CASE REPORT AND LITERATURE REVIEW

Rheumatology Quarterly

DOI: 10.4274/qrheumatol.galenos.2023.15870
Rheumatology Quarterly 2023;1(4):169-73

INFLIXIMAB TREATMENT OF CROHN'S DISEASE AND SECONDARY AMYLOIDOSIS: CASE REPORT AND LITERATURE REVIEW

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Abstract

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) that affects the digestive system from the mouth to the ans. Joint involvement is common among extraintestinal findings. Renal involvement is seen in IBD and often in the form of nephrolithiasis, tubulointerstitial nephritis, glomerulonephritis, and amyloidosis. Secondary amyloidosis is a rare but serious complication of CD. In this case report, we present a 58-year-old male patient with CD who developed nephrotic syndrome due to renal amyloidosis. Renal functions and general condition of this patient, who was being treated with infliximab (IFX), were good in the follow-up. Here we review similar cases with successful treatment with IFX. In this case, we wanted to emphasize the early recognition of amyloidosis and rapid initiation of IFX treatment.

Keywords: Crohn's disease, renal failure, amyloidosis, infliximab

INTRODUCTION

Crohn's disease (CD) is an inflammatory bowel disease (IBD) in which transmural inflammation can affect the digestive tract, from the oral cavity to the anus, and is characterized by skip lesions. IBD is a multisystemic disease, with extraintestinal manifestations ranging from 21% to 36%. The most frequently involved organs are the joints (peripheral arthritis, sacroiliitis, ankylosing spondylitis), skin, eyes, liver, and biliary tract (1).

The intestinal joint relationship was first described in 1922, and the presence of sacroiliitis in patients was also described in the late 1950s (2). Intestinal dysbiosis and increased intestinal permeability due to local inflammation are believed to play a role in this pathogenesis. Luminal epithelial inflammation initiates an inflammatory cascade, followed by the translocation of immune complexes to the joints. Most extraintestinal manifestations are directly related to ongoing intestinal activity (3).

Chronic diarrhea, bloody stools, abdominal pain, fever, weight loss, weakness, and perianal disease (pain, abscess, or fistula) can be seen in the IBD clinic. In the laboratory, elevated acute phase reactants, anemia, low albumin, and electrolytes are also clinical findings (1,4). Renal involvement is seen in patients with IBD and is often in the form of nephrolithiasis, tubulointerstitial nephritis, glomerulonephritis, and amyloidosis (5). Amyloidosis occurs when insoluble fibrillar proteins aggregate in the extracellular tissue of various organs and eventually cause dysfunction. Secondary amyloid A (AA) amyloidosis can occur as a result of many chronic inflammatory diseases, including IBD. The incidence of secondary AA amyloidosis varies from 0.3% to

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Received: 26.10.2023 **Accepted:** 18.12.2023

10.9% in patients with CD. Amyloidosis is a rare but important complication, and the presence of renal amyloidosis may be more prognostic than the underlying disease (6).

Here, we present a male patient with CD who first presented with arthritis and then developed nephrotic syndrome due to renal amyloidosis. He was successfully treated with infliximab (IFX) with a good response and absence of complications.

CASE REPORT

A 58-year-old male had right knee pain and swelling as the first complaint, which started 10 days ago and gradually increased. In his history, knee pain was severe in the mornings and was accompanied by stiffness for approximately an hour. He stated that he took painkillers when his pain was severe and benefited from them. The patient had no history of trauma, infection, or family history of autoimmune or autoinflammatory disease.

On musculoskeletal examination, the bilateral knee was painful and swollen with movement, consistent with active arthritis. The patient's left knee effusion was aspirated by ultrasonography, and fluid analysis (culture-staining-crystal) was performed. Septic arthritis was ruled out, and no crystals were found.

Laboratory examinations showed moderate leukocytosis and rising levels of erythrocyte sedimentation rate: 67 mm/hour (n=0-20) and C-reactive protein (CRP): 19.8 mg/dL (n=0-5). Blood urea nitrogen, creatinine, and liver function tests were all normal, and rheumatoid factor and anti-cyclic citrullinated peptide tests were negative.

A non-steroidal anti-inflammatory drug was started with a preliminary diagnosis of undifferentiated peripheral arthritis. Due to bilateral ankle swelling in the follow-ups, sulphasalazine (500 mg 2x2/day) was added to the treatment. Two months later, when the patient's arthritis persisted and he could not tolerate sulphasalazine well, he was treated with methotrexate (15 mg/week).

The patient was referred to gastroenterology after 2 months because of weight loss (6 kg/month) and diarrhea. The patient who did not undergo colonoscopy had severe abdominal pain, watery diarrhea 7-8 times a day, and a weight loss of approximately 15 kg after three months. In the laboratory values of the patient, was 716 U/L and lactate dehydrogenase was 405 U/L. Human leukocyte antigen was negative. Abdominal computed tomography showed that the liver size increased by 20 cm, and intra- and extrahepatic bile ducts were evaluated as normal. He underwent endoscopy and colonoscopy. Endoscopy was within the normal range. Colonoscopy revealed edematous and hyperemic descending colon mucosa and rectosigmoid colon. Histopathological examination showed ulcerous inflammation in a microscopic focus and reactive and hyperplastic changes in a few crypts around the ulcer. A diagnosis of CD was made for the patient, who was managed with corticosteroids followed by azathioprine (2.5 mg/kg).

The patient was followed up for 6 months until he was admitted again because of weight loss (10 kg/month) and peripheral edema in both lower extremities. Laboratory examinations revealed creatinine levels of 2.21 mg/dL and urinary protein excretion of 6.98 g/day. The serum albumin level was 2.4 g/dL. A kidney biopsy was performed because it was suspicious of secondary amyloidosis. Congo red-stained cells were examined by light microscopy and polarized light, which showed amyloid deposits. He was treated with intravenous IFX (5 mg/kg at 0, 2, and 6 weeks). The patient has been receiving IFX treatment regularly for three years. While serum creatinine (2.35 mg/dL) was at the same level, urinary protein excretion (3.7 g/day) also decreased; before treatment, it had been 6.98 g/day. The patient's clinical and general condition has been good since treatment.

DISCUSSION

Crohn's disease is characterized by chronic recurrent intestinal inflammation and is among the spondyloarthritis (SpA) group of diseases known as enteropathic arthritis. In SpA patients, 25-49% of subclinical inflammation is seen with ileocolonoscopy, and this rate increases to 50-60% with microscopic examination (7).

Findings of chronic inflammation in SpA, high CRP levels, radiological sacroiliitis, and peripheral arthritis are considered risk factors for IBD (8).

Musculoskeletal manifestations occur in approximately 40% of patients with IBD and are the most common extraintestinal manifestations. Peripheral arthritis is seen in 20% of Crohn's patients and is classified as type 1 or type 2 peripheral arthritis. In type 1 peripheral involvement, oligoarticular involvement is mostly seen in the lower extremities (most commonly the knee and ankle), and it is a self-limited, non-erosive type of involvement that is closely related to intestinal activity (3,9). Our patient was diagnosed with IBD, which started with monoarthritis and then continued with oligoarthritis in the lower extremity. In this state, there was a clinical similarity to type 1 arthritis. The patient did not describe inflammatory lower back pain, and there was no axial involvement in his imaging.

His general condition deteriorated while he had been followed up for CD, and his treatment was changed when renal AA amyloidosis was detected on suspicion of amyloid secondary to inflammation. Secondary amyloidosis, especially secondary to familial Mediterranean fever, is a rare but serious complication

that can worsen the prognosis of patients with cancer, infection, or chronic inflammatory disease, including IBD and CD. The relationship between IBD and amyloidosis was first described in 1936 (10).

The time interval between the onset of IBD and AA diagnosis is different. In IBD, secondary amyloidosis occurs because of long-term uncontrolled inflammation. AA is usually diagnosed 10-15 years after the diagnosis of IBD, sometimes discovered at the same time as IBD, and rarely identified before the onset of IBD (11).

Anti-tumor necrosis factor (TNF) agents can improve amyloid nephropathy in inflammatory diseases through two mechanisms: 1) by reducing glomerular inflammation and the increase in glomerular permeability to albumin induced by TNF cytokines and interleukin-6; and 2) by reducing the synthesis of acute-phase proteins mediated by the same cytokines.

Basturk et al. (12) predicted secondary amyloidosis to occur as an early complication of CD based on the fact that hypoalbuminemia and proteinuria were detected in a 31-year-old male patient approximately one year after initiation of gastrointestinal therapy.

Amyloidosis is frequently described as a major cause of death in patients with CD, with long-term mortality between 40% and 60% (13). Although there is no definite cure for amyloidosis, the main treatment is to control the disease that causes chronic inflammation, which is a constant source of serum AA. Various therapeutic interventions have been tried, such as azathioprine, colchicine, dimethyl sulfoxide, IFX, and elemental diets, but there is no definitive cure for secondary amyloidosis in CD. Renal transplantation may offer the best prospect for patients who have developed amyloidosis (12,14). Anti-TNF therapy has been an important agent used in CD for a long time. The characteristics of three cases treated with IFX after amyloidosis secondary to IBD (CD) are summarized in Table 1.

In the first case, in which successful results were obtained with the IFX treatment presented by Park et al. (15), amyloidosis was observed differently in the thyroid. Our case was older than the other cases, and the difference between the time of renal amyloid occurrence and the age at diagnosis of the disease was much shorter than that of the other cases.

In the second case, Cabezuelo et al. (16) found that amyloidosis and CD were diagnosed simultaneously, although minor and non-specific digestive manifestations had been present for

Table 1. Comparison of clinical and laboratory features of the patients

	1	2	3	Our case
Age/gender	34-year-old male	33-year-old male	24-year-old male	61-year-old male
Age at diagnosis of IBD	23	18	18	58
Clinical findings	Diffuse abdominal pain, watery diarrhea, and peripheral edema in both lower extremities	Iron-deficiency anemia, gastroesophageal reflux, and postprandial heaviness, without any other gastrointestinal manifestations	Terminal ileitis and right-sided colitis complicated with pararectal fistula, persistent abdominal pain, anemia, and marked peripheral edema in the lower extremities developed due to hypoalbuminemia, small ascites, diarrhea, and severe malnutrition	Lower extremity oligoarticular involvement, followed by diarrhea and weight loss, and peripheral edema in both lower extremities
Laboratory findings	The size of the right lobe of the thyroid was 8.5 cm, and the left was 7.5 cm Proteinuria was 7.3 g/day with a decreased creatinine clearance of 40.4 mL/min	Cr: 1.47 mg/dL; eFGR: 59 mL/min/1.73 m proteinuria: 200 mg/24 hours	Serum amyloid A protein level was increased to 1.082 mg/L, CRP level was increased to 13.0 mg/L, and serum creatinine level was 0.88 mg/dL	Cr: 2.21 mg/dL; urinary protein excretion was 6.98 g/day.
Prior treatments	5-ASA, azathioprine, and metronidazole	Azathioprine at 1-1.5 mg/kg/day	5-ASA and azathioprine	Sulphosalazine, methotrexate, and corticosteroids were followed by azathioprine (2.5 mg/kg)

Table 1. Continued

Amyloid involvement sites	The kidney, colon, and thyroid revealed AA-type amyloid deposits	Renal AA amyloidosis	Renal AA amyloidosis	Renal AA amyloidosis
Time between IBD symptom onset and amyloid development	11 year	15 year	6 year	3 year
Patient's condition after treatment	Improvement of renal function and proteinuria, reduction of thyroid mass, and decrease of SAA protein level	The renal parameters improved, with no major complications of CD or side effects. from the medication	Significant improvement after IFX induction therapy: SAA protein level decreased to 22.5 mg/L (by 97.9%) and CRP to 3.9 mg/L (by 70%); there had been no notable changes in proteinuria (13.2 g/day), but significant reductions in renal function had been noticed during the treatment; a progressive increase in Cr level to 3.69 mg/dL	While Cr. (2.35 mg/dL) was at the same level, urinary protein excretion (3.7 g/day) also decreased The patient's clinical and general conditions were good

IBD: Inflammatory bowel disease, eFGR: Glomerular filtration rate, CRP: C-reactive protein, Cr: Serum creatinine, 5-ASA: 5-aminosalicylate, SAA: Serum amyloid A, IFX: Infliximab, CD: Crohn's disease, AA: Amyloid A

several years. Here, it was emphasized that CD extraintestinal involvement played an important role in the development of amyloidosis, similar to the previous oligoarticular involvement in our patient.

In the third case, a younger patient first developed a pararectal fistula at the age of 18 years. Amyloid-related nephrotic syndrome has emerged. After IFX induction therapy, serum amyloid levels decreased, but proteinuria (13.2 g/day) continued. As can be seen, the other cases were younger than our patient. In our patient, the time between CD and secondary amyloidosis was shorter than that in other cases. All patients tolerated IFX treatment well.

CONCLUSION

Secondary AA amyloidosis may occur because of many inflammatory diseases, and there are opinions that the relationship may be more common in chronic diseases than previously thought. Renal amyloidosis is a serious cause of mortality. Therefore, close monitoring of the clinical situation and regular urine testing for proteinuria will be helpful for the early diagnosis of amyloidosis in CD. Early recognition of amyloidosis and appropriate treatment of the underlying disease are essential.

Ethics

Informed Consent: Informed consent was obtained verbally and in writing from the patient and his relatives.

Authorship Contributions

Surgical and Medical Practices: K.A.A., Concept: K.A.A., Ö.A., Design: K.A.A., Ö.A., Data Collection or Processing: K.A.A., Analysis or Interpretation: K.A.A., Literature Search: K.A.A., Ö.A., Writing: K.A.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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