LETTER TO THE EDITOR

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Cyclophosphamide therapy for secondary amyloidosis in a patient with juvenile idiopathic arthritis unresponsive to tumor necrosis factor α inhibitor therapy

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To the Editor,

Secondary amyloidosis is an important complication of several chronic inflammatory conditions, including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), and ankylosing spondylitis [1]. It has been demonstrated biochemically that amyloidosis results from abnormal binding of proteins, which are deposited as insoluble fibrils in tissue, leading to disruption of their normal function. An underlying disease of long duration and high activity is the most important factor associated with development of secondary amyloidosis [1]. Treatment of secondary amyloidosis involves suppression of the underlying inflammatory condition. Cytotoxic agents such as cyclophosphamide, chlorambucil, and azathioprine have been shown to have activity against secondary amyloidosis. Tumor necrosis factor α (TNF-α) inhibitor is reportedly effective in controlling the progression of renal amyloids in patients with RA and JIA [2]. Recent biochemical research revealed that synthesis of serum amyloid A (SAA) is controlled by proinflammatory cytokines such as interleukin 6 (IL-6), TNF-α, and IL-1. Control of SAA synthesis could be beneficial to the treatment of amyloidosis, and anti-cytokine therapies are effective in this regard. In particular, inhibition of IL-6 is critical to suppression of SAA production [3]. Recently, the use of biologic agents instead of cytotoxic agents has increased due to their enhanced tolerability and effectiveness [3]. In this paper, we report the use of cyclophosphamide therapy for secondary amyloidosis in a patient with JIA unresponsive to TNF-α inhibitor therapy.

A 32-year-old woman was hospitalized for generalized edema and chronic diarrhea. At 12 years of age, she had been diagnosed, based on the International League of Associations for Rheumatology classification criteria, with JIA of the polyarticular, rheumatoid factor-negative type. She had been treated with several disease-modifying RA drugs, including the TNF-α inhibitor adalimumab, 6 months prior. These failed to achieve complete suppression of disease activity. She presented with clinical symptoms of gradually increasing generalized edema and continuous diarrhea of several weeks' duration. Her medical history

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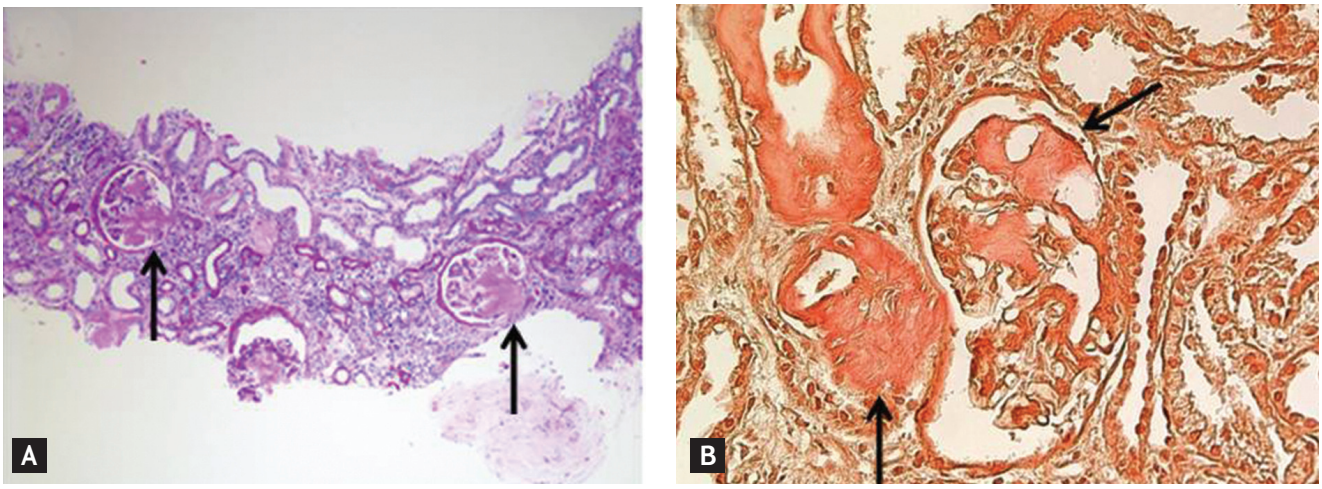

Figure 1. Pathologic findings of renal biopsy. Deposition of amyloid in glomerular mesangium and interstitium (arrows) (A, H&E, ×100; B, Congo Red staining, ×400).

was negative for hypertension and renal disease other than JIA. She did not smoke or drink alcohol. Upon physical examination, the patient was normotensive with a regular pulse rate, her lung sounds were clear, her heart sounds were regular, and her abdomen was soft; however, her bowel sounds were mildly increased. She had grade 3 pitting edema on a pretibial lesion. Neurologic examination was normal, and an electrocardiogram showed a normal sinus rhythm.

Laboratory test results revealed the following: proteinuria (+++), blood (trace), erythrocytes in the urine (1 to 4/high power field), and a 24-hour quantitative protein level of 3,782 mg/day. Her serum creatinine level was elevated to 2.70 mg/dL, and her fractional excretion of sodium was 2.34. Her hemoglobin level was 11.5 g/dL, hematocrit concentration was 37.8%, white blood cell count was 9,590/mm^3 (neutrophils, 79.6%), platelet count was 537,000/mm^3, sodium level was 138 mEq/L, potassium level was 4.0 mEq/L, total protein level was 5.2 mg/dL, albumin level was 1.7 mg/dL, and procalcitonin level was 0.264 ng/mL (reference range, 0 to 0.5). No white blood cells were evident upon microscopic examination of the patient's stool. The results of other tests were as follows: antinuclear antibody (–), rheumatoid factor 10.4 IU/mL (reference range, 0 to 15), anti-cyclic citrullinated peptide antibody (–), free kappa light chain 67 mg/L, free lambda light chain 229 mg/dL, hepatitis B surface antigen (–), hepatitis B surface antibody (+), anti-hepatitis C virus antibody (–), and human immunodeficiency virus test (–).

The patient had nephritic-range proteinuria and an elevated serum creatinine; therefore, she underwent a renal biopsy. Light microscopy showed homogenous amorphous material in the glomerular mesangium and interstitium. Congo red staining was positive with birefringence in the arteries, arterioles, interstitial areas, and mesangium of the glomeruli (Fig. 1). Duodenal endoscopy and colonoscopy were performed to identify involvement of other organs. Amorphous material was seen in the mucosa and submucosa of the duodenum and in the muscular layer of the wall of the rectum (Fig. 2). Neither cardiac wall thickness nor a granular sparkling appearance was identified by echocardiogram.

Based on the results of renal, duodenal, and rectal biopsies, we diagnosed secondary systemic amyloidosis as a result of long-standing JIA. Due to the resistance to previous TNF-α inhibitor therapy and elevation of the serum creatinine level, treatment with cyclophosphamide and a glucocorticoid was started. Cyclophosphamide pulse therapy at a dose of 500 mg/m^2 was administered intravenously at 1-month intervals for a 6-month period. After 6 months of treatment, the serum creatinine had normalized, proteinuria had been reduced (1,119 mg/day), the C-reactive protein level was 0.1 mg/dL, and the edema had disappeared. Additionally, the patient's disease activity was improved after 6 months of cyclophosphamide treatment. Based on the European League Against Rheumatism response criteria, the patient showed a good response range. Her laboratory findings on admission and at the 6-month

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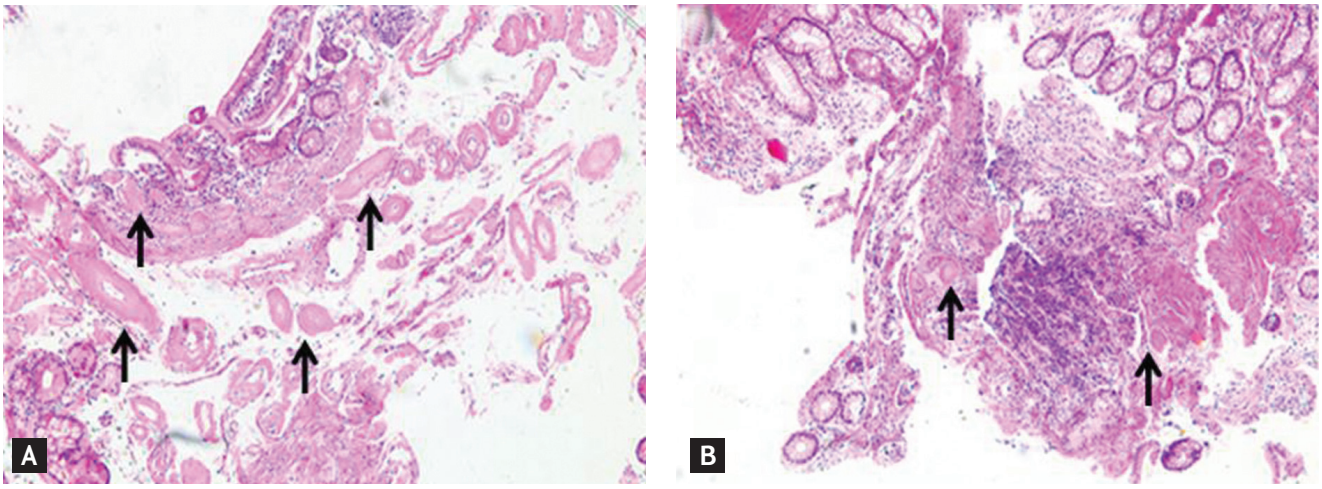

Figure 2. Pathologic findings of endoscopic biopsy. (A) Deposition of amyloid in mucosa and submucosa of duodenum and (B) in muscular layer of rectum (arrows; H&E, ×40).

Table 1. Laboratory findings from baseline to 6 months after cyclophosphamide plus glucocorticoid treatment in secondary amyloidosis patient

Follow-up, mon	Erythrocyte sedimentation rate, mm/hr	C-reactive protein, mg/dL	Proteinuria, mg/day	Serum creatinine, mg/dL	Serum albumin, g/dL
Admission	66	1.88	3,792	2.70	1.77
2	39	0.08	2,244	1.30	2.28
4	31	0.42	1,230	0.99	2.49
6	19	0.13	1,119	1.13	2.95

follow-up from the nephrology clinic are presented in Table 1. At the time of this writing, the patient was undergoing treatment with an oral steroid at 30 mg/day and hydroxychloroquine at 400 mg/day.

Secondary systemic amyloidosis is a serious complication of chronic inflammatory disease and results in the deposition of amyloid fibrils in various organs [4]. These fibrils are derived from circulating acute-phase reactant SAA protein. Currently, the most common cause of amyloidosis is inflammatory arthritis; e.g., RA and JIA. It is estimated that 5% of adults with RA will develop secondary amyloidosis. The main feature of amyloidosis at diagnosis is renal dysfunction, and the most common finding is proteinuria, which is not necessarily present at disease onset. Traditional management of secondary amyloid has been to target the disease underlying the inflammation [4].

Several case studies have shown benefits with the use of methotrexate and azathioprine or prednisolone in patients with rheumatoid-associated amyloid A (AA) amyloidosis, but the response is often slow. Cytotoxic agents, such as chlorambucil and cyclophosphamide, have been shown to be beneficial in clinical trials, but these drugs are associated with myelotoxicity, leukemia, and sterility. Moreover, several trials have reported that the TNF-α inhibitor etanercept is more effective than cyclophosphamide [3]. In recent years, the use of biologics with activities against proinflammatory cytokines such as TNF-α, IL-1, and IL-6 for diseases such as RA, psoriatic arthritis, and ankylosing spondylitis has increased. This class of drugs has become more clinically available. TNF-α may be involved in the deposition of amyloid and the development of nephrotic syndrome. TNF-α stimulates hepatocytes to produce SAA and has also been shown to have a direct inflammatory effect on the glomerular basement membrane. Elevated levels of SAA in RA are known to predispose to amyloidosis. Anti-TNF-α therapy suppresses SAA,

and maintaining an SAA level of < 10 mg/L is associated with potential recovery of amyloidotic organs in AA amyloidosis. IL-6 blockade using the humanized anti-IL-6 receptor antibody tocilizumab may be more effective than TNF blockade in terms of normalizing SAA levels in patients with rheumatic disease, suggesting it to be a more effective strategy for treating AA amyloidosis in these disorders [5].

Our patient exhibited marked resistance to treatment with a steroid and TNF-α inhibitor, and she had nephrotic-range proteinuria and reduced renal function. We administered cyclophosphamide plus a glucocorticoid instead of other biologic agents and achieved a good outcome. Use of biological modifiers represents an important therapeutic strategy for secondary amyloidosis, but cases unresponsive to TNF-α treatment are frequently reported. In such cases, cyclophosphamide should be considered as a second-line therapy.

Keywords: Cyclophosphamide; Amyloidosis; Juvenile idiopathic arthritis

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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