

Case Report

AA Amyloidosis and Atypical Familial Mediterranean Fever with Exon 2 and 3 Mutations

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Keywords

AA amyloidosis · Familial Mediterranean fever · Atypical type

Abstract

A 54-year-old Japanese man presented with recurrent abdominal pain, fever lasting >5 days, and renal failure. AA amyloidosis was proven by renal and gastric biopsy. Symptoms subsided with the administration of colchicine, but a subsequent recurrence of symptoms did not respond to colchicine. Mediterranean fever gene (MEFV) analysis showed that he was heterozygous for mutations in exon 2 (E148Q/R202Q) and exon 3 (P369S/R408Q), although he had none of the exon 10 mutations known to be closely related to AA amyloidosis. He did not respond to infliximab, but tocilizumab therapy was successful. The present case is a rare report of AA amyloidosis associated with familial Mediterranean fever in Japan.

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Published by S. Karger AG, Basel

Introduction

Familial Mediterranean fever (FMF) is an inherited autoinflammatory disorder that is characterized by recurrent episodes of fever and serosal or cutaneous inflammation. It is caused by mutations of the Mediterranean fever (MEFV) gene, which encodes pyrin protein. The commonest mutations are M694V, M694, 726A, M680I, and E148Q, most of which are located on exon 10 [1]. Chronic inflammation can lead to secondary AA amyloidosis due to the accumulation of extracellular amyloid protein in various tissues, and this is the most severe complication of FMF. It has been reported that AA amyloidosis is associated with the M694V mutation in patients from the eastern Mediterranean region and with M694I in Japanese patients [2–4]. We report an FMF patient without exon 10 mutation who developed end-stage renal failure due to secondary amyloidosis.

Case Report

In October 2013, a 54-year-old Japanese man was admitted to our hospital for evaluation of periodic fever, nausea, vomiting, abdominal pain, watery diarrhea, and renal dysfunction.

Since he was a child, he had suffered from recurrent abdominal pain lasting for several days and resolving spontaneously. In his late twenties, he developed 2 episodes of ileus-like syndrome. Laparotomy was performed once, but there were no significant findings. Around 2010, proteinuria was detected by an annual screening test, but no action was taken. In January 2011, he complained of fever, abdominal pain, and diarrhea persisting for more than 5 days. Serum creatinine (Cre) was 0.75 mg/dL (eGFR 86 mL/min), C-reactive protein (CRP) was 6.15 mg/dL, and serum amyloid A protein (SAA) was 31.5 µg/mL (normal: <13.0 µg/mL). Antinuclear antibody (ANA), anti-double-stranded DNA antibody, anti-proteinase-3 (PR-3) anti-neutrophil cytoplasmic antibody (ANCA), and myeloperoxidase ANCA (MPO-ANCA) were all negative. Immunoglobulin (Ig) G was 1230 mg/dL, IgA was 211 g/dL, and IgM was 96 mg/dL; CH50 was 39 U/mL (normal: >30 U/mL). Urinary protein excretion was 3.15 g/day. The urinary sediment contained less than 1 erythrocyte per high-power field. There was no cast in urine sediments. Renal biopsy was performed for evaluation of the severity of his renal disease.

Renal Biopsy

Light microscopic examination of a renal biopsy specimen containing 46 glomeruli showed no global sclerosis. In almost all of the glomeruli, there was no mesangial expansion or mesangial cell proliferation, but amorphous deposits were seen in the glomerular vascular pole and the interlobular artery. These deposits were positive for Congo red stain and amyloid A, but negative for kappa and lambda chains, β₂ microglobulin, and prealbumin (Fig. 1).

Gastrointestinal Biopsy

Endoscopic biopsy of the stomach revealed amorphous deposits in the small arteries and surrounding tissues of the submucosal layer. These deposits were positive for amyloid A, therefore AA amyloidosis was diagnosed (Fig. 2).

Clinical Course

Treatment with colchicine was started, resulting in an improvement of symptoms. Periodic fever (up to 39°C) recurred in August 2013, but administration of colchicine was not effective. In early September 2013, the patient developed nausea, vomiting, abdominal pain, loss of appetite, and watery diarrhea. On September 8, hemodialysis was started for chronic renal failure (serum Cre: 9.0 mg/dL). Treatment with a chimeric anti-TNF monoclonal antibody (infliximab) was started on September 25, but was not effective. On October 2, laboratory findings were as follows: white blood cell count was 11,400/ μ L, total protein was 5.5 g/dL, albumin was 1.7 g/dL, serum urea nitrogen was 92 mg/dL, serum Cre was 9.48 mg/dL, total cholesterol was 80 mg/dL, CRP was 9.3 mg/dL, and SAA was 557 μ g/mL.

Treatment with a humanized anti-interleukin-6 (IL-6) receptor antibody (tocilizumab) was initiated. His abdominal pain, fever, and diarrhea promptly resolved. CRP decreased to 0.0 mg/dL and SAA also decreased to 5.0 μ g/mL. However, his renal function did not improve and he has remained on hemodialysis.

Genetic Analysis and Diagnosis

Analysis of the MEFV gene was performed because the patient had a history of recurrent abdominal pain associated with periodic fever. After this test was approved by the Ethics Committee at Toranomon hospital and informed consent was obtained, analysis of all 10 exons of the MEFV gene was performed by direct sequencing according to the previously reported method [4], and 2 compound heterozygous mutations were detected (E148Q/R202Q in exon 2 and P369S/R408Q in exon 3) [5].

His two daughters had also been hospitalized with periodic fever and abdominal pain of unknown origin, and the older girl was found to have R202Q in exon 2.

On the other hand, the clinical characteristics of this patient were consistent with tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS), including fever persisting for longer than 5 days and ineffectiveness of colchicine. Therefore, analysis of the TNF receptor superfamily member 1A (TNFRSF1A) gene (exons 1–10) was also performed, but no significant mutations were identified.

Since the patient did not have typical FMF with exon 10 mutation, atypical FMF was diagnosed, along with secondary AA amyloidosis based on the results of renal and gastric biopsy.

Discussion

FMF can be classified as “typical” or “atypical” based on clinical findings and the results of genetic analysis [6]. According to the Tel Hashomer criteria, typical FMF episodes last from 12 h to 3 days and feature fever accompanied by peritonitis, pleuritis, and/or monoarthritis of the hip, knee, or ankle [7]. Some of the clinical features of our patient differed from typical FMF, including prolonged fever and no response to colchicine when it was administered a second time.

On the other hand, he exhibited some of the clinical manifestations of TRAPS. This is an autosomal dominant autoinflammatory disease caused by mutations of the TNFRSF1A gene encoding the TNF receptor, and is characterized by episodes of fever associated with abdominal pain, pleurisy, myalgia, skin rashes, and arthritis [8]. The diagnosis of TRAPS is confirmed by the detection of TNFRSF1A mutation.

Our patient was found to have 2 MEFV gene mutations and no TNFRSF1A mutations, so a diagnosis of atypical FMF was considered. Migita et al. [6] reported that 43% of Japanese patients had atypical FMF according to the Tel Hashomer criteria.

Although genotype-phenotype correlations have not been established precisely for FMF, many studies have suggested that M694V is associated with the development of amyloidosis in eastern Mediterranean patients [2, 3]. In addition, the allelic frequency of M694I was reported to be higher in Japanese FMF patients with AA amyloidosis [4]. Mutations in exon 10 of the MEFV gene are frequently identified in patients with FMF-associated amyloidosis. However, the present patient had no exon 10 mutations, although E148Q/R202Q in exon 2 and P369S/R408Q in exon 3 were found.

Migita et al. [9] previously reported 2 FMF patients with AA amyloidosis who had MEFV mutations in exons 2 or 3, even though these are considered to be low-risk mutations for FMF-related AA amyloidosis.

Although colchicine is the gold standard treatment for FMF, there has been an increasing number of case reports suggesting that biologic agents which directly target proinflammatory cytokines, including IL-1 and IL-6 (tocilizumab), may be effective in patients resistant to colchicine [10]. Hamanoue et al. [11] reported a 51-year-old Japanese man with the compound heterozygous mutation of E148Q/M694I and AA amyloidosis. Soon after initiation of tocilizumab, symptoms including arthritis and abdominal pain subsided, CRP and proteinuria declined, and repeat gastric biopsy showed a marked decrease of A amyloidosis.

In conclusion, we reported a 54-year-old Japanese man who had amyloidosis and atypical FMF without any of the MEFV exon 10 mutations known to be closely related to AA amyloidosis.

Acknowledgments

This study was funded by the Okinaka Memorial Institute for Medical Research.

Statement of Ethics

This study was approved by Toranomon Hospital institutional review board and the patients gave written informed consent.

Disclosure Statement

All authors have no conflicts of interest. The authors declare no competing financial interests.

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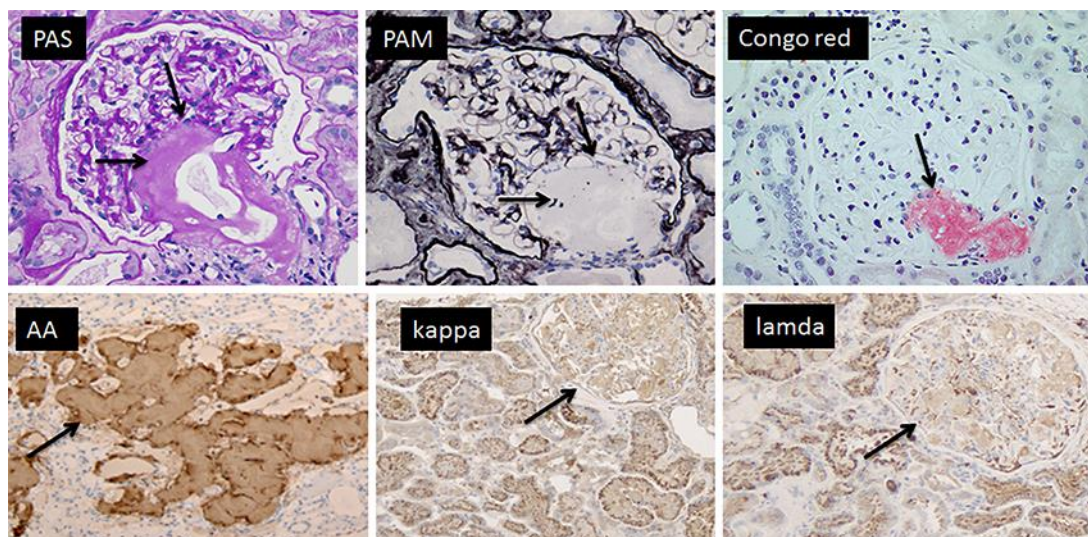


Fig. 1. Renal biopsy. Amorphous deposits (arrows) by periodic acid-Schiff (PAS) stain and periodic acid-methenamine-silver (PAM) stain were seen in the glomerular vascular pole and interlobular artery. These deposits were positive for Congo red (arrow) and amyloid A (AA) staining (arrow), but negative for kappa and lambda chain (arrow), β_2 microglobulin, and prealbumin.

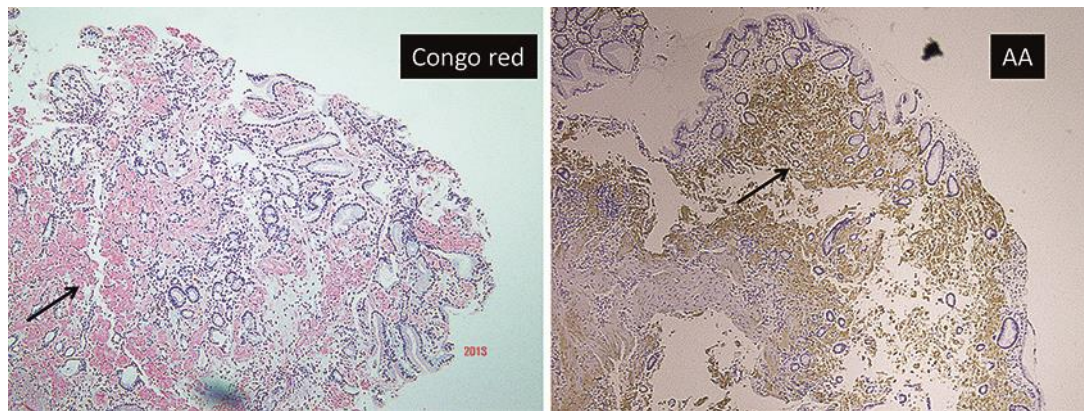


Fig. 2. Gastric biopsy. Amorphous deposits showing positivity for Congo red (arrows) were seen in the small arteries and surrounding tissues of the submucosa. These deposits were positive for amyloid A (AA) (arrow).