Successful Use of Maintenance Infliximab for Nephropathy in a Patient with Secondary Amyloidosis Complicating Crohn’s Disease

Yasumasa Tada¹, Shunji Ishihara¹, Takafumi Ito², Kosuke Matsui², Hiroki Sonoyama¹, Akihiko Oka¹, Ryusaku Kusunoki¹, Nobuhiko Fukuba¹, Yoshiyuki Mishima¹, Naoiki Oshima¹, Ichiro Moriyama¹, Takafumi Yuki³, Kousaku Kawashima¹, Shuichi Sato³, Kyoichi Adachi⁴, Hiroki Ikeuchi⁵ and Yoshikazu Kinoshita¹

Abstract

Systemic AA amyloidosis is a complication of various inflammatory diseases including Crohn’s disease (CD). Amyloid nephropathy is the most common clinical presentation of AA amyloidosis leading to renal failure, and affected patients often require hemodialysis and ultimately renal transplantation. We herein report the successful use of infliximab as maintenance therapy for amyloid nephropathy in a patient with CD. In the present patient, surgical treatment and infliximab infusion immediately induced a remission of CD, and scheduled infliximab therapy successfully maintained the patient’s stable condition for three years, with a significant decrease in the serum creatinine level.

Key words: Crohn’s disease, amyloid nephropathy, infliximab

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Introduction

Crohn’s disease (CD) is a chronic intestinal immune-mediated disorder often associated with several clinical complications involving organs outside the alimentary tract. Systemic AA amyloidosis is a complication of various inflammatory diseases, including CD (1). Furthermore, renal failure resulting from amyloid nephropathy is a common cause of death in CD patients (2). Recently, infliximab, a monoclonal antibody against tumor necrosis factor (TNF)-α, has been recognized to be effective for treating CD (3). However, there are few clinical reports showing the therapeutic effects of infliximab in patients with amyloid nephropathy associated with CD. We herein report the successful use of infliximab as maintenance therapy for amyloid nephropathy in patient with CD.

Case Report

A 34-year-old Japanese woman was diagnosed with ileocolonic CD at 17 years of age based on her clinical symptoms, and typical colonoscopy (Fig. 1A) and histological findings. After receiving this diagnosis, the patient was treated with an elemental diet, in addition to the administration of 5-aminosalicylic acid (5-ASA) and corticosteroids, although these therapies were not fully effective. In June 2009, the intestinal inflammatory lesions recurred, along with multiple perianal abscesses and a rectovaginal fistula (Fig. 1B). In addition, mild renal dysfunction (creatinine: 1.01 mg/dL) with proteinuria appeared. For induction therapy, we initially selected surgery, and ileocecal resection, rectum amputation and colostomy were performed in January 2010. Two weeks after the operation, an increased level...
of creatinine (2.53 mg/dL) was detected with exacerbation of proteinuria. To clarify the cause of the renal dysfunction, a renal biopsy was performed in February 2010. Widely spread amyloid deposits were observed in renal histological sections (Fig. 2A-a) with deposition of amyloid AA proteins confirmed on immunohistochemistry (Fig. 2A-b). However there was no amyloid deposition in the colonic mucosa. No cardiac or liver dysfunction was clinically observed. To exclude other inflammatory and collagen diseases associated with amyloid nephropathy, we performed radiological examinations and blood tests to detect various biochemical and immune markers, which revealed no other diseases. Based on these findings, we ultimately diagnosed the patient with secondary renal AA amyloidosis associated with CD. Because controlling CD is essential for treating renal amyloidosis, we administered infliximab. Prior to the infliximab infusion, laboratory tests showed the following results: leukocytes: 7,660/μL, hemoglobin: 10.5 g/dL, platelets: 41.8×10^8/L, albumin: 3.2 g/dL, creatinine: 2.06 mg/dL, C-reactive protein (CRP): 0.20 mg/dL, ESR: 134 mm, serum amyloid A (SAA): 58 μg/dL and urine protein: 2.0 g/day. The patient received initial infusions of infliximab (5 mg/kg at 0, 2 and 6 weeks) as induction therapy beginning in March 2010, after which scheduled infliximab infusions (every eight weeks) were continued until the writing of this study. This therapeutic regimen successfully maintained the patient’s CD disease condition and renal function for at least two years (Fig. 2B). In January 2013, the findings of urine protein became negative and the results of laboratory tests significantly improved (creatinine: 1.09 mg/dL, CRP: 0.06 mg/dL, SAA: 7 μg/dL).

Discussion

AA type amyloidosis occurs in patients with chronic in-
Inflammatory diseases, such as rheumatoid arthritis (RA), ankylosing spondylitis, juvenile idiopathic arthritis and inflammatory bowel disease (IBD). Amyloid A protein is synthesized primarily in the liver under the production of inflammation-related cytokines, after which it is deposited in various organs. Amyloid nephropathy is the most common clinical presentation of AA amyloidosis leading to renal failure, and affected patients often require hemodialysis and ultimately renal transplantation. In CD patients, the prevalence of systemic AA amyloidosis is relatively low (0.5-6%) (1), although renal AA amyloidosis is one of the most common causes of death in such cases (2).

In the present patient, proteinuria and a low-grade increase in the creatinine level were observed approximately six months prior to intestinal resection. However, we were unable to diagnose the patient with secondary amyloidosis at that time. The initial diagnosis was renal amyloidosis after transient exacerbation of the renal function was observed following surgery. Since kidneys with amyloid deposition can easily become damaged by various systemic factors, we speculate that the surgical procedures influenced the transient exacerbation of the renal function in this case.

In previous reports of amyloid nephropathy associated with CD, amyloid deposition was observed in the intestinal mucosa in most patients. Although we examined the colo-rectal and ileal biopsy samples obtained prior to surgery, no amyloid deposition was detected in the histological sections. In addition, we subjected the surgically resected intestinal samples to conventional and specific staining to detect mucosal amyloid deposition, the results of which also showed no intestinal amyloid deposition. In patients with secondary amyloidosis associated with inflammatory diseases, amyloid A proteins synthesized in the liver are deposited in various organs. In the present case, we speculate that synthesized amyloid proteins were predominantly deposited in the kidneys rather than other organs, although the precise mechanism remains unclear. Gastroduodenal endoscopy and biopsies of the duodenal mucosa have been reported to be sensitive for diagnosing amyloidosis (4, 5); we did not perform these tests. In addition, conducting a histological examination of the duodenal mucosa may have been useful for confirming the presence of intestinal amyloid deposition in this case.

Selecting an effective therapeutic approach to reduce amyloid A protein production is essential for preventing secondary amyloidosis in patients with various inflammatory diseases. Since long-term and uncontrolled intestinal inflammation can induce amyloid A protein production, appropriate anti-inflammatory therapy should be administered to prevent amyloid nephropathy in CD patients. Recently, infliximab, an anti-tumor necrosis factor (TNF)α agent, has become widely used in both induction and maintenance therapy to treat several immune-mediated disorders, including CD, due to its strong anti-inflammatory effects (3). It is well known that secondary amyloidosis occurs in patients with poorly controlled RA. Previous studies have demonstrated that infliximab therapy is useful for treating amyloid nephropathy associated with RA, although its curative effects vary (6, 7). Furthermore, several recent case reports have demonstrated the effects of anti-TNF-α therapy in patients with amyloid nephropathy associated with CD (8-13) (Table). In these reports, the therapy induced rapid responses in proteinuria accompanied by the suppression of disease activity, although the serum creatinine level was not always reversible, even after the administration of infliximab. In the

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Sex</th>
<th>Anti-TNFα therapy</th>
<th>Concomitant therapy</th>
<th>Follow-up</th>
<th>Proteinuria</th>
<th>Serum Creatinin (mg/dL) Before treatment</th>
<th>Ref.</th>
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<td>2006</td>
<td>Iizuka M</td>
<td>Male</td>
<td>IFX</td>
<td>PSL, DMSO</td>
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<td>no reported</td>
<td>4 2 8</td>
<td></td>
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<td>Male</td>
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<td>AZA, Colchicine</td>
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<td>9</td>
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<tr>
<td>2008</td>
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<td>Male</td>
<td>IFX</td>
<td>5-ASA, AZA</td>
<td>8 weeks / Alive</td>
<td>improvement</td>
<td>2.2 2 10</td>
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<tr>
<td>2010</td>
<td>Fidalgo C</td>
<td>Male</td>
<td>Switch from IFX to ADA</td>
<td>no reported</td>
<td>8 months / Alive</td>
<td>no change</td>
<td>normal range 11</td>
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<td>5-ASA, Metronidazole</td>
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<td>improvement</td>
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<td>2012</td>
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<td>Male</td>
<td>IFX</td>
<td>AZA</td>
<td>4 years / Alive</td>
<td>improvement</td>
<td>1.7 1.5 13</td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>This case</td>
<td>Female</td>
<td>IFX</td>
<td>5-ASA, PSL</td>
<td>2 years / Alive</td>
<td>improvement</td>
<td>2.06 1.06</td>
<td></td>
</tr>
</tbody>
</table>

IFX: Infliximab, ADA: adalimumab, DMSO: Dimethylsulfoxide, 5-ASA: 5-aminosalicylic acid, AZA: Azathioprine
present case, surgical treatment and infliximab infusion immediately induced a remission of CD, and scheduled infliximab therapy successfully maintained a good disease condition for at least three years, with a significant decrease in the serum creatinine level. We speculate that resection of the involved intestinal lesions followed immediately by the administration of infliximab therapy effectively suppressed the disease activity and contributed to the improvement of amyloid nephropathy in our case. Further studies are needed to clarify the effects of infliximab in patients with secondary amyloidosis associated with CD.

The authors state that they have no Conflict of Interest (COI).

References