IgA nephropathy associated with ankylosing spondylitis is not controlled by infliximab therapy

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Abstract

The association between seronegative spondyloarthropathies and IgA nephropathy is well documented, mainly in cases of ankylosing spondylitis (AS). However, although these diseases have been associated, the physiopathological links between each other appear unclear. Anti-TNFα agents have transformed the outcome of axial forms of AS resistant to conventional anti-inflammatory therapies. Infliximab, a monoclonal anti-TNFα antibody, has greatly improved the evolution of AS although several adverse events have been described. On the other hand, infliximab has been demonstrated to reduce renal symptoms associated with chronic inflammatory rheumatological diseases, such as amyloid A (AA) amyloidosis, but few data are available on its efficacy in controlling IgA nephropathy associated with AS [1,2]. We report here a case of IgA nephropathy associated with AS that became symptomatic, whereas infliximab therapy efficiently controlled the rheumatological disease. This suggests that even though infliximab therapy effectively controls rheumatological manifestations, it may not be able to prevent IgA nephropathy associated with AS. Thus, this case report illustrates the complexity of the physiopathology of both diseases.

Keywords: ankylosing spondylitis; IgA nephropathy; infliximab; TNFalpha

Case report

An HLA-B27 37-year-old man with an axial form of AS diagnosed in 1993 was initially treated with non-steroidal anti-inflammatory drugs (NSAIDs). Nevertheless, the disease was persistently active despite NSAIDs treatment with a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of 51. Thus, infliximab (5 mg/kg/10 weeks) was started in April 2002. At the time of the initiation of this treatment, the patient's urinalysis was normal (no haematuria or proteinuria), and his estimated glomerular filtration rate (eGFR) by the Modification of Diet in Renal Disease (MDRD) formula was 81.4 ml/min/1.73 m². Rheumatological symptoms quickly resolved with anti-TNFα therapy: the BASDAI score markedly decreased to a score of 8 at week 20 and remained almost stable over time. Two years after the start of infliximab treatment, the patient developed microscopic haematuria (80 000 red cells/ml) and proteinuria increased to 0.54 g/day, but with no alteration of his renal function. Urological investigations including renal ultrason and intravenous urography showed no abnormalities. Three years after the start of infliximab treatment, haematuria was still present (100 000 red cells/ml) and proteinuria increased to 1.75 g/day. The serum creatinine concentration was 109 µmol/l (eGFR 68.4 ml/min/1.73 m²). Anti-proteinuric treatment with an angiotensin receptor blocker (ARB) was started (irbesartan, 150 mg/day and then 300 mg/day). Despite this treatment, haematuria increased (550 000 red cells/ml) and renal function worsened [serum creatinine 137 µmol/l, eGFR (MDRD) 52.4 ml/min/1.73 m²], whereas proteinuria was 0.24 g/l. ANA and dsDNA antibodies were slightly positive (ANA: 1/80, dsDNA: 13 UI), and anti-neutrophil cytoplasmic autoantibodies (ANCA), anti-glomerular basal membrane antibodies and cryoglobulinaemia were negative. The serum complement was normal, but serum IgA levels were increased (5.13 g/l, normal: 0.7–4 g/l). A renal biopsy was performed. Light microscopy revealed mesangial expansion without endocapillary or extracapillary proliferation in all glomeruli, associated with flocule-capsular synechias in 25% of the glomeruli, and with moderate inflammatory interstitial fibrosis and tubular atrophy (Figure 1). Congo red staining was negative. Immunofluorescence microscopy demonstrated IgA deposits, predominantly within the mesangium of all glomeruli, leading to the diagnosis of IgA nephropathy (Figure 2). Treatment was continued with ARB alone. Six months after this diagnosis, the renal function and proteinuria remained stable.
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Discussion

Tumour necrosis factor-alpha (TNFα) is a pro-inflammatory cytokine involved in many chronic inflammatory diseases, which mainly include ankylosing spondylitis (AS), psoriatic arthritis, rheumatoid arthritis and Crohn’s disease. Thus, therapies using anti-TNFα are now major agents taking part in the treatment of these inflammatory diseases.

IgA nephropathy and secondary amyloid A (AA) amyloidosis are the most common glomerulonephritis classically associated with AS [3]. Serum IgA levels are frequently elevated in both IgA nephropathy and spondyloarthropathies, suggesting that IgA-containing immune complexes are involved in the pathogenesis of both diseases [4,5]. The physiopathology of IgA nephropathy remains unclear, and extremely complex, involving several molecules, cytokines and immune cells [4]. In IgA nephropathy, deposits mainly consist of polyclonal sub-class IgA1. Deposits may be the consequence of IgA glycosylation abnormalities inducing a decrease in IgA clearance, facilitating IgA capillary deposits and inducing circulating immune complexes [6]. These complexes activate mesangial cells after their fixation to the mesangial CD71 receptor, inducing pro-inflammatory mediators (IL1, IL6, IL8, IP10, MIP) and growth factors (TNFα, TGFβ) production, able to induce mesangial cell proliferation and extra-cellular matrix increase [7]. The hypothesis of anti-TNFα action in IgA nephropathy is supported by the fact that levels of TNFα renal transcripts are correlated with the severity of the disease [8]. Moreover, TNFα released by mesangial cells after IgA deposition may activate renal cell proliferation and cytokine synthesis, which can be blocked by TNFα antagonists in vitro [9].

Infliximab decreases proteinuria during renal AA amyloidosis among patients treated for AS or other forms of inflammatory arthritides [1,2]. This effect of anti-TNFα therapy may be explained by a blockade of the TNFα renal actions, as TNFα is known to induce glomerular inflammation and to increase glomerular permeability [10]. Therefore, anti-TNFα treatments may generally improve proteinuria regardless of the initial glomerulopathy. There are few data on the efficacy of infliximab treatment for IgA nephropathy associated with chronic inflammatory rheumatological diseases. Sakellariou et al. recently reported two patients with secondary IgA nephropathy and psoriatic arthritis treated with infliximab [11]. Both patients presented a simultaneous improvement of proteinuria and rheumatologic symptoms. One patient had a relapse 1.5 years after the initiation of infliximab therapy (reoccurrence of rheumatological symptoms and proteinuria deterioration); this was successfully treated with rescue treatment (methotrexate and cyclosporine) in addition to infliximab.

Anti-TNFα therapies may act on the effector phase but not on the initiation phase that can be regulated differently leading to different expression in both diseases. In addition, TNFα antagonist therapy not only inhibits TNFα action, but also induces a shift from a TH1 pattern (e.g. IL1, TNF and interferon gamma) to a TH2 pattern (e.g. IL-4, IL-5, IL-6, IL-10 and IL-13), thereby promoting the development of manifestations related to antibody-mediated immunity. Two cases of IgA-associated vasculitis have been reported during anti-TNFα therapy for AS and were associated with renal involvement [12]. In three cases of anti-TNFα-associated vasculitis, extracapillary lesions were therefore identified. This could suggest that the TNFα antagonist may promote autoimmunity and may favour the development of antibody-mediated injury. We reported a patient with IgA nephropathy associated with AS whose condition was clearly not improved by infliximab treatment, even though the treatment was effective against the rheumatological symptoms. For our patient, haematuria associated with mild proteinuria and rheumatologic symptoms. One patient had a relapse 1.5 years after the initiation of infliximab therapy (reoccurrence of rheumatological symptoms and proteinuria deterioration); this was successfully treated with rescue treatment (methotrexate and cyclosporine) in addition to infliximab.
downstream IgA interaction with mesangial cells, but its exact role has yet to be well defined. The dissociation between rheumatological symptoms and renal manifestations observed in our patient after anti-TNFα therapy suggests that the role of TNFα in IgA nephropathy is not prominent, and that blocking the TNFα pathway is not sufficient to prevent renal IgA deposition and this nephropathy.

Conclusion

The anti-TNFα agent infliximab is effective in treating rheumatological symptoms of AS, but does not necessarily control associated IgA nephropathy, suggesting that the mechanisms involved in AS and the development of AS-associated IgA nephropathy are different. Thus, IgA nephropathy can occur although AS seems well controlled by infliximab, which is contrary to AA amyloidosis.

Conflict of interest statement. None declared.

References


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Enormous brachio-cephalic arteriovenous fistula aneurysm after renal transplantation: case report and review of the literature

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Abstract

Creation of arteriovenous fistulae provides readily available vascular access for haemodialysis in patients with end-stage renal disease. However, it is associated with various potentially serious complications if left unattended.

We report a case of a 73-year-old male presenting with an enormous brachio-cephalic fistula aneurysm measuring 70–5.4 cm 20 years after successful renal transplantation. Despite attending regular renal outpatient clinic follow-up, this was only noticed as an incidental finding when the patient attended the emergency department after a fall that severely bruised his access. The patient subsequently underwent ligation with complete removal of the aneurismal fistula and discharged to a rehabilitation unit 3 days post-operatively.

Systematic closure of an arteriovenous fistula should be considered in all patients after successful renal transplantation to avoid potentially catastrophic complications of an arteriovenous fistula. In patients in whom the closure of vascular access is contraindicated, it is crucial to regularly