Glomerulonephritis and Anti-TNF Therapy in Patients with Rheumatoid Arthritis: A Case Report and Literature Review

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ABSTRACT

Herein we report a case of rheumatoid arthritis (RA) and immunoglobulin A nephropathy (IgAN) in a 68-year-old woman after 2 years of initiating etanercept (25mg weekly), a decoy receptor that binds to TNF. Because the patient presented progressively increased proteinuria associated with hematuria following etanercept initiation, we performed a renal biopsy to study the glomerulonephritis with mesangial and parietal IgA deposits. We suspected that IgAN was an adverse event related to use of etanercept. Proteinuria improved one year after etanercept was interrupted. The study period lasted from the time etanercept was started and the onset IgAN to improvement of glomerulonephritis after discontinuance of etanercept. No relapse of heavy proteinuria or hematuria was found in the RA patient during the recurrence free follow-up period.


Key words : Glomerulonephritis, Rheumatoid arthritis, Anti-TNF therapy, Etanercept

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Introduction

Rheumatoid arthritis (RA) is a chronic idiopathic systemic autoimmune disorder characterized by synovial inflammation in which autoantibody targets IgG. Extra-articular features are common manifestations in patients with RA, in whom are found renal disease involving glomerulonephritis (GN), interstitial nephritis, or secondary amyloidosis.[1] Certain drugs have been correlated with renal problems, particularly non-steroidal anti-inflammatory drugs.[2] However, there are limited published data regarding drugs that might induce immunoglobulin A nephropathy (IgAN) in RA patients.

Tumor necrosis factor-alpha (TNFα) mediates the immune response by increasing the transport of leukocytes to sites of inflammation. Among biologics currently in use, etanercept interrupts the action of naturally present TNF as a decoy receptor binding to TNF, and this anti-inflammatory response is particularly useful for autoimmune diseases.[3] Etanercept also indirectly modulates different biological responses involving the expression of adhesion molecules E-selectin, intercellular adhesion molecule 1, the production of interleukin-6, and matrix metalloproteinase 3 as well as interleukin 1.[4]

IgAN may be related to the administration of anti-TNFα agents, one distinctive feature being a deposition of IgA-containing immune complexes in the renal mesangium. Anti-drug antibodies against glycan structures of TNFα inhibitors may cross react against serum aberrant IgA1 resulting in large antigen-antibody complexes. These large polymeric IgA complexes are able to deposit in the mesangium and activate a complementary cascade.[5] Herein we report a rare case involving a RA patient treated with etanercept suffering from a mesangial IgAN.

Case Report

A 68-year-old woman was admitted to our hospital with 20 years of gradually progressive rheumatoid arthritis, although she had taken disease modifying anti-rheumatic drugs with analgesics, corticosteroids, and sulfasalazine. Due to insufficient response to those medications, we initiated etanercept (25mg weekly for 2 years), a TNF antagonist. Six months following initiation of etanercept, urinalysis revealed urinary protein of 2+. After 2 years of follow-up visits, the occurrence of foamy urine was associated with heavy proteinuria (3.18g/day) and hematuria (occult blood of 1+, RBC of 2-5) while still on etanercept. Her blood pressure was 151/75 mmHg. Laboratory results showed leukocyte of 10010 cumm, hemoglobin of 13.2g/dL, C-reactive protein of 1.3mg/dl, rheumatoid factor of 559U, albumin of 4.6g/dL, total cholesterol of 326mg/dL, and triglyceride of 180mg/dL, blood urea nitrogen of 18mg/dL, and creatinine of 0.8mg/dL. Her immunologic profile was characterized by elevated rheumatoid factor. Other studies for antineutrophil cytoplasmic antibody, anti-nuclear antibody, anti-glomerular basement membrane antibody, hepatitis B surface antigen and anti-hepatitis C virus antibodies were unremarkable. Due to the persistence of proteinuria, a renal biopsy was performed and revealed Hass class II of IgAN and chronic interstitial nephritis associated with tubular atrophy (Figure 1). Indeed, five glomeruli showed
minimal mesangial hyperplasia and segmental sclerosis. The interstitium had severe focal sclerosis and mild chronic inflammation. In other segments, the mesangium was large, with cell proliferation. Immunofluorescence revealed mesangial and parietal immunoglobulin A deposits, and immunoglobulin M deposits in some segments (Figure 1A, B, C, D). Etanercept was stopped, and she had a good enough clinical outcome to allow discharge. At one year of follow-up, proteinuria had continued to decrease to 0.27g/day and no relapse of foamy urine was observed.

Discussion

The association between IgAN with diagnosed RA being treated with ertanercept remains unknown. One hypothesis is that anti-TNFα results in IgAN, as suggested by the rapid resolution of this nephropathy after discontinuation of anti-TNFα therapy. Five patients have been previously reported with GN complicating anti-TNFα, but the case reported herein is the first to our knowledge to be one of simultaneously diagnosed anti-TNFα and IgAN in a patient with RA. New onset of

Figure 1. A: Protein cast in tubule. B: Mesangial cell proliferation, minimal mesangial hyperplasia and segmental sclerosis. C: The interstitium has focal severe sclerosis and mild chronic inflammation. D: Immunofluorescence revealed mesangial and parietal IgA deposits, and IgM deposits in some segments.
Gln following administration of anti-TNFα therapy is often accompanied by new autoantibodies in patients who have had no prior evidence of renal disease. A review of the literature revealed 6 adult patients (median age 55), 5 females, all with longstanding RA (range, 10-30 years), 5 of whom received corticosteroids, one patient having deceased. Etanercept was initiated in five patients, though infliximab was a substitute for etanercept in one of them. One patient received adalimumab. Anti-TNFα was utilized for 3 to 30 months (median 8 months), indicating that GN did not appear in any drug formulation and developed after months of therapy. Three subjects had newly detected autoantibodies at the time of onset of renal disease, consistent with drug-induced autoimmunity. In our patient, on the other hand, proteinuria and renal impairment occurred from the beginning of anti-TNFα therapy, and clinical condition improved in the months after the treatment was stopped. No relapse of IgAN in RA patient has occurred during the 9 months of a recurrence free follow-up period. In the literature, only one patient in whom etanercept was not discontinued progressed to multisystem vasculitis and subsequently died despite cytotoxic therapy. It is an intriguing question to know whether discontinuation of anti-TNFα led to the improvement in renal impairment in 5 patients, which might suggest a pathogenic role for anti-TNFα-induced autoimmunity.[4] One possible mechanism implying this linkage is that immune complexes of anti-TNF/TNF may be precipitated in small capillaries and lead to a type III hypersensitivity reaction.[4] It also has been demonstrated that TNF antagonist can increase IFN production by plasmacytoid dendritic cells, resulting in the onset of autoimmune diseases such as vasculitis and systemic lupus erythematosus.[7] Indeed, CTLA4 gene polymorphism has been reported to be associated with IgAN.[3] Nevertheless, the mechanisms underlying anti-TNFα induced autoimmunity remain controversial.

In conclusion, it is important to emphasize the need to investigate the role of anti-TNFα in the development of IgAN in patients with RA in further studies. Proteinuria and hematuria occurred in our patient with RA and mesangial glomerulopathy following the use of anti-TNFα agents. Prospective studies may be necessary to study this in these patients because the natural course and the importance of such disease combination are not fully understood.

Abbreviation: GN: glomerulonephritis; IgAN: immunoglobulin A nephropathy; RA: Rheumatoid arthritis; TNFα: Tumor necrosis factor-alpha.

Conflicts of Interest Statement

The authors declare no conflicts of interest.

References


風濕性關節炎病患使用腫瘤壞死因子抑制劑
t治療與腎絲球腎病變的相關性：
個案報告與文獻回顧

王貞懿 1 林瑞祥 2,3 王偉傑 2,4 鄭美華 1 林明慧 5,*

摘 要

我們報導一位68歲女性患者有類風濕性關節炎病史服用免疫抑制劑—恩博(etanercept)治療。由於蛋白尿狀況逐漸惡化並且伴隨血尿出現，因此建議執行腎臟切片，其結果顯示A型免疫球蛋白腎病(IgA nephropathy)。A型免疫球蛋白腎病被視為etanercept所產生的副作用。將藥物停止使用一年內，蛋白尿大幅改善，使用etanercept引起A型免疫球蛋白腎病的時間相當於停藥etanercept後逐漸改善蛋白尿的時間，後續也沒有蛋白尿與血尿出現。

關鍵詞：腎絲球腎病變、風濕性關節炎、腫瘤壞死因子抑制劑治療、恩博