Case Report

Two Familial Cases with Tumor Necrosis Factor Receptor-Associated Periodic Syndrome Caused by a Non-Cysteine Mutation (T50M) in the TNFRSF1A Gene Associated with Severe Multiorganic Amyloidosis

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ABSTRACT. An adolescent boy had had recurrent episodes of fever, abdominal pain, and arthralgias since the age of 7 years. Progressive renal failure due to renal amyloidosis developed, leading to renal transplant at the age of 14.5 years. Five years later, he developed AA amyloidosis in the transplant as well as the thyroid gland. His father had had similar symptoms including systemic amyloidosis since the age of 6 years. DNA sequence analysis revealed a heterozygous mutation in the *TNFRSF1A* (TNFα-receptor 1) gene (T50M) in both father and son causing tumor necrosis factor receptor-associated periodic syndrome (TRAPS). Previous phenotype/genotype analyses have proposed that this mutation is usually not associated with the occurrence of amyloidosis. This difference in the clinical course in different families may indicate a strong influence of modifier genes. Treatment with a TNFRSF1B fusion protein TNF antagonist (etanercept) favorably influenced the disease course. (J Rheumatol 2004;31:2519–22)

Key Indexing Terms:
HEREDITARY PERIODIC FEVER SYNDROMES AMYLOIDOSIS
ETANERCEPT NONSTEROIDAL RENAL TRANSPLANT

Tumor necrosis factor-α (TNF-α) receptor-associated periodic syndrome (TRAPS) is a rare autosomal dominant inherited autoinflammatory disease characterized by recurrent febrile episodes of various durations often associated with skin and musculoskeletal involvement[1]. A severe longterm complication of this disease is the development of secondary amyloidosis. TRAPS is caused by missense mutations of the TNFα receptor 1 (*TNFRSF1A*) gene usually involving residues within the first 2 cysteine-rich domains of the receptor[2].

It has been proposed that substitution of cysteine residues is often associated with the occurrence of secondary amyloidosis. So far only one case with a non-cysteine mutation developing systemic amyloidosis has been reported[3].

We describe a father and son with the non-cysteine mutation T50M in their *TNFRSF1A* genes who had severe systemic amyloidosis involving kidneys, liver, gut, and thyroid gland, and recurrence in renal allografts. In the son, application of anti-TNF-α therapy has favorably influenced the disease course.

CASE REPORT

A 20-year-old male patient originating from Poland had had recurrent inflammatory episodes of general weakness, abdominal pain, arthralgias/arthritis of the knees and elbows, and fever since the age of 7 years. The attacks were self-limiting, lasted up to 3 weeks, and were associated with increased levels of acute phase proteins, accelerated blood sedimentation rate, and leukocytosis. These attacks were not triggered by any specific factor. No rash, signs of myositis, or occurrence of edema was observed. At the age of 13 years a nephrotic-range proteinuria was noted and a renal biopsy revealed amyloidosis (type AA). The further clinical course was complicated by recurrent attacks and progressive renal failure, requiring maintenance hemodialysis at the age of 14 years. Two months later he received a cadaveric renal transplant. Immunosuppression consisted of tacrolimus, azathioprine, and low dose prednisolone (4 mg/m^2 per day).

His father presented with a similar clinical history, with episodes of recurrent arthralgias/arthritis and fever since the age of 6 years. At age 28, marked proteinuria was noted. Three years later hemodialysis was started because of endstage renal disease. Further investigation preceding renal

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transplant revealed marked atherosclerosis plaques of the abdominal aorta and the iliacal and femoral arteries. Systemic amyloidosis was proven by amyloid type AA deposits in tissue specimens of kidney, liver, colon, and rectum. In addition, he developed goiter. At age 35 years he received a cadaveric renal allograft.

At first the diagnosis of familial Mediterranean fever (FMF) was presumed in father and son, and colchicine therapy was started in 1996 in both patients. However, this treatment was not effective with respect to the frequency, severity, and duration of the inflammatory attacks.

Five years after the renal transplant, the son presented with progressive weight loss of 5 kg within 4 months, general weakness, persistent elevation of C-reactive protein (CRP), rise in serum creatinine (167 µmol/l), severe proteinuria (2 g/day), and a large firm goiter (Figure 1). Autoimmune thyroiditis was ruled out by screening for autoantibodies, thyroid-stimulating hormone, and thyroid hormones as well as a homogeneous echogenicity on ultrasound. Immunglobulin D serum concentrations were within normal range. Biopsies of the renal transplant and of the thyroid gland revealed recurrence and development of type AA amyloidosis, respectively (Figure 2).

In view of the apparent dominant mode of inheritance and the clinical course of the disease, the diagnosis of TRAPS was presumed. DNA sequence analysis was performed, revealing one of the 24 known disease-associated *TNFRSF1A* mutations (T50M) in our index patient and his father, confirming the diagnosis of TRAPS (Figure 3). Shortly after this disease was diagnosed, the father died from complications of atherosclerosis.

Treatment with etanercept, an anti-TNF-α agent (0.4 mg/kg subcutaneously, 2 injections per week), resulted in rapid amelioration of the clinical symptoms, normalization of CRP levels, and stabilization of renal function within a short time. Immunosuppression including low dose prednisolone remained unchanged. Six months after starting etanercept treatment the patient showed a cumulative weight gain of 8 kg, and serum creatinine declined to 142 µmol/l and proteinuria to 1 g/day. The size of the goiter appeared unchanged by regular ultrasound examinations.

The TRAPS pedigree supports an autosomal dominant inheritance and occurrence of a spontaneous mutation in II.10 (Figure 4). No relatives except the index patient and his father had any history or clinical signs of TRAPS. No other case of death related to complications of amyloidosis were reported. Sequence analyses were performed in all siblings of the index patient and his father (II.3–II.9 and III.2) that revealed no T50M mutation (except in III.2, the sister of the index patient, with an unremarkable history and clinical status) heterozygous for this mutation.

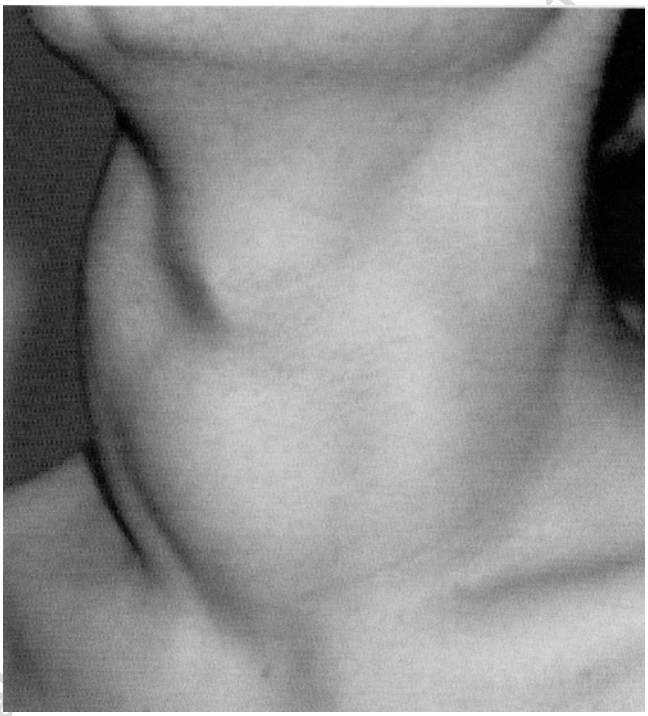

Figure 1. Goiter of the thyroid gland; age 19 years.

DISCUSSION

Our patients presented with severe episodes of TRAPS with systemic amyloidosis leading to endstage renal failure, followed by recurrence of amyloid accumulation in renal grafts. Secondary amyloidosis is characterized by the extracellular deposition of linear fibrils, affecting primarily the spleen, liver, and kidneys[4]. Rheumatic diseases, severe infections, malignancies, and inherited (periodic) febrile syndromes have been identified as underlying conditions. In TRAPS, about 14% of all patients are affected by this severe complication[3].

Our patients developed severe relapsing multiorgan secondary amyloidosis with deposition of AA amyloid in the kidneys, the digestive tract, and the thyroid gland (Figure 2). Although amyloid accumulation in thyroid is frequently observed in secondary amyloidosis, it rarely causes the development of goiter[5]. In patients with FMF, another inherited autoinflammatory disease characterized by recurrent fever associated with serositis, the development of amyloid goiter has been observed in several cases[6], and can even be the initial manifestation of systemic amyloidosis[7]. To our knowledge, only one other patient with TRAPS showing this rare complication has been reported[8].

In both father and son, the single base-pair mutation ACG → ATG was found within the *TNFRSF1A* gene, causing a threonine to methionine exchange at amino acid position 50. Several reports provide evidence that there is a mutational hot spot at this position that can be screened by a restriction analysis[3,9].

In the largest published cohort of TRAPS, only one out of 41 cases presenting with a non-cysteine mutation developed secondary amyloidosis[3]. In contrast, mutations resulting in substitution of cysteine residues increased the probability for the deposition of amyloid up to 24%. Considering our patients and previous cases[3,9,10] together, the non-cysteine T50M mutation in patients with TRAPS would be associated with a 13% risk for the development of amyloidosis (i.e., 3 patients with amyloidosis out of 23 reported patients). Thus patients with this mutation apparently also have a high risk to develop amyloidosis. Hence, in some families non-cysteine mutations may lead to amyloidosis more frequently than previously assumed. We recommend a regular clinical examination for the presence of amyloidosis in various organs, including ultrasound of the thyroid gland, in all patients with TRAPS, irrespective of the underlying mutation.

It is proposed that mutations in the *TNFRSF1A* gene affecting cysteine residues lead to a disruption of cysteine bonds and inadequate intrachain and interchain disulfide bond formation. Consequently, the conformation of the

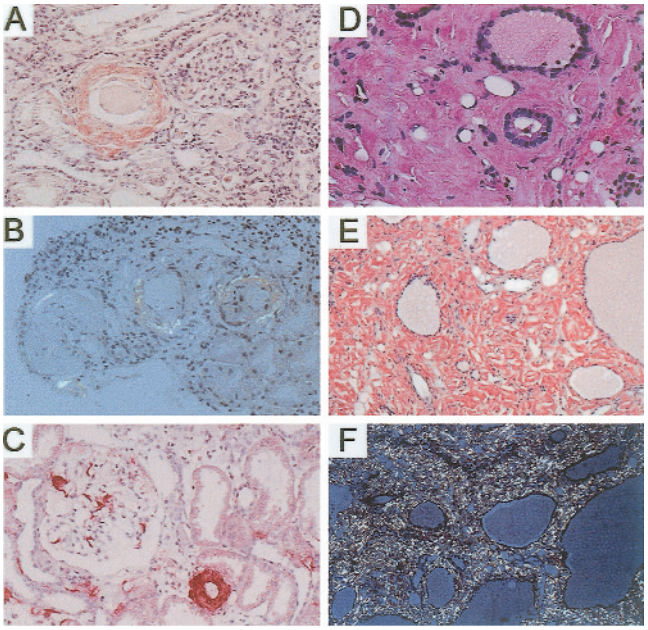

Figure 2. Amyloid deposits in the renal transplant (A–C) and thyroid gland (D–F). Congo red staining according to Puchtler reveals amyloid deposition in an artery (A). Under polarized light, congo-red amyloid appears as apple-green birefringence in small arteries and the Bowmann capsules (B). Standard APAAP technique was performed[15]. The antibody against SAA (clone mc1, mouse IgG2a; Dako, Hamburg, Germany) strongly stained arteries and the glomerular mesangium, and partially the tubular basement membranes (C). In the H&E staining, thyroid follicles appear variable in size, often compressed by amyloid (D). Amyloid deposition is characterized by an eosinophilic amorphic staining (D and E). Congo red staining according to Puchtler confirms the presence of amyloid deposits (D); this appears as apple-green birefringence under polarized light (F).

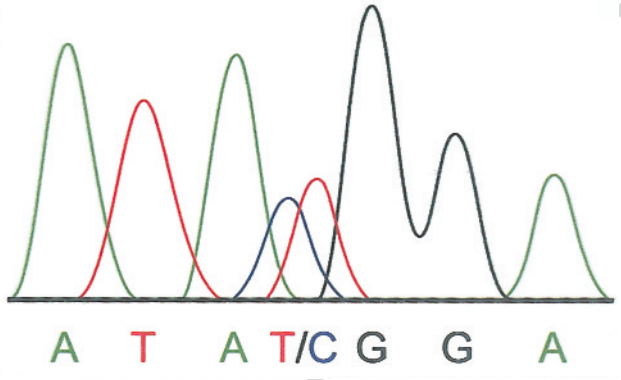

Figure 3. DNA sequence electropherogram illustrating heterozygosity of thymidine and cytosine on position 236 causing the T50M mutation.

receptor might change, resulting in inappropriate molecule function[2]. In the non-cysteine T50M mutation, the threonine on position 50 provides an intrachain hydrogen bond. Disruption of this stabilizing interaction might change the receptor conformation and impair its function[2].

Interestingly, the sister of the index patient, with no history or clinical signs of TRAPS, was found at the age of 25 years to be heterozygous for the T50M mutation. Thus, the T50M mutation does not exhibit a full penetrance for the development of TRAPS. Previous phenotype/genotype analysis in patients with TRAPS revealed a high penetrance of 94% (17/18) in individuals carrying T50M mutations[3].

In contrast to other reports[3], expression of the T50M mutation in this family was associated with a severe phenotype in 2 family members, i.e., development of systemic amyloidosis, but to date has spared a third family member. These differences indicate a strong influence of modifier

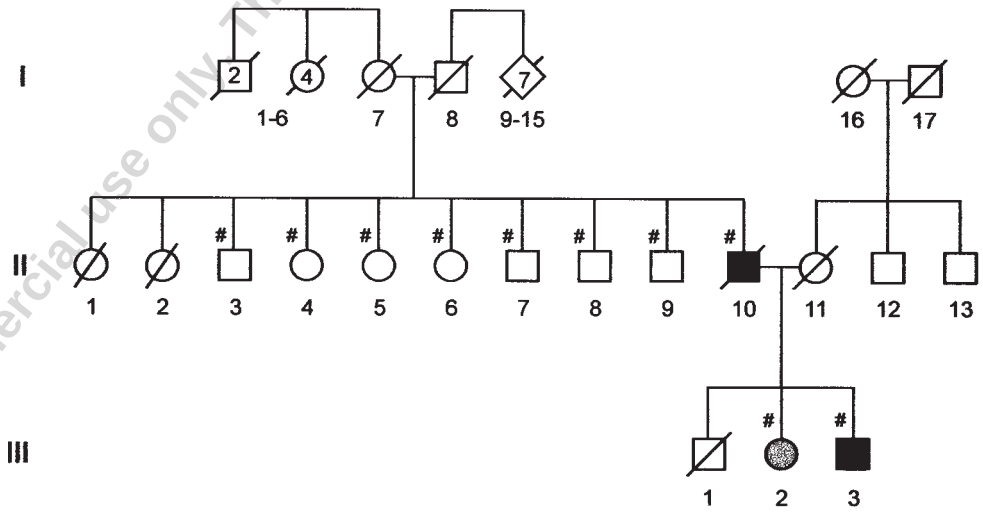

Figure 4. The family pedigree. Offspring of I.1-6 and 9-15 as well as II.1-9, 12, and 13 are not shown. Among these offspring there is none with TRAPS-like symptoms or amyloidosis. Black symbols indicate affected individuals; the T50M mutation-positive sister of the index patient (III.2) had no history or clinical sign of TRAPS. #Subjects analyzed for the T50M mutation.

genes on the development of this complication in TRAPS, as similarly reported for another form of hereditary fever syndrome, FMF. For this disease, 2 studies have identified the serum amyloid A1 α/α (SAA1α/α) genotype as such a genetic factor predisposing individuals to amyloidosis[11,12].

In accord with previous reports[13], in our case colchicine treatment was not effective for control of the attacks, and did not prevent recurrence of amyloidosis in the renal allograft. In addition, the immunosuppressive medication to prevent transplant rejection had no clear beneficial effect on the attacks, and could not prevent the deposition of amyloid in the graft.

Recently, it has been reported that etanercept might be a promising treatment for TRAPS. This drug is a TNFR2:Fc fusion protein, which restores the pool of soluble TNF-α binding proteins and thereby prevents interaction of this cytokine with membrane-bound receptors[13,14]. After the diagnosis of TRAPS was confirmed, therapy with subcutaneous etanercept was introduced in the son. After that, renal function stabilized and proteinuria decreased to non-nephrotic range. In addition, it led to an increase in food intake resulting in a sustained weight gain. So far no additional oral prednisolone has been needed to control the inflammatory activity, which has encouraged us to continue the therapeutic and prophylactic application of etanercept in this patient.

We describe a severe presentation of TRAPS with systemic amyloidosis recurring in a renal graft, despite a supposedly benign underlying mutation. Our patient's good clinical response to etanercept therapy is encouraging.

Note added to proof: At the age of 26 years, the sister of the index patient (Figure 4; III, 2) developed marked proteinuria, and subsequent biopsy of the kidney revealed amyloidosis, type AA.

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