal biopsy was negative for amyloidosis and several case reports have described the efficacy of anti-TNF-α treatment on amyloid nephropathy complicating long-standing Crohn's disease, a treatment which induces a rapid response in proteinuria and a suppression of the renal disease activity [1–6].

Two drugs could be potentially responsible for this disease: etidronate and IFX. Although renal damage has previously been reported under biphosphonate therapy [7–9], in our case etidronate was probably not involved because it was discontinued 5 months before occurrence of the nephrotic syndrome and its half-life is short (6.0 ± 0.7 hours). In addition, the clinical course strongly incriminated anti-TNF-α therapy, since the proteinuria and edematous syndrome appeared 24 hours after the infusion of IFX. The nephrotic syndrome persisted after IFX withdrawal but infliximabemia was detectable more than 8 weeks after the infusion. Some cases of granulomatous nephritis have been reported after anti-TNF-α therapy [10, 11] as well as cases of interstitial nephritis [12] or membranous nephropathy [13], so that the occurrence of renal damage under anti-TNF-α therapy appears plausible. A nephrotic syndrome developed in a patient with rheumatoid arthritis during treatment with a fully human recombinant monoclonal antibody anti-TNF (adalimumab) was also previously described [14].

After initial improvement of kidney damage following anti-TNF-α withdrawal, our patient experienced a new relapse, which could suggest autonomy of the kidney disease. The development of steroid dependency in patients with nephrotic syndrome may require long-term multidrug therapy, which increases the risk of drug toxicity and renal failure. Our patient had steroid-dependent UC and osteoporosis due to prolonged steroid therapy. Rituximab may be an alternative to immunosuppressive therapies for difficult-to-treat nephrotic syndrome as it is known to assist tapering steroids [15, 16]. It may also play a role in IBD control [17].

CONCLUSION

This case of IFX-induced nephrotic syndrome is, to the best of our knowledge, the first case described in a patient with inflammatory bowel disease.

Conflicts of interest: X.T. received consulting fee from MSD, Ferring, Norgine Pharma and is funder of Inception IBD, San Diego, Ca, SUA. Y.B. has received consulting fee from Sanofi and Roche, advisory board membership fee from Abbvie, Norgine Pharma, MSD, Takeda Millenium and lectures fee from Abbvie, Falk, Ferring, Given Imaging, Mayoli-Spindler, Norgine Pharma, Vifor Pharma. Y.B. declares shareholding in a company: Inception IBD, San Diego, Ca, USA. None for the remaining authors.

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