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CASE REPORT

A case of familial Mediterranean fever-associated systemic amyloidosis

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Abstract Familial Mediterranean fever (FMF) is a chronic inflammatory disease, characterized by recurrent fever and polyserositis (pleuritis and/or peritonitis). The most important complication of FMF is amyloidosis, which causes chronic renal failure. Colchicine is the most effective treatment in acute attacks and amyloidosis development. However, the majority of patients with amyloidosis have a relentless progression to end-stage renal disease despite initiation of colchicine treatment. We present the case of a 38-year-old man with FMF-associated chronic renal failure due to systemic amyloidosis. The patient suffered from periodic fever and renal insufficiency, and was admitted to our hospital. Laboratory examination revealed an inflammatory reaction, renal dysfunction (serum creatinine 2.5 mg/dl), and proteinuria. Renal biopsy revealed segmental mesangial AA amyloid deposits in several glomeruli and the walls of several vessels. Genetic analysis showed that the patient was heterozygous for the MEFV gene (E148Q/M694I). Thus, he was diagnosed with FMF, and colchicine treatment was initiated. He remained almost attack free, with decreasing serum creatinine levels (1.6 mg/dl) and diminishing urinary protein excretion. In conclusion, renal amyloidosis is the most important long-term complication of FMF, and treatment with colchicine is effective for preventing progression. Therefore, colchicine treatment should be initiated as early as possible after the diagnosis of FMF.

Keywords Amyloidosis · Colchicine · Familial Mediterranean fever

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Introduction

Familial Mediterranean fever (FMF) is a chronic inflammatory disease, characterized by recurrent fever and polyserositis (pleuritis and/or peritonitis). It is the most prevalent periodic fever syndrome, affecting more than 100,000 patients worldwide. FMF is prevalent in populations that surround the Mediterranean Sea. However, in recent years, an increasing number of cases have been reported in countries far away from this area, such as the US and Japan [1]. FMF is caused by mutations in the MEFV (Mediterranean fever) gene, which encodes pyrin [2]. This protein is primarily expressed in the myeloid/monocytic cells and regulates IL-1β processing, NF-κB activation, and apoptosis [3]. Thus, mutated pyrin probably results in uncontrolled inflammation.

The most important complication of FMF is amyloidosis, which causes chronic renal failure (CRF). The prevalence of amyloidosis differs among various ethnic groups [4]. Furthermore, CRF due to amyloidosis appears to have a poor prognosis.

Colchicine is most effective in the prevention of acute attacks and development of amyloidosis. However, the majority of patients with amyloidosis have a relentless

progression to end-stage renal disease despite the initiation of colchicine treatment.

We present a patient with FMF-associated CRF (initial serum creatinine level >2.0 mg/dl) due to systemic amyloidosis. The patient showed partial CRF remission with a stable clinical course over 5 years after colchicine treatment.

Case report

A 38-year-old man with high fever consulted a general hospital in his neighborhood. Laboratory examinations performed at that hospital revealed renal insufficiency (serum creatinine 2.3 mg/dl). The patient was admitted to our hospital because of fever of unknown origin and renal insufficiency. Fever continued intermittently and was not an infectious disease.

Physical examination revealed that he had thyroid struma and pretibial edema, while laboratory examination showed an inflammatory reaction (WBC 16,070/ml, CRP 11.4 mg/dl) and renal dysfunction (serum creatinine 2.5 mg/dl, BUN 28 mg/dl). Urinary protein excretion was 2.2 g/g creatinine, and the serum amyloid A protein level was 282 g/ml. Renal biopsy revealed segmental mesangial AA amyloid deposits in several glomeruli and the walls of several vessels (Fig. 1). AA amyloid deposits were also detected in the thyroid gland, duodenum, and rectum.

Initially, we suspected an infectious disease, a collagen disease, or a vasculitis syndrome. However, laboratory examination confirmed that he did not have any of these diseases. Therefore, we interviewed him in detail regarding his symptoms. The interview revealed that he experienced recurrent episodes of fever accompanied by chest and abdominal pain. Genetic analysis showed that he was heterozygous for the MEFV gene (E148Q/M694I). Thus, he was diagnosed with FMF according to the criteria described by Livneh et al. [5] for FMF diagnosis. Thus, 1 mg colchicine was orally administered twice daily, and the patient's condition was followed up clinically.

After colchicine treatment, his transaminase level increased, which was believed to be due to the adverse effect of the drug, and thus, treatment was terminated. After some time, 0.5 mg colchicine was orally administered once daily. The patient remained almost attack free with no increase in transaminase levels. Moreover, the serum creatinine level decreased (1.6 mg/dl) and urinary protein excretion diminished (0.18 g/g creatinine).

Discussion

FMF is a hereditary autosomal recessive disease characterized by recurrent attacks of fever and polyserositis. FMF

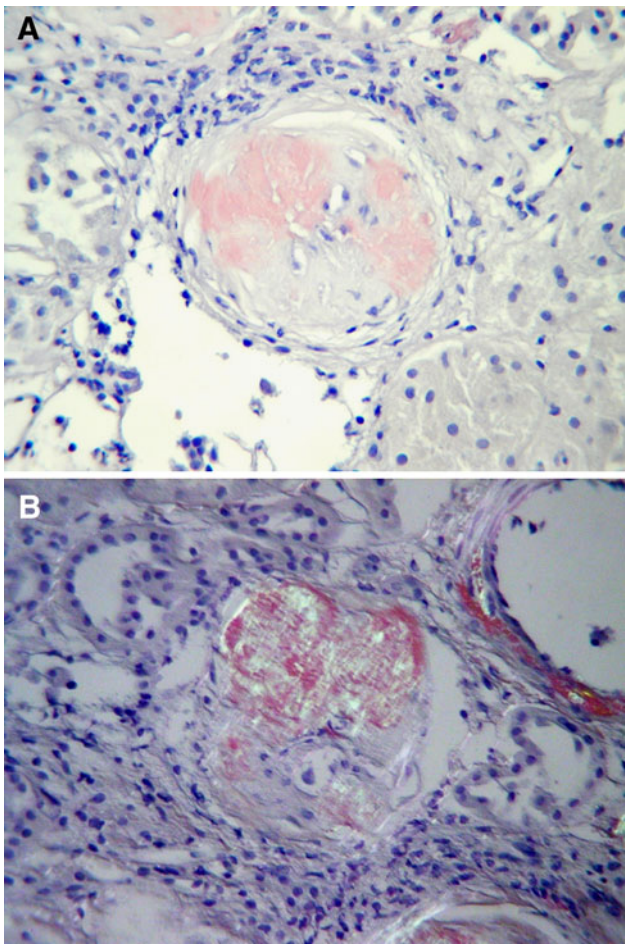

Fig. 1 Renal biopsy. **a** Congo red staining of the renal biopsy specimen demonstrating salmon pink staining of the mesangial amyloid deposits. **b** Polarizing microscopy demonstrating flashed amyloid depositions in the glomeruli

is caused by mutations in the MEFV gene, which encodes pyrin. This protein is primarily expressed in the myeloid/monocytic cells and regulates IL-1β processing, NF-κB activation, and apoptosis. Thus, mutated pyrin probably results in uncontrolled inflammation [1–3].

Renal involvement with type AA amyloidosis secondary to FMF is the most important long-term complication. Renal involvement varies from asymptomatic proteinuria to nephritic syndrome and may progress to end-stage renal disease. In the majority of renal amyloidosis cases, CRF develops within 5 years after the onset of proteinuria [6].

Although colchicine treatment is known to prevent or decrease the frequency as well as severity of attacks and amyloidosis development, partial remission of renal involvement with amyloidosis secondary to FMF after colchicine treatment has rarely been reported. However, a few studies have reported that colchicine decreases proteinuria and prevents FMF-associated renal amyloidosis [7–9]. The following factors were considered to predict a

better clinical response: (1) initial level of serum creatinine less than 1.2 mg/dl; (2) administration of high-dose colchicine (1.5–2 mg/day); (3) absence of tubulointerstitial changes; (4) compliance of patients with treatment [7, 8]. Although the initial serum creatinine level in our patient was more than 2.0 mg/dl, he showed partial CRF remission (serum creatinine level 1.6 mg/dl and a decrease in the proteinuria level) after administration of the minimum dose of colchicines (0.5 mg/day). On the basis of this result, we consider this represents a very interesting case.

There are several possible mechanisms for the efficacy of colchicine treatment in FMF patients. The anti-inflammatory effect of colchicine may be mediated not only through direct interaction with microtubules, but also changes at the transcriptional level [10]. Colchicine also has an anti-fibrotic effect [11] since it impairs collagen synthesis and enhances collagenase activity [12]. Therefore, it may prevent the deposition of serum amyloid A fibers.

The reason for improvement in renal function in this case remains unknown, although it is possible that the anti-fibrotic effect of colchicine may have inhibited amyloid deposition in the glomeruli in our patient.

Initially, we did not consider our patient to have FMF, since this disease is very rare in Japan. However, recently, there has been a gradual increase in the number of FMF cases in Japan [13, 14]. Therefore, when AA amyloidosis of unknown origin is encountered, it is important to interview the patient in detail regarding the symptoms to eliminate the possibility of FMF.

In conclusion, renal amyloidosis is the most important long-term complication of FMF. Colchicine treatment is effective for preventing progression of renal amyloidosis. Thus, colchicine treatment should be initiated as early as possible after the diagnosis of FMF.

Conflict of interest None declared.

References

1. Onen F. Familial Mediterranean fever. Rheumatol Int. 2006;26:489–96.
2. Centola M, Wood G, Grucht DM. The gene for familial Mediterranean fever, MEFV, is expressed in early leukocyte development and is regulated in response to inflammatory mediators. Blood. 2000;95:3223–31.
3. Masumoto J, Dowds TA, Schaner P, Chen FF, Ogura Y, Li M, et al. ASC is an activating adaptor for NF-kappa B and caspase-8-dependent apoptosis. Biochem Biophys Res Commun. 2003;303:69–73.
4. Pras M, Bronshpigel N, Zemer D, Gafni J. Variable incidence of amyloidosis in familial Mediterranean fever among different ethnic groups. Johns Hopkins Med J. 1982;150:22–6.
5. Livneh A, Langevitz P, Zemer D, Zaks N, Kees S, Lidar T, et al. Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum. 1997;40:1879–85.
6. Livneh A, Langevitz P, Zemer D, Padeh S, Migdal A, Sohar E, et al. The changing face of familial Mediterranean fever. Semin Arthritis Rheum. 1996;26:612–27.
7. Livneh A, Zemer D, Langevitz P, Laor A, Sohar E, Pras M. Colchicine treatment of AA amyloidosis of familial Mediterranean fever. An analysis of factors affecting outcome. Arthritis Rheum. 1994;37:1804–11.
8. Öner A, Erdoğan Ö, Demircin G, Bűbűl M, Memis L. Efficacy of colchicines therapy in amyloid nephropathy of familial Mediterranean fever. Pediatr Nephrol. 2003;18:521–6.
9. Zemer D, Livneh A, Langevitz P. Reversal of the nephritic syndrome by colchicines in amyloidosis of familial Mediterranean fever (letter). Ann Intern Med. 1992;116:426.
10. Ben-Chetrit E, Bergmann S, Sood R. Mechanism of the anti-inflammatory effect of colchicine in rheumatic diseases: a possible new outlook through microarray analysis. Rheumatology. 2006;45:274–82.
11. Schattner A. Colchicine-expanding horizons. Prostagrand Med J. 1991;67:223–6.
12. Bauer EA, Valle KJ. Colchicine-induced modulation of collagenase in human skin fibroblast cultures. Stimulation of enzyme synthesis in normal cells. J Invest Dermatol. 1982;79:398–402.
13. Tomiyama N, Higashiuesato Y, Oda T, Baba E, Harada M, Azuma M, et al. MEFV mutation analysis of familial Mediterranean fever in Japan. Clin Exp Rheumatol. 2008;26:13–7.
14. Sugiura T, Kawaguchi Y, Fujikawa S, Hirano Y, Kawamoto M, Takagi K, et al. Familial Mediterranean fever in three Japanese patients, and a comparison of the frequency of MEFV gene mutations in Japanese and Mediterranean populations. Mod Rheumatol. 2008;18:57–9.