Effect of Infliximab Induction Therapy on Secondary Systemic Amyloidosis Associated with Crohn's Disease: Case Report and Review of the Literature

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ABSTRACT

Secondary systemic (AA) amyloidosis is reported as a serious complication that occurs in long-standing Crohn's disease (CD), with an incidence of 0.3–10.9%. Various therapeutic approaches using medicines and elemental diet have been recomended, but still there are no established standards of treatment for secondary systemic amyloidosis in CD. Only a few studies have shown the role of TNFα ihibitors in the treatment of AA amyloidosis over a long term period. We report the case of a 24-year-old male with CD complicated by AA amyloidosis with renal and gastrointestinal tract involvement treated with infliximab as induction therapy. Intestinal AA amyloidosis progression occurred at the same time with the development of CD as an early complication, whereas duration of CD prior to the diagnosis of renal AA amyloidosis was 6 years. Infliximab therapy (3 infusions) caused a significant decrease of serum amyloid A protein (by 97.9%), C-reactive protein (by 70%), improvement of disease activity index, and CD caused clinical symptoms. At the same time gradual progression of the renal damage (reduction of renal function) was not affected by the treatment. Direct efficacy of infliximab infusions on serum amyloid protein level may support the hypothesis of TNFα induced reduction on the progression of AA amyloidosis described in previous study reports. Targeted histological analysis of tissue biopsy is crucial to clarify the presence of AA amyloidosis in CD induced multiorgan damage cases.

Key words: Crohn's disease — secondary systemic amyloidosis — infliximab.

INTRODUCTION

Crohn's disease (CD) is a heterogeneous, chronic inflammatory disease primarily affecting the gastrointestinal tract. Secondary systemic (AA) amyloidosis is a rare but serious complication and a major cause of death in patients with CD setting long-term mortality between 40% and 60% [1-3]. Renal involvement is the most common manifestation of AA amyloidosis, ranging from nephrotic syndrome to renal failure. Multiple organ damage results from the extracellular deposition of proteolytic fragments of the acute-phase reactant serum amyloid A (SAA) as amyloid fibrils [4].

Infliximab (IFX) is a monoclonal antibody against tumor necrosis factor alpha (TNF-α) and is proven to induce clinical response and remission in CD patients. Unfortunately, only a few case reports have shown the therapeutic effects of IFX on CD-associated amyloidosis [5-9]. In those cases, long term treatment with IFX caused a decrease in SAA circulating levels, thereby stabilizing or even improving renal function. Although the detailed mechanisms are unknown, it has been suggested that TNF-blocking agents might not only reduce the synthesis of amyloid precursors but also decrease the formation of amyloid depositions [10].

We report the case of a young patient with CD complicated by AA amyloidosis, a rapidly progressive nephrotic syndrome and chronic kidney disease (CKD), who was treated with a combination of 5-aminosalicylate (5-ASA), prednisolone, azathioprine and IFX as induction therapy.

CASE REPORT

The patient was a 24-year-old man diagnosed with CD terminal ileitis and right side colitis complicated with pararectal fistula at the age of 18 years (A2 L3 B2 B3 according to Montreal

classification). The patient was treated with 5-ASA and azathioprine maintenance therapy and was clinically stable. He had visited the hospital irregularly for general check-ups without signs of disease progression in the last 6 years.

Last year he was admitted to the Pauls Stradins Clinical University Hospital with CD relapse (Harvey-Bradshaw index = 9): persistent abdominal pain, anemia, marked peripheral edema in lower extremities developed due to hypoalbuminemia, small ascites, diarrhea and severe malnutrition (BMI=18.5 kg/m^2). Laboratory tests revealed the nephrotic syndrome. Renal biopsy was performed and confirmed the suspicion of renal AA amyloidosis with glomerular, vascular and tubular amyloid mass deposition (Figs. 1, 2). Serum amyloid A protein level was increased to 1,082 mg/l (normal value <6.4 mg/l), C-reactive protein (CRP) to 13.0 mg/l (normal value <5.0 mg/l). Laboratory findings showed proteinuria 18.0 g/day, serum creatinine level 0.88 mg/dL and normal estimated glomerular filtration rate (eGFR) 113 ml/min/1.73m^2.

The patient received treatment with corticosteroids (i.v. prednisolone), azathioprine (2.5 mg/kg), enteral and parenteral nutrition (glucose, amino acid solutions, and fat emulsion for infusion) aiming to achieve remission of CD. Additionally, induction treatment with IFX was started to reduce the complications of AA amyloidosis. The stage 2 CKD was confirmed by the level of eGFR (72 ml/min/1.73m^2) before treatment with IFX. The patient received IFX (5 mg/kg body weight) in three repeated infusions at 0, 2, 6 weeks. Treatment with IFX was started 4 months after the diagnosis of renal AA amyloidosis. There have been no adverse or side effects from the medication.

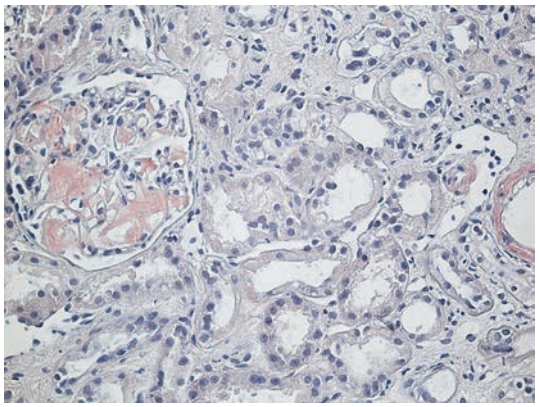

Fig. 1. Extensive affection of glomerular mesangium and vascular wall by amyloid deposits (Congo Red stain x 250).

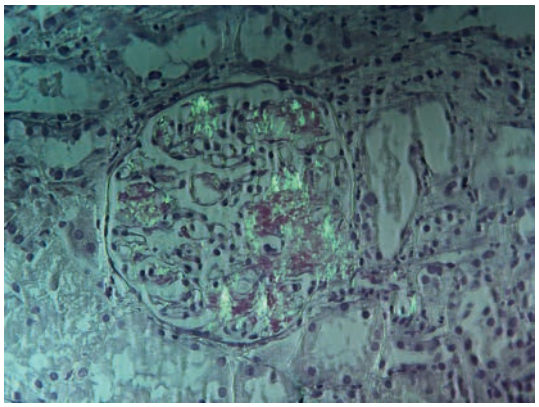

Fig. 2. Glomerular and vascular amyloid deposition. Amyloid deposits stain red but some bundles are pale green (Congo Red stain. Polarized light x 400).

The blood analysis demonstrated 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%). Disease activity index (Harvey-Bradshaw index = 5), malnutrition (BMI = 20 kg/m^2) and quality of life improved. 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 serum creatinine level to 3.69 mg/dL and decreased eGFR confirming the 4th stage of CKD. The patient is currently undergoing maintenance treatment with IFX every 8th week.

The last colonoscopy was performed 5 years before, because the patient had refused it since then. Histological examination of colon biopsy specimen (obtained during colonoscopy) demonstrated amyloid deposits also in the bowel mucosa (Fig. 3). The Congo red positive deposits showed apple-green birefringence in polarized light. The basal aspects of mucosa crypts and vascular beds showed Congo red positivity too. Therefore, we can conclude that intestinal AA amyloidosis occurred with CD either simultaneously or as an early complication of CD.

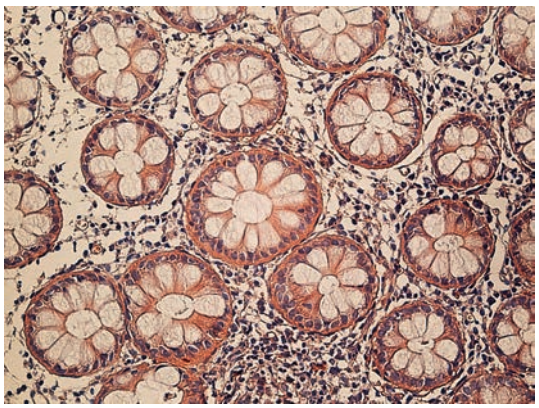

Fig. 3. The colon mucosa crypts show positivity for amyloid deposits with Congo Red stain (x 250).

The lesions found in the colon mucosa and submucosa were compatible with CD: crypt alteration and destruction, lymphoplasmacytic infiltration, occasional presence of neutrophils and eosinophils, adipose tissue accumulation, granuloma formation, and vascular changes (Fig. 4).

DISCUSSION

Secondary systemic (AA) amyloidosis is a long-term complication of several chronic inflammatory disorders, including inflammatory bowel diseases, rheumatoid arthritis, autoimmune syndromes, malignancies and conditions predisposing to recurrent infections [4]. The incidence of the association of AA amyloidosis in patients with CD has been reported to range from 0.3% to 10.9%, showing a wide geographic variation [1, 2, 11-13].

In the literature, the time lapse between the onset of CD and the diagnosis of amyloidosis has been reported to range

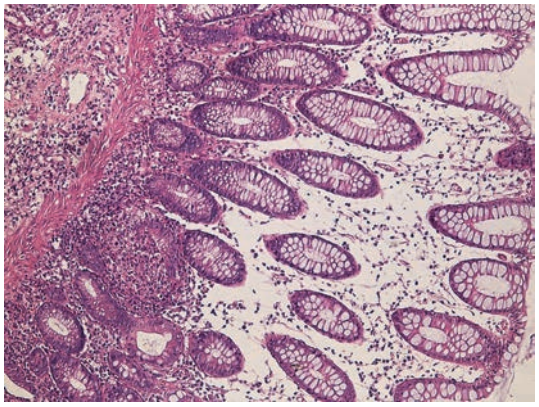

Fig. 4. A prominent inflammatory involvement of colon mucosa, vascular changes in the submucosa (H&E, x 100).

from 1 to 21 years [14, 15]; in exceptional cases, the diagnosis of both clinical entities occurs simultaneously [1]. In our patient, duration of CD prior to renal AA amyloidosis diagnosis was 6 years. Repeated histological examination of biopsy specimen, when renal AA was confirmed, revealed colon amyloid deposits, and, thereby, substantiated that intestinal AA amyloidosis occurred with CD simultaneously or apparently as an early complication of CD.

It has been observed that patients with inflammatory bowel disease who develop AA amyloidosis do not show more extraintestinal manifestations than patients who do not develop amyloidosis [1, 2, 16]. Other extraintestinal complications had not developed in our patient. Studies have demonstrated also that the fistulizing-stenotic form of CD is more often associated with AA amyloidosis [1, 2]. The patient reported by us had a combined fistulizing and stricturing disease phenotype.

Abnormalities of the connective tissue, such as adipose tissue changes, fibrosis, smooth muscle proliferation, neuronal and vascular changes, are common microscopic features of CD [17]. Subcompensated stenosis in the ileocecal region was observed in our patient during colonoscopy. According to the literature data, strictures show marked expansion of the muscularis mucosae by an irregular increase in the number of smooth muscle cells and the presence of collagen, laminin and tenascin confirmed by histopatology and immunohistochemistry [18].

It is interesting that the colon biopsy specimen from our patient demonstrated mucosal adipose tissue accumulation and macrophage infiltration. During the last decade adipose tissue has been shown to contribute to the endocrine signaling via secretion of numerous adipocytokines, such as adiponectin, resistin, leptin, and local tissue mediators such as pro-inflammatory cytokines IL-6, TNF-a, and others. Leptin has been suggested to have a pro-inflammatory effect in many diseases such as inflammatory bowel disease, rheumatoid arthritis and atherosclerosis [18]. Another important adipocytokine, adiponectin, can reduce TNF-α secretion in macrophages, thereby presenting anti-inflammatory properties [19]. The presence of inflammatory cells in the adipose tissue suggests these cells as another likely source of potential contributors to inflammatory changes observed in CD [20].

The main objective of the treatment is to achieve remission of CD and to prevent further progression of AA amyloidosis induced complications such as chronic kidney disease. Various therapeutic attempts have been tried but there is no definite treatment for secondary amyloidosis in CD [21].

In this rare CD case combined with AA amyloidosis, a significant decrease of serum amyloid A protein level was achieved by the IFX induction treatment. Large cohort studies have shown that renal prognosis and survival significantly correlate with SAA concentration during follow-up [22]. It has been demonstrated that elevated levels of SAA indicated poor prognosis, and even a mild raise in SAA levels increased five fold the risk of death [22].

An expected stabilization of renal function after IFX induction therapy was not achieved due to irreversible systemic amyloidosis damage. Theoretically, long-term IFX treatment may delay the progression of amyloidosis and prevent further progression of the renal failure.

Renal transplantation may offer the best prospect for patients with CD who developed amyloidosis and end-stage renal failure [23]. A recent multicenter study showed that the recurrence rate of AA amyloidosis nephropathy after renal transplantation was 14% but the overall 5- and 10-year patient survival were significantly lower for the AA amyloidosis patients than for a control group of renal transplant recipients [24].

CONCLUSION

It is important to recognize and diagnose systemic amyloidosis, especially since TNF-α inhibitors have been proposed as a suitable treatment. Therefore, histopathological examination of a bowel biopsy specimen has to be more thorough and complete, allowing the diagnosis of this serious complication.

Conflicts of interest. None to declare.

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