Successful treatment with tofacitinib for renal disorder due to amyloid A amyloidosis and immunoglobulin A nephropathy in a patient with rheumatoid arthritis

Sirs,

Amyloid A (AA) amyloidosis is a rare but serious complication of chronic inflammatory diseases like rheumatoid arthritis (RA), causing progressive organ dysfunction in the kidneys, neurons, or gastrointestinal tract (1).

Tofacitinib is an oral, small-molecule Janus kinase (JAK) inhibitor, used for the treatment of moderate and severe RA (2, 3). Here, we report a case of a 76-year-old woman with RA who developed renal disorder due to AA amyloidosis and immunoglobulin A nephropathy (IgAN). Tofacitinib therapy improved her kidney involvement.

This patient developed RA at the age of 60. Anti-tumour necrosis factor α (anti-TNF-α) agents, infliximab and golimumab, tocilizumab (TCZ), and abatacept (ABA) were administered, in that order, to treat her active RA.

In December 2014, the patient, who was receiving ABA, was admitted to our department due to worsening kidney function. Signs of declining kidney function included a serum creatinine (s-Cr) level of 1.18 mg/dL (normal, 0.41-0.75), a proteinuria of 2.60 g/day (normal, <0.15), and over 100 red blood cells (RBCs) per high power field (/HPF) (normal, <5) with granular and erythrocytic casts.

On admission, her physical examination revealed active polyarthritis and pitting edema around the ankles bilaterally. Blood testing indicated C-reactive protein level of 7.34 mg/dL (normal, <0.30), IgA level of 583 mg/dL (normal, 110-410), and serum AA (SAA) level of 192.9 μg/mL (normal, <8.0). Serum auto-antibodies, including anti-dsDNA and anti-neutrophil cytoplasmic antibodies, were not detected. A renal biopsy revealed mesangial matrix expansion and cell proliferation in the glomeruli (Fig. 1A). Immunofluorescent staining showed mild deposits of IgA (Fig. 1B). Further, Congo red and AA staining revealed AA proteins in the mesangial regions and the small vessel walls (Figs. 1C-D). AA amyloidosis and IgAN were determined to be the cause of renal disorder.

Her therapeutic regimen was changed from ABA to tofacitinib to manage active RA. After the initiation of tofacitinib, her arthralgia immediately disappeared and acute phase reactant levels declined. In addition, urinary abnormalities and kidney dysfunction gradually ameliorated. One year later, RA remained in clinical remission, s-Cr decreased to 0.97 mg/dL, and urinary protein excretion and RBCs were at 0.04 g/day and 1-4/HPF, respectively. Moreover, the levels of IgA and SAA decreased to 301 mg/dL and 8.4 μg/mL, respectively. During the follow-up period, she had received no regular treatment with glucocorticoids.

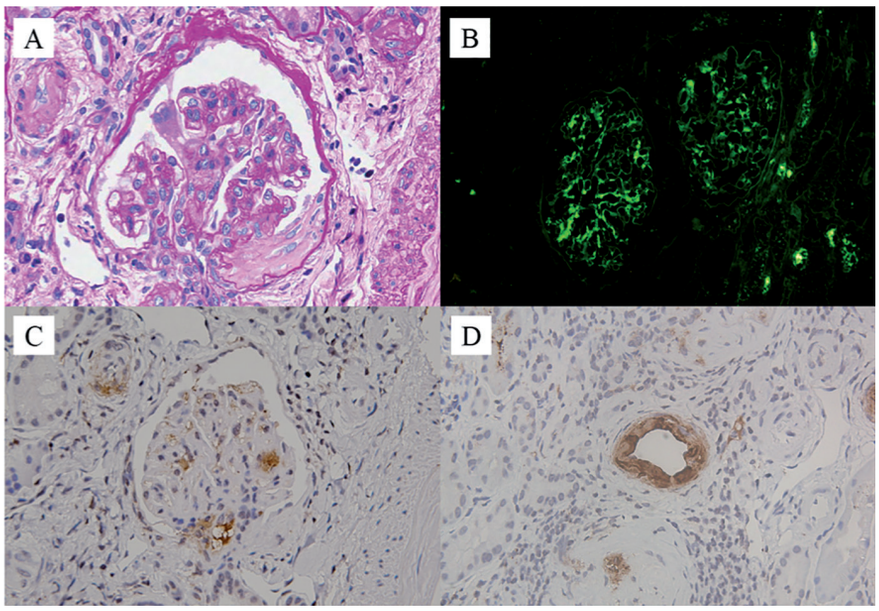

Fig. 1. Findings of renal biopsy.
A: Periodic acid-Schiff stain: mesangial matrix expansion and cell proliferation with fibrous crescent (original magnification, x40);
B: Immunofluorescent stain for IgA: mild positive IgA within the glomeruli (original magnification, x20);
C: Immunostaining for amyloid A (AA) (brown): AA proteins were positive in the glomeruli (original magnification, x40);
D: Immunostaining for AA (brown): positivity of AA proteins in small vessel walls (original magnification, x40).

The production of SAA, related to the development of AA amyloidosis, is driven by the synergistic effects of proinflammatory cytokines, especially interleukin-6 (IL-6) (4). According to Migita *et al*., JAK inhibitors blocked IL-6-induced SAA production from rheumatoid fibroblast-like synoviocytes and hepatocytes (5). Additionally, they reviewed the effects of tofacitinib in reducing the levels of SAA and IL-6 in RA patients (6). JAKs control the signaling pathways of many cytokines other than IL-6 that are involved in immunity, inflammation, and haematopoiesis (7, 8). Based on this evidence, tofacitinib therapy might ameliorate both AA amyloidosis and IgAN. Several retrospective case studies have described the efficacy of anti-TNF-α drugs and TCZ against AA amyloidosis secondary to rheumatic diseases, where TCZ had greater clinical utility than anti-TNF-α therapy (9, 10). In our patient, both anti-TNF-α and TCZ therapies were insufficient to control RA activity. Thus, we could use neither anti-TNF-α agents nor TCZ for treating AA amyloidosis

In this case, we could not exclude the possibility of spontaneous renal improvement. Further, we were unable to investigate the pathological findings of AA amyloidosis and IgAN after tofacitinib treatment. However, judging from the available clinical data, tofacitinib would probably improve renal abnormalities.

In conclusion, treatment with tofacitinib could provide a new immunosuppressive therapeutic strategy for AA amyloidosis and IgAN secondary to rheumatic diseases.

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