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LESSONS FOR THE CLINICAL NEPHROLOGIST

Late initiation of anakinra can induce complete renal response in renal AA amyloidosis secondary to Familial Mediterranean Fever

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The case

A 37-year-old man presented with progressively worsening kidney function and proteinuria. Approximately 7 years earlier, he had episodes of lower back pain and intense abdominal pain, leading to multiple visits to the emergency department, but no cause was identified. When anterior abdominal pain occurred, the patient took an antalgic position with anterior flexion of the torso to relieve the intense pain. No nocturnal episodes were reported. Initially presenting without fever, after 5 years these painful abdominal attacks became associated with fever (up to 38 °C), accompanied by profound weakness and, at times, bilious vomiting. There were no chills, joint pain, skin rashes, difficulty breathing, or chest pain. A few years later, the patient reported episodes of recurrent fever and pain generally once a month. The duration of pain was rather constant between episodes (48 h), with sudden spontaneous resolution in the absence of pain-relieving medications. Concomitantly, he developed nephrotic syndrome, prompting specialist evaluation.

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Born in Egypt to consanguineous parents (second-degree cousins), he moved to Italy at the age of 20 and worked as a carpenter. Both parents were reportedly in good clinical conditions. He had two brothers and four sisters all in good health, except one brother who had a not otherwise specified renal disease since childhood. He had no history of tobacco or alcohol use and had a stable body mass index (20.9 kg/m^2). Laboratory test results indicated systemic inflammation with elevated levels of C-reactive protein (CRP) (2.84 mg/dL, reference range < 0.75) and erythrocyte sedimentation rate (ESR) (55 mm/h, reference range < 25). Abdominal X-ray showed mild air-fluid levels, while ultrasound revealed dilatation of intestinal loops and minimal ascites. Urine examination showed non-selective nephrotic-range proteinuria (> 5 g/24 h). Serum creatinine levels were 1.25 mg/dL (GFR 73 ml/min/1.73 m^2). Kidney biopsy was performed and a diagnosis of secondary renal amyloidosis was made. Periumbilical fat biopsy showed Congo red–positive deposits, suggestive of amyloidosis. Since an autoinflammatory disease (periodic fever, undefined abdominal pain, young age, systemic inflammation, exclusion of infectious or neoplastic causes) was suspected, genetic studies were performed and two pathogenic mutations in the MEFV gene (c.2040 G > A and c.2082 G > A) were found. Both of these variants were previously published and classified as pathogenic. A diagnosis of Familial Mediterranean Fever (FMF) and associated renal amyloidosis was made. No cardiac, hepatic or gastrointestinal involvement was observed.

Treatment with colchicine was started but suboptimal response was seen during a 2-year follow-up, with various serum inflammatory markers (fibrinogen, CRP, serum amyloid A [SAA]) being intermittently identified above the normal range, despite complete control of symptoms (recurrent fevers and abdominal pain). Therefore, we decided to

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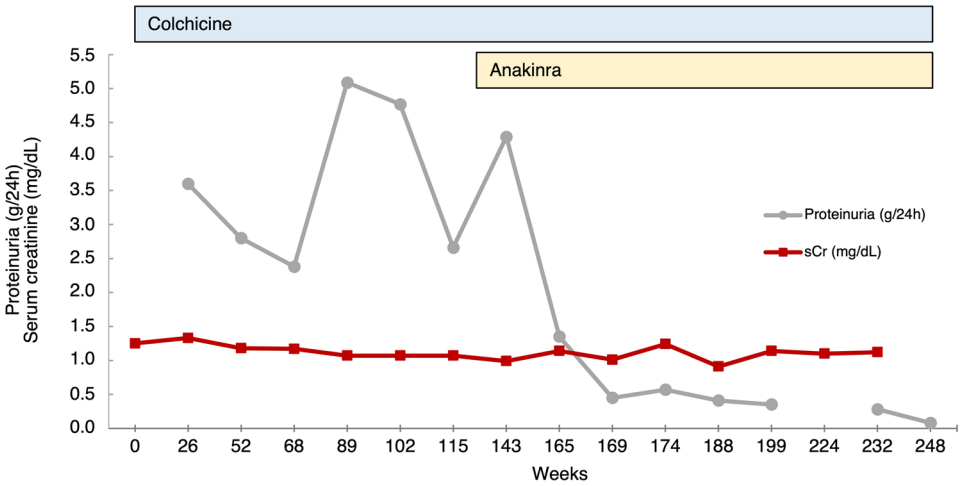

Fig. 1 Timeline of renal function tests and treatment. This timeline represents longitudinal assessments of 24-h proteinuria (grey dots) and serum creatinine levels (red squares) over weeks following the first immunological visit in January 2019; duration of treatment with colchicine and anakinra is depicted with boxes

administer subcutaneous injections of anakinra at a daily dose of 100 mg. During the first 6 months of anakinra treatment, inflammatory markers (CRP and ESR) completely normalized. Nonetheless, after 6 months from the beginning of anti-IL-1 treatment, anakinra had to be adjusted to 100 mg every other day because of neutropenia (nadir 890 cells/mm^3), and has been maintained at this regimen since then. Despite the reduction in the anakinra dose, a substantial decline in proteinuria was observed, together with stable serum creatinine levels (Fig. 1) and normal levels of CRP, serum amyloid A and ESR. Twenty-seven months after the beginning of treatment with anakinra, the patient showed complete normalization of 24-h proteinuria (0.08 g/24 h at the last follow-up visit) (Fig. 1). Colchicine was never discontinued, but maintained at the tolerated dosage of 1 mg daily concurrently with anakinra treatment, together with valsartan 160 mg daily, which was increased to 320 mg daily because of uncontrolled hypertension.

Lessons for the clinical nephrologist

Autoinflammatory diseases encompass a heterogeneous group of systemic disorders characterized by dysregulated innate immune responses, leading to recurrent and exaggerated inflammation. The most common autoinflammatory disease is FMF, which is an autosomal recessive autoinflammatory disorder primarily affecting individuals of Mediterranean descent. Prolonged and recurrent inflammation in unrecognized FMF can lead to significant and severe complications, with renal amyloidosis being the primary concern. AA amyloidosis can be caused by chronic inflammation, leading to deposition of amyloid fibrils in various organs [1]. Renal involvement is a common and significant manifestation of AA amyloidosis, often resulting in progressive kidney damage and impaired kidney function. Amyloid clearance (i.e., the removal of amyloid deposits from affected tissues) is a crucial aspect of managing amyloidosis. The clearance of amyloid fibrils is challenging, and the effectiveness of therapeutic strategies in promoting amyloid removal is the subject of ongoing research. Current treatment strategies for FMF and associated renal AA amyloidosis involve colchicine, which is the oldest therapy for FMF. However, in cases where colchicine is insufficient or poorly tolerated, IL-1 inhibitors (anakinra and canakinumab) have been investigated to address the underlying inflammation and potentially improve amyloid clearance [2]. In this context, we present a patient with FMF-related renal AA amyloidosis, focusing on the role of anakinra as an effective therapy for FMF-related renal AA amyloidosis.

There is limited information available regarding the clinical remission of renal AA amyloidosis secondary to FMF [3–5]. While isolated amyloid fibrils demonstrate stability in vitro, AA amyloid deposits undergo continuous turnover in vivo. Organ involvement is reversible in AA amyloidosis, but amyloid clearance is organ-specific. Renal clearance of amyloid deposits is very slow, therefore suboptimal suppression of systemic inflammation may lead to a mild but continuous deposition of serum amyloid A in the kidney and persistence of renal damage. In our patient, despite colchicine therapy, some of the monitored inflammatory markers remained elevated (ESR), and kidney function did not show any improvement. After administering anakinra, improvements in systemic inflammation and 24-h proteinuria were observed. Although clinical symptoms were effectively managed under colchicine treatment, there was no improvement in 24-h proteinuria. However, upon initiation of anakinra, we observed progressive normalization of 24-h urinary protein excretion. In this patient, anakinra may have contributed to an increase in the rate of amyloid clearance in the kidney, thereby causing rapid and sustained renal improvement. This result demonstrates the efficacy of anakinra as an

add-on therapy for managing FMF-related renal AA amyloidosis and questions the timing for its initiation.

Anakinra is a recombinant form of the human IL-1 receptor antagonist (IL-1Ra), which competitively inhibits IL-1 from binding to its receptor. This prevents IL-1 from exerting its proinflammatory effects. Anakinra plays a crucial role in attenuating the IL-1-mediated inflammatory process, which is central to the pathogenesis of both FMF and AA amyloidosis. In chronic inflammatory conditions, including FMF, IL-1 stimulates hepatocytes to produce serum amyloid A, which is the precursor of AA amyloid. Elevated circulating levels of serum amyloid A lead to the deposition of AA amyloid in various organs, particularly kidney, liver, gastrointestinal tract, spleen, and occasionally heart. Amyloid deposition in the kidneys is responsible for nephrotic syndrome and renal dysfunction. By reducing the availability of precursor proteins for amyloid fibril formation, anakinra is effective in reverting FMF-related renal AA amyloidosis. Notably, FMF patients with renal involvement were excluded in the first randomized controlled trial that demonstrated the efficacy of anakinra in controlling joint attacks in colchicine-resistant patients [6]. Reports from individual cases have indeed suggested that anti-IL-1 inhibitors might have the potential to either prevent or slow down the development of amyloidosis in patients with FMF [7]. Nonetheless, in kidney transplanted patients, Simsec et. al. observed de novo vascular amyloid deposition during anti-IL-1 treatment, whereas Ugurlu et al. observed improved or stable kidney function [8, 9]. It is essential to underline the importance of fine-tuning the doses of IL-1 inhibitors to effectively control inflammation, especially in individuals who already have amyloidosis [7]. An additional, clinically relevant consideration pertains to the utility of longitudinally monitoring inflammatory markers in order to identify suitable candidates for anti-IL-1 therapy among patients with FMF under colchicine treatment early enough to prevent renal disease. In this context, serum amyloid A, CRP, and ESR are essential, however, fibrinogen levels may be challenging because of the potential confounding influence of concurrent nephrotic syndrome.

In conclusion, this case report highlights the positive outcomes of anakinra therapy in a patient with renal AA amyloidosis secondary to FMF, also in established kidney involvement. These findings support the role for anakinra in the management of FMF-related renal complications and warrant further investigation to establish its long-term maintenance efficacy. In those patients with persistent proteinuria and suboptimal response to colchicine and/or steroids, anakinra, even if started late, can induce additional deep inflammatory inhibition and an unexpected complete renal response.

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Data availability statement Data are available upon reasonable request.

Declarations

Conflict of interest None.

Ethical approval Ethics Committee approval was not required for the report of a single case.

Informed consent to participate Informed written consent was given by the patient.

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