

Successful Treatment of Rheumatoid Arthritis-Associated Renal AA Amyloidosis with Tocilizumab

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Rheumatoid arthritis (RA) is associated with systemic inflammation. Poorly controlled inflammation may lead to systemic AA amyloidosis [1,2]. Among pro-inflammatory cytokines, interleukin 6 (IL-6) may play an important role in driving systemic inflammation and thus AA amyloidosis [1, 3].

In AA amyloidosis, AA amyloid protein is produced by hepatocytes, forming insoluble extracellular deposits. Kidneys are most often affected; however, amyloid deposition may also occur in the spleen, liver, heart, adrenal glands, thyroid glands, lungs, and, the gastrointestinal tract. The disease less frequently involves the skin, bones, peripheral nerves, lymph nodes, and synovial membrane. Altogether 7% to 29% of renal biopsies performed in patients with active RA showed amyloid deposits. Predisposing factors include long-standing disease, high disease activity, and inefficient treatment. Early, aggressive treatment, which sets C-reactive protein (CRP) levels almost back to normal, can significantly reduce the incidence of amyloidosis [1-3].

Involvement of kidneys, which is largely irreversible, can range from mild proteinuria and hematuria to severe nephrotic syndrome [1]. Cardiac manifestations include conduction abnormalities, low voltage or restrictive cardiomyopathy. Amyloidosis of the gastrointestinal system causes constipation or diarrhea, malab-

sorption, bleeding, and ulceration [1,3]. In a large autopsy study, Bely and Apathy [2] collected 161 patients with RA who developed AA amyloidosis. In this study, in cases of mild amyloidosis, the disease started earlier and had a longer course, but it did not show significant differences compared to the severe form of the disease. In cases of severe amyloidosis, patients had significantly poorer survival [2].

Shen et al. [4] reported that circulating serum amyloid A (SAA) levels in RA patients were considerably higher than in patients with osteoarthritis, SLE, and healthy controls. SAA levels showed a correlation with RA disease activity (DAS28), erythrocyte sedimentation rate (ESR), and CRP concentrations [3].

PATIENT DESCRIPTION

This case study focuses on a 52-year-old female patient who had shown symptoms of rheumatoid arthritis since 1990. Her previous treatments included gold salts, methotrexate, and later leflunomide and sulphasalazine. In 2010, because of deterioration of her condition an additional etanercept treatment was administered, but after a year she developed erysipelas and as a result her targeted therapy was discontinued. Later intermittent microscopic haematuria and more signs of chronic renal failure occurred and she was diagnosed with renal AA-amyloidosis in 2014. Since IL-6 plays an important role in the synthesis of AA amyloid, anti-IL-6 biological treatment (monthly tocilizumab IV infusions) was introduced in 2015. She had been receiving monthly

IV tocilizumab treatment and IL-6 receptor inhibition resulted in significant improvement not only of her rheumatic condition but simultaneously of her renal function. Her lab results almost normalized with no more signs of hematuria.

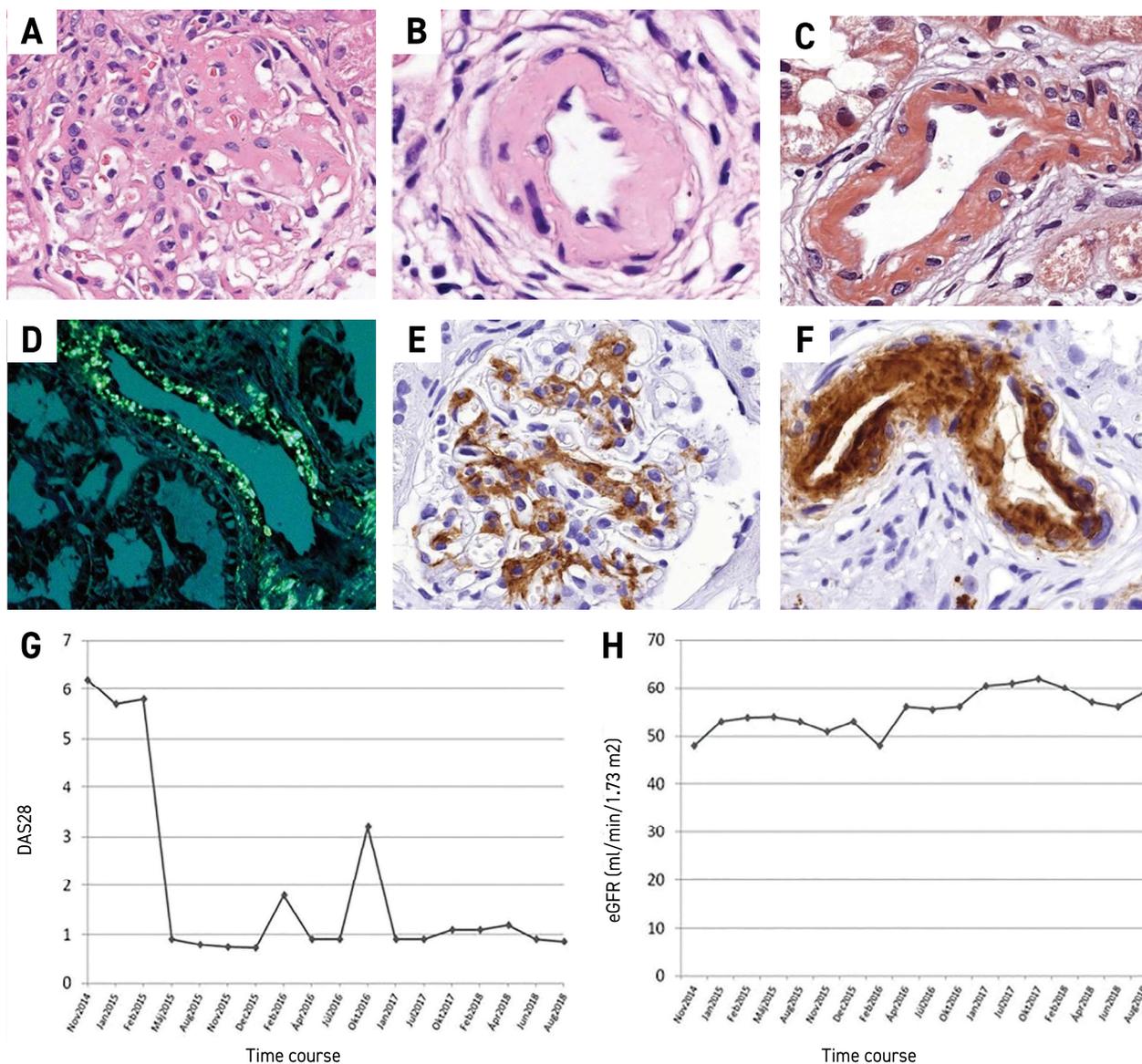
COMMENT

The medical history of our 52-year-old female patient did not include any previous illnesses. Her musculoskeletal symptoms, which mainly affected the small joints of the hands and feet, started in 1990. Her symptoms started as arthralgia and, a few weeks later, significant joint swelling occurred.

Laboratory tests showed signs of systemic inflammation (ESR, CRP) as well as rheumatoid factor seropositivity. Based on the clinical symptoms and laboratory signs, the definitive diagnosis of RA was established. Between 1990 and 1998, she was treated with intramuscularly administered gold salt, which was terminated due to loss of efficacy. Oral methotrexate therapy was initiated at 10 mg/week in 1998. The dose of methotrexate was gradually increased to 20 mg/week; however, this therapy was halted due to severe gastrointestinal side effects. In September 1998, sulfasalazine therapy was initiated, at a dose of 2 × 1000 mg. Later in 2000, it was supplemented by a daily dose of 500 mg chloroquine. This combination of disease-modifying anti-rheumatic drugs (DMARDs) was not fully successful; therefore, in May 2002, there was an attempt to reintroduce a low dose (7.5 mg/week) of methotrexate. However, due

Figure 1. Renal AA amyloidosis secondary to rheumatoid arthritis in our patient

[A] Homogeneous eosinophilic material, amyloid deposition in the glomerulus, it dominantly affects the mesangium (H-E staining), [B] amyloid deposition can be observed in the walls of blood vessels (H-E), [C] amyloid positivity demonstrated by Congo red staining, [D] under polarized light, AA amyloid shows double apple green birefringence, [E,F] immunohistochemistry shows type AA amyloid, It consists of ultrastructurally irregularly falling fibrils with a diameter of 7–10 nm. (microphotographs were provided by Prof. Dr. Éva Kemény, Institute of Pathology, University of Szeged), [G] change of disease activity (DAS28) over time, [H] change of eGFR (ml/min/1.73 m²)



to stomach upset and diarrhea, even this low dose was not well tolerated by the patient. Although parenteral methotrexate was also offered, the patient did not give consent. In November 2002, 20 mg/day of leflunomide and 2 × 1000 mg/day sulfasalazine were started and this DMARD combination was able to keep her arthritis under control for years.

In May 2010, due to a high RA activity (DAS28: 7.16) despite combined DMARD therapy, she was again admitted to our hospital. Hand and foot X-ray showed erosions. As there were no contraindications for biological therapy. In June 2010, 50 mg/week SC etanercept was introduced. The patient's condition significantly improved in 3

months (DAS28: 4.62). Unfortunately, in November 2011 severe erysipelas occurred on her right lower limb; therefore, etanercept therapy was discontinued. After the healing of erysipelas, her treatment was limited to the previous DMARD combination therapy. Unfortunately, the patient was lost to follow-up for several months.

In 2014, intermittent microscopic hematuria occurred and chronic renal insufficiency was reported. The patient was admitted to a nephrology department. Due to hematuria and renal function deterioration (eGFR: 37 ml/min/1.73 m²), the patient underwent renal biopsy at the University of Szeged. Histopathology confirmed a diagnosis of AA amyloidosis [Figures 1A-1F]. Amyloid deposits were observed in the mesangium of the glomerulus, in the walls of the arterioles and the arteries, and to a minimum extent, also in a small nodule in the interstitium.

IL-6 may play an important role in the development of AA amyloidosis due to systemic inflammation [1,3]. Therefore, also considering that low disease activity was not reached upon combined csDMARD therapy, the IL-6 receptor inhibitor tocilizumab was initiated. The patient received the first IV tocilizumab infusion in February 2015. At that time DAS28 was 5.68 and eGFR was 44 ml/min/1.73 m². At the 3-month follow-up examination, the patient reported significant improvements in her joints, accompanied by a marked decrease in inflammatory parameters and no proteinuria (DAS28: 0.84, We: 1 mm/h, CRP: 1.6 mg/l, VAS: 20 mm, eGFR: 50 ml/min/1.73 m²). Since then, the patient has continued to receive monthly tocilizumab

infusions. Her RA is still in remission and her renal function improved with no recurrence of hematuria [Figures 1G and 1H].

Untreated or undertreated RA patients with high disease activity have shorter life expectancy as compared to the general population. In cases of RA with continuously high inflammatory activity, the possibility of amyloidosis should also be considered, especially when RA is accompanied by proteinuria, microscopic hematuria, progressive renal insufficiency, peripheral edema and cachexia [1]. Biopsy of the involved organ is necessary. Hematoxylin-eosin staining shows AA amyloid deposits in the kidneys, with homogeneous eosinophilic stains that in case of Congo red staining will bind the stains, resulting in apple-green birefringence under polarized light [2]. Our patient had hematuria but no significant proteinuria.

The treatment of secondary AA amyloidosis is based on an early and aggressive treatment of the primary inflammatory disease, and the reduction of circulating acute-phase reactant levels [1]. Both TNF and IL-1 inhibition may decrease circulating levels of CRP and SAA, proteins also involved in the pathogenesis of AA amyloidosis [1,4]. However, as IL-6 is the major driver of CRP and SAA production,

IL-6 receptor blockade by tocilizumab is probably a better therapeutic option [3,5]. Indeed, like our presented case, tocilizumab was effective in reducing AA amyloid deposition in various organs including kidneys or gastric mucosa in patients with AA amyloidosis secondary to RA [3,5].

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Capsule

Rapid reconstruction of SARS-CoV-2 using a synthetic genomics platform

Reverse genetics has been an indispensable tool revolutionizing insights into viral pathogenesis and vaccine development. Large RNA virus genomes, such as from Coronaviruses, are cumbersome to clone and manipulate in *E. coli* due to size and occasional instability. Therefore, an alternative rapid and robust reverse genetics platform for RNA viruses would benefit the research community. **Thao** et al. showed the full functionality of a yeast-based synthetic genomics platform to genetically reconstruct diverse RNA viruses, including members of the *Coronaviridae*, *Flaviviridae* and *Paramyxoviridae* families. Viral subgenomic fragments were generated using viral isolates, cloned viral DNA, clinical samples, or synthetic DNA, and reassembled in one step in *Saccharomyces*

cerevisiae using transformation associated recombination (TAR) cloning to maintain the genome as a yeast artificial chromosome (YAC). T7-RNA polymerase has been used to generate infectious RNA to rescue viable virus. Based on this platform the authors have been able to engineer and resurrect chemically-synthesized clones of the recent epidemic SARS-CoV-2 in only a week after receipt of the synthetic DNA fragments. The technical advance the authors describe here allows a rapidly response to emerging viruses as it enables the generation and functional characterization of evolving RNA virus variants, in real-time, during an outbreak.

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