Tocilizumab Resistant Nephrotic Syndrome and Protein Losing Gastroeneropathy Due to Amyloidosis in Chronic Kidney Disease

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ABSTRACT

We report the case of a 75-year-old woman who suffered chronic kidney disease with severe nephrotic syndrome (NS) and protein losing gastroenteropathy due to tocilizumab (TCZ), anti-IL-6 receptor monoclonal antibody resistant amyloidosis. The patient was admitted for fever, dyspnea and anasarca. Chest x-ray and computed tomography showed massive pleural effusion. She had past history of rheumatic arthritis treated with methotrexate and TCZ before admission. Presenting symptoms almost consistently involved hypoalbuminemia due to severe NS and protein losing diarrhea, resulting hypovolemia and prerenal acute kidney injury. Due to infectious disease, we could not continue TCZ treatment.

Light microscopic findings of biopsy specimens from gastrointestinal tract revealed Congo red positive staining area, meaning gastrointestinal amyloidosis. Based on these findings, the patient was diagnosed with gastrointestinal and possible renal amyloidosis in chronic kidney disease, resulting protein losing gastroenteropathy and end-stage renal disease.

TCZ is widely used for treatment of secondary (AA) amyloidosis with rheumatic arthritis. However, TCZ resistant renal and gastrointestinal amyloidosis is not a common.

Keywords: Amyloidosis, chronic kidney disease (CKD), nephrotic syndrome (NS), protein losing gastroenteropathy, tocilizumab (TCZ)

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INTRODUCTON

Secondary (AA) amyloidosis induced-nephrotic syndrome (NS) and protein losing gastroenteropathy with rheumatic arthritis (RA) could deteriorate renal function (1-3). AA amyloidosis induced-NS is usually severe and shows immune-suppressive therapy resistant.

Recent studies suggest that interleukin (IL)-6 plays a significant role in the development of AA amyloidosis induced-NS and protein losing gastroenteropathy (4, 5). Also, excessive production of IL-6 increases vascular endothelial growth factor (VEGF) in the kidney which could affect the glomerular permeability and could be critical for maintenance of the glomerular filtration barrier (6-9). The main treatment strategy of AA amyloidosis is the decreases in inflammatory states which could induce multiple organ disorder (10). Tocilizumab (TCZ) is a human monoclonal antibody directed against the receptor for IL-6 (IL-6R) (11). Basically, this biologics could reduce the production of serum amyloid and the deposition of amyloid fibrils in several organs including kidney and gastrointestinal tract (6, 12, 13). However, in our case, TCZ treatment could not decrease proteinuria and improve protein losing gastroenteropathy.

CASE REPORT

A 75-year-old woman suffered from rheumatic arthritis for more than 35 years. Also, she was diagnosed with chronic kidney disease (CKD) G3b (eGFR: 40.1ml/min/1.73m^2) 2 years ago. She

had been treated with methotrexate and TCZ before admission, though AA amyloidosis remained active and proteinuria was not decreased. The renal function went gradually downhill due to CKD. The patient was admitted for high fever, dyspnea, anasarca and diarrhea. When admission, renal function significantly decreased (eGFR: 6.8ml/min/1.73m^2). On physical examination, she had kyphosis, severe edema and low grade fever. Moist crackle was at bilateral lower lung by auscultation. Her blood pressure was 109/73 mmHg and body temperature was 37.1 ºC. She had orthopnea, but did not have jugular venous distention. Family history was not remarkable. The chest x-ray and computed tomography (CT) showed congestion and pleural effusion and atelectasis (Fig.1 A and B).

At first, we guessed the pathogenesis of these symptoms pneumonia accompanied with congestive heart failure. TCZ was terminated and administration of ceftriaxone (1g) was started. However, infectious symptoms were not improved, so that ceftriaxone was switched to imipenem/cystatin (0.25g), minocycline hydrochloride (200mg). Later, klebsiella pneumoniae was detected from blood culture and candida antigen and aspergillus antigen were found to be positive, so that tobramycin (60mg) and micafungin sodium (100mg) were added. Despite a continued therapy, a decline in renal function was observed (eGFR: 3.6ml/min/1.73m^2) and anasarca was not changed. Thus, on the fifth day, hemodialysis was started.

A transthoracic echocardiography showed pericardial effusion and left ventricular

hypertrophy, suggesting cardiac amyloidosis. Due to kyphosis, renal biopsy could not be performed. However, several samples from colon showed deposits of AA amyloid in basal lamina, interstitium around glands, and in artery walls from mucosa or submucosa (Fig.2).

Laboratory examinations showed anemia, hypoalbuminemia and prerenal azotemia. Serum levels of matrix metalloproteinase-3 was elevated (297.2ng/ml). Thyroid function was almost within normal limits (Table 1).

Although intensive therapy; administration of antibiotics and antifungal drugs, and hemodialysis, AA amyloidosis remained active, and diarrhea and malnutrition were worsened. Due to low blood pressure, hemodialysis was terminated and the status went gradually downhill. On the one hundred tenth day, suddenly, respiratory failure and hypoglycemia were occurred and she died on that day.

DISCUSSION

Our patient presented with the symptoms of TCZ resistant NS and protein losing gastroenteropathy in CKD. The result of biopsy samples from colon provided a diagnosis of AA amyloidosis. AA amyloidosis induced-NS and protein losing gastroenteropathy, although infrequent, has been reported, however our case is first report that TCZ resistant AA amyloidosis induced-NS and protein losing gastroenteropathy in CKD.

Like RA, prolonged inflammation increases in pro-inflammatory cytokines (IL-6, tumor necrosis factor (TNF)-α and IL-1) (14-16). They could stimulate serum amyloid A (SAA) synthesis in the liver and play a significant role in the development of AA amyloidosis(17). The extracellular accumulation of proteolytic fragments of the SAA as insoluble amyloid fibrils induces multiple organ damages including kidney (3, 18). Thus, these cytokines could be a significant role in the development of nephropathy. Furthermore, it has been reported that inflammatory cells are recognized in the renal glomeruli before the overt glomerular and interstitial pathologies even in nonimmune renal diseases(19). Thus, induction of anti-inflammatory cytokines could be helpful. As in our case, when the initiating inflammation state could not be controlled, suppression of SAA is not sufficient, and deposition in the organs persists, resulting disease progression. Also, IL-6 could regulate the production of VEGF, which could affect the glomerular permeability and could be critical for maintenance of the glomerular filtration barrier (9).

TCZ is a humanized anti-human IL-6R monoclonal antibody that binds to the soluble and membrane-bound IL-6R (11). TCZ inhibits IL-6 pro-inflammatory activity, decreasing SAA production, and interferes with T-cell function (20). Thus, TCZ could be a biological therapy for autoimmune and chronic inflammatory diseases; it has been mainly used for the treatment of RA and systemic juvenile idiopathic arthritis (21).

Recent reports show that treatment with TCZ dramatically reduces proteinuria and improves renal function (4, 22). This response is mainly derived from TCZ-induced anti-inflammatory effects, resulting decreases in SAA (20). Furthermore, TCZ suppresses IL-6 which effects on the glomerular filtration barrier more directly (4). However, it seems that regression of the existing amyloid could not be recognized quickly; TCZ could decrease SAA or precursors to mature amyloid fibrils have potential effects resulting proteinuria and decrease new amyloid deposits which have a stronger nephrotoxic effects than existing amyloid deposits already exacerbated the organs.

To conclude, we reported a case of chronic kidney disease with severe NS and protein losing gastroenteropathy due to TCZ resistant amyloidosis.

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Table: Laboratory findings

Variable	Value	Variable	Value	Variable	Value
White blood cell count/mL	20,400	Total cholesterol (mg/dL)	225	Proteinase-3 anti-neutrophil cytoplasmic antibody (IU/mL)	<2
Red blood cell count/mL	3,590,000	Sodium (mmol/L)	142	Myeloperoxidase anti-neutrophil cytoplasmic antibody (IU/mL)	<3.5
Hemoglobin (g/dL)	11.5	Potassium (mmol/L)	2.6	Anti-glomerular basement membrane antibody (U/mL)	<7
Platelet count/mL	251,000	Calcium (mg/dL)	8.3	Rheumatoid factor (IU/mL)	29
Asparate aminotransferase (units/L)	10	Phosphorus (mg/dL)	12.5	Matrix metalloproteinase-3	297.2
Alanine aminotransferase (units/L)	2	C-Reactive protein (mg/dL)	13.2	Cyclic citrullinated peptide antibody (U/mL)	3.7
Lactate dehydrogenase (units/L)	251	Immunoglobulin G (mg/dL)	865	Complement component 3 (mg/dL)	123

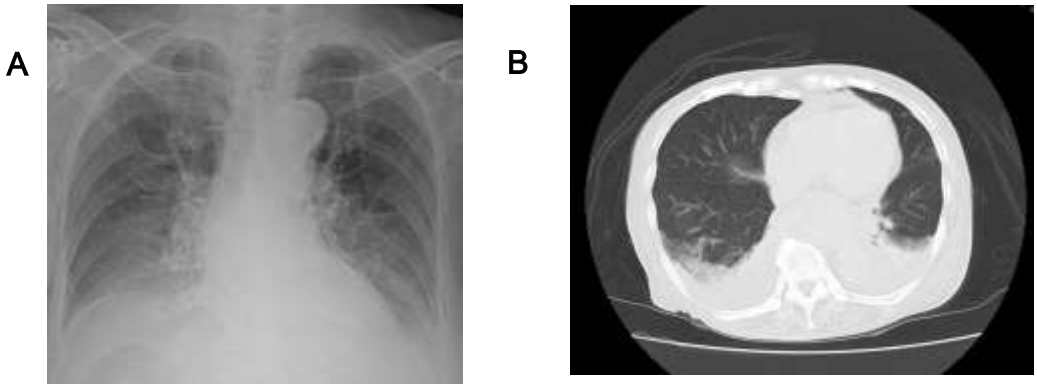

Fig 1: (A) Chest X-ray and (B) CT scan from this case.

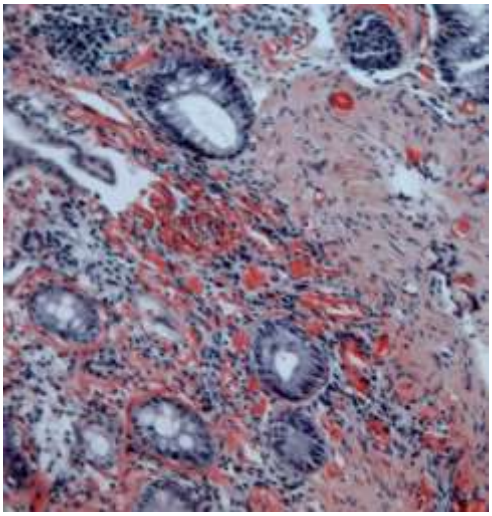

Fig 2: Biopsy from the colon. Light microscopic picture from this case. Congo red stain.