The effect of etanercept on a case of amyloidosis secondary to ankylosing spondylitis: results of 2-year follow-up

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RESUMO

Secondary amyloidosis (type AA) is rarely encountered but can be a significant complication of ankylosing spondylitis (AS) and may lead to proteinuria and renal dysfunction. Anti-tumor necrosis factor-alpha (anti-TNF-α) agents may be used to induce clinical remission by suppressing systemic inflammation in secondary amyloidosis. The patient described, with the diagnosis of AS, was diagnosed with secondary amyloidosis, despite treatment with disease modifying anti-rheumatic medication. He developed marked proteinuria, renal dysfunction and low levels of serum albumin. Diagnosis of amyloidosis was confirmed by renal biopsy. During a 2-year treatment period with etanercept, an anti-TNF-α agent, a definite improvement was determined in all parameters. This case illustrates that in the treatment of secondary amyloidosis related to AS, etanercept, an anti-TNF-α agent, can be considered an effective therapeutic option.

Keywords: Ankylosing Spondylitis, secondary amyloidosis, etanercept, renal function.

INTRODUCTION

Amyloidosis is a clinical entity, the presentation of which results from the deposition of a protein in tissues and organs at an abnormal rate. However, amyloid is the term where this protein is histopathologically demonstrated in tissues. Secondary amyloidosis, whose main protein is AA, is a type of amyloidosis seen together with chronic inflammatory disorders\(^1\). Secondary amyloidosis is seen in 5% of patients with chronic inflammatory uncontrolled diseases such as rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), familial Mediterranean fever (FMF) and ankylosing spondylitis (AS)\(^2\) and the most common clinical presentation is seen in the form of renal involvement such as renal failure and/or proteinuria\(^3\). For secondary amyloidosis, no specific therapeutic regimen is available and the best choice is to treat the underlying disorders. The outcomes of secondary amyloidosis can be improved by suppressing acute inflammatory responses\(^4\). In several studies, patients were reported to benefit from medications such as colchicine, chlorambucil, azathioprine and methotrexate\(^5\).\(^7\). A soluble receptor of TNF-α, etanercept, decreases amyloid deposits and improves renal function by attaching to this cytokine in circulation\(^3\). In light of such data, anti-TNF-α agents may promote clinical remission in secondary amyloidosis.

In our case study, the disease activity and renal function were improved in a patient with secondary amyloidosis and renal involvement due to AS with the help of a 2-year treatment of etanercept.

CASE-DESCRIPTION

A 41-year-old male patient had been diagnosed with AS at the age of 27 and treated with sulfasalazine (2g/day-12 years), various NSAIDs and methotrexate (10mg/week-2 years) due to the existence of peripheral arthritis in different centers until 2010. In January 2010, he sought assistance at our clinic with complaints of inflammatory type of lumbar pain, sleep disrupting backache, hip pain and morning stiffness. On physical examination, the back, hips and neck movements were painful, and no non-axial involvement was present. The disease was active when the patient was admitted to our clinic. BASDAI and BASFI were found to be 9.28
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C reactive protein (CRP) was 22.9 mg/dl, erythrocyte sedimentation rate (ESR) was 67 mm/h and hemoglobin, 11.8 g/dl. A 24-h proteinuria, serum albumin and serum creatinine were found to be 6200.2 mg, 2.7 g/dl (normal ≥ 3.5 g/dl) and 0.8 mg/dl, respectively. After performing renal biopsy, amyloid deposition expressed with crystal violet staining (+) was detected on glomeruli, arterial and arteriolar walls, and the patient was diagnosed with amyloidosis and started treatment with 25 mg of subcutaneous etanercept twice a week. After 12 months, the rate of proteinuria in 24-h urine had already been markedly decreased. The condition was accompanied by an increase in serum albumin, stabilization of renal function and a decrease in the scores of BASDAI and BASFI, CRP and ESR. The patient’s follow-up over 2 years may be seen in Table I.

### DISCUSSION

We describe a case of secondary amyloidosis in a patient with AS that received a well-tolerated 2-year treatment of etanercept. Renal biopsy confirmed a type AA amyloidosis responsible for severe proteinuria and low level of serum albumin. In addition, the patient with secondary amyloidosis had no other organ involvements, except for renal involvement.

Secondary amyloidosis is a rare complication of AS and results in the accumulation of amyloid fibrilles in various organs. This disorder leads to high morbidity and mortality on account of end-stage renal failure, heart failure, intestinal perforation or digestive hemorrhage. In secondary amyloidosis, kidneys are the most commonly involved organs and proteinuria is the most widespread presentation of amyloid nephropathy. Poor prognostic factors are a high rate of proteinuria in 24-h urine and a decrease in serum albumin and high creatinine levels. High levels of serum amyloid A may lead to end-stage renal failure, especially in those whose levels are persistently over 10 mg/l. TNF-α plays a key role in the pathogenesis of amyloidosis. TNF-α, like other pro-inflammatory cytokines such as interleukin-1 (IL-1) and interleukin-6 (IL-6) stimulates hepatocytes to produce SAA, the precursors of amyloid fibrilles. In addition, TNF-α is of crucial significance in the proteolysis of SAA into AA and supports the expression of receptors for advanced glycation end products (RAGE) through macrophages in amyloid deposits. Interaction of RAGE with amyloid fibrilles is involved in tissue injury and cytotoxicity.

Anti-TNF-α agents may be promising in the treatment of secondary amyloidosis by disrupting the spread of amyloidogenesis and decreasing load of amyloids. In the literature, there are very few reports on the effectiveness of anti-TNF-α agents in secondary amyloidosis with proteinuria due to renal involvement. In a study performed by Kobak et al., a definite improvement was determined in disease activity, proteinuria, renal functions and levels of serum albumin in three cases with AA amyloidosis related to AS during 1-year treatment with etanercept.

In another study, Fernandez-Nebro et al. reported that as a result of treatment with anti-TNF-α, proteinuria decreased in nine of 18 patients with both renal failure and proteinuria related to secondary amyloidosis due to rheumatic inflammatory disease. Furthermore, Fernandez et al. reported two cases of secondary amyloidosis from RA which responded well to the treatment with etanercept, and Ishii et al. described another case of a patient with systemic reactive AA amyloidosis to RA successfully treated with prednisolone and etanercept with proven marked regression of gastro-duo-

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**TABLE I. TWO-YEAR CLINICAL AND LABORATORY FOLLOW-UPS OF THE CASE WITH SECONDARY AMYLOIDOSIS DURING THE TREATMENT WITH ETANERCEPT**

<table>
<thead>
<tr>
<th></th>
<th>BASDAI (0-10 cm)</th>
<th>BASFI (0-10 cm)</th>
<th>CRP (mg/dl)</th>
<th>ESR (mm/h)</th>
<th>Albumin (mg/dl)</th>
<th>Serum Creatinine</th>
<th>Urine protein (mg/24-h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>9.28</td>
<td>8.52</td>
<td>22.9</td>
<td>67</td>
<td>2.7</td>
<td>0.80</td>
<td>6200.2</td>
</tr>
<tr>
<td>6th month</td>
<td>7.49</td>
<td>6.60</td>
<td>3.36</td>
<td>20</td>
<td>3.4</td>
<td>0.67</td>
<td>6016.5</td>
</tr>
<tr>
<td>12th month</td>
<td>3.48</td>
<td>5.47</td>
<td>3.41</td>
<td>15</td>
<td>3.8</td>
<td>0.71</td>
<td>1442.5</td>
</tr>
<tr>
<td>24th month</td>
<td>0.63</td>
<td>4.9</td>
<td>3.8</td>
<td>12</td>
<td>4.7</td>
<td>0.73</td>
<td>587.25</td>
</tr>
</tbody>
</table>
renal mucosal amyloid deposits within only 4 months\textsuperscript{15}. Another case with FMF resistant to colchicine was reported to respond well to the treatment with etanercept in a study performed by Ertan et al\textsuperscript{16}.

The progression of our case with secondary amyloidosis to AS was in agreement with these observations. Consequently, etanercept, an anti-TNF-\(\alpha\) agent, should be considered an effective and reliable therapeutic option in the treatment of renal involvement due to secondary amyloidosis to AS. However, prospective studies with greater number of participants are needed in order to confirm the effectiveness and reliability of this drug.

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