Rheumatoid Arthritis with Secondary Amyloidosis and Chronic Kidney Disease with a Good Response to Etanercept

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Secondary amyloidosis is a severe complication of refractory rheumatoid arthritis for which no effective treatment exists. Although the benefits of tumor necrosis factor alpha inhibitors in rheumatoid arthritis treatment are well known, their role in renal amyloidosis secondary to rheumatoid arthritis is unclear and their safety in patients with chronic kidney disease is not well reported. We present an unusual case of a 65-year-old female with moderate renal failure and severe proteinuria, who was diagnosed with secondary amyloidosis associated with refractory rheumatoid arthritis subsequent to treatment with corticosteroids, methotrexate, hydroxychlorquine, and leflunomide. She was treated with etanercept 25 mg, administered as a subcutaneous injection twice weekly for 8 months. The patient had no complications following the treatment. Treatment with etanercept led to a decrease in proteinuria and stabilization of renal function over time.

Key Words. Amyloidosis, Chronic renal insufficiency, Etanercept, Rheumatoid arthritis

Introduction

It has been reported that some patients with poorly controlled rheumatoid arthritis (RA) have complicated to secondary amyloidosis (1). Successful treatment with multiple disease-modifying antirheumatic drugs (DMARDs) can lead to stabilization of organ function or improvement in function of the involved organ and partial resolution of amyloid deposits (2). Unless the activity of the underlying disease can be effectively controlled, the development of secondary amyloidosis is associated with poor prognosis and reduces the survival rate of these patients (1). In addition, there are considerable difficulties in the treatment of RA patients, who already have impaired renal function because several DMARDs such as methotrexate, cyclosporine, non-steroidal anti-inflammatory drugs (NSAIDs) may contribute to additional nephrotoxicity in these patients.

Due to the possibility of controlling the inflammatory activity, it has been suggested that anti-tumor necrosis factor-alpha (TNF-α) agents could be the best treatment option for secondary amyloidosis (3). Anti-TNF-α agents also have emerged as an effective treatment for refractory RA patients (4). However, experience with anti-TNF-α agents in patients with secondary amyloidosis and renal insufficiency is scarce in Korea.

Herein, we describe the case of a patient with secondary amyloidosis and renal failure associated with refractory RA, who was successfully treated with etanercept.

Case Report

A 65 year old female with rheumatoid factor positive RA for the past 6 years presented with aggressive disease: rheumatoid factor 310 IU/mL, anti-cyclic citrullinated peptide antibody >100 U/mL, erythrocyte sediment rate (ESR) 120 mm/hr, and C-reactive protein (CRP) 11.06 mg/dL at the time of her first visit to the department. Despite treatment with corticosteroids, methotrexate, hydroxychlorquine, and leflunomide, she had experienced persistent joint pain and swelling involving hands, feet and ankles.
Three months before hospitalization, the patient developed gravitational edema of the lower limbs. At the time of admission, laboratory examination revealed an elevated serum creatinine level from 1.0 mg/dL to 1.7 mg/dL over the time of 3 months, a serum albumin concentration of 2.9 g/dL, a 24-hr urine protein of 3.6 g, urine protein electrophoresis of glomerular pattern, and an estimated glomerular filtration rate of 32 ml/min per 1.73 m². Immunologic studies revealed normal serum complements (C3/C4) levels and antinuclear and anti-neutrophil cytoplasmic antibodies were negative. Ultrasound of the kidney was found to be normal. Subsequently, renal biopsy was performed, which showed: 41 glomeruli, 21 with global sclerosis (51%), eosinophilic material deposition in mesangial matrix and capillary loop; patchy areas of interstitial fibrosis; and focal moderate infiltration of mononuclear cells (Figure 1). The deposits tested positive for Congo red staining with green birefringence under polarization microscopy and immunohistochemical staining detected the presence of amyloid A protein (Figure 2).

Ten months after the diagnosis of secondary renal amyloidosis and treatment with prednisolone 2.5 mg/day, methotrexate 10 mg/week, leflunomide 10 mg/day, hydroxychloroquine 200 mg/day, and valsartan 160 mg/day, she had aggravated kidney function (serum creatinine 2.4 mg/dL) with an increase in 24-hr proteinuria to 9.0 g/day, ESR 90 mm/hr, CRP 10.55 mg/dL, and persistence of the articular involvement. Since that time, all DMARDs except prednisolone 2.5 mg/day were discarded and valsaratan 160 mg/day was taken continuously. However, her renal function and proteinuria were not improved after 2 months (serum creatinine 2.4 mg/dL and 24-hr urine protein 9.0 g/day, respectively). At that time, anti-TNF-α treatment (etanercept 25 mg subcutaneous injection twice weekly) was instituted. Eight months after the onset of etanercept and a low dose steroid (prednisolone 2.5 mg) administration, marked improvement in the arthritis with reduction in ESR and CRP (64 mm/hr and 0.48 mg/dL, respectively), decrease in proteinuria to 1.8 g/day, and preserved renal function with serum creatinine level of 1.8 mg/dL, were observed, indicating that progression of the renal disease along with improvement of the arthritis, indicated by RA disease activity score (DAS) 28, was under control with subcutaneous administration of etanercept (Figure 3).
Discussion

Secondary amyloidosis is caused by deposits of amyloid originating from acute-phase proteins. Many chronic inflammatory diseases such as RA, ankylosing spondylitis, inflammatory bowel diseases and chronic pyogenic infections can cause secondary amyloidosis (1) and among these, RA accounts for up to 40 percent of secondary amyloidosis (5). This process could result in target organ dysfunction and failure, such as end-stage renal disease (1). Small, non-controlled studies have shown that the use of cytotoxic agents and immunosuppressants in secondary amyloidosis improve survival rate and preserve renal function in subjects (6), however, current therapeutic approaches have shown poor results in cases with refractory underlying disease.

Patients with RA are more prone to renal failure than normal individuals due to the potential toxicity of drugs used in their treatment (7) and associated complications such as development of secondary amyloidosis (1). Renal failure in patients with RA causes many restrictions to the management of RA because most of the drugs used in the treatment of these patients are associated with a high risk of renal toxicity.

Etanercept, one of the anti-TNF-α drugs, is effective in the treatment of refractory RA (4). Since etanercept is hydrolyzed at lysosomes and seems not to be influenced by renal function, it has been suggested that this drug may be an alternative treatment option in RA patients with renal dysfunction (8). To date, only a few reports have demonstrated efficacy and safe nature of etanercept in RA patients with secondary amyloidosis and renal failure (3,9,10). Recently, a small retrospective observation study comparing the effectiveness of cyclophosphamide and etanercept in RA patients with secondary amyloidosis showed that etanercept was more effective in improving the decreased renal function caused by secondary amyloidosis than cyclophosphamide (10). In addition, Fernández-Nebro et al. reported that etanercept significantly reduced acute-phase reactants and proteinuria and stabilized renal function in RA patients with renal failure and secondary amyloidosis (3). However, in Korea, there are limited data available about the use of anti-TNF-α drugs in patients with RA and secondary amyloidosis. Kim et al. reported a case of secondary amyloidosis in a 71 year old woman who responded to infliximab therapy (11). However, she had a normal renal function but died of sepsis 7 weeks after infliximab therapy. To our knowledge, our case is the first in Korea that showed good response to etanercept in a patient with RA and renal failure caused by secondary amyloidosis. In the present case, the patient did not show any clinical improvement upon treatment with traditional DMARDs or immunosuppressants such as prednisolone, methotrexate, leflunomide and hydroxychloroquine, and demonstrated persistent elevated levels of proteinuria and serum creatinine until etanercept was administered. Improvement of her renal function and proteinuria was observed along with improvement of the arthritis and reduction of RA disease activity indices such as ESR, CRP and DAS 28. Thus, the good response to etanercept in this patient seems to be related to its ability to control disease activity of RA. Although we did not evaluate the mechanisms of anti-TNF-α drugs such as etanercept which can improve secondary renal amyloidosis, it has been hypothesised that the improvement in patients with RA and renal amyloidosis is related to inhibition of the hepatic synthesis of acute phase protein induced by TNF-α, and reduction in glomerular inflammation and the increase in the glomerular permeability to albumin induced by the same cytokine (3).

Summary

Our report suggests that etanercept therapy may be useful in RA patients with renal failure induced by secondary amyloidosis. This treatment can significantly reduce proteinuria and also can stabilize renal function in refractory RA patients with renal failure and secondary amyloidosis.

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