Favorable Outcome after Treatment Using Antibiotics and Hydroxychloroquine in a Patient with Tumor Necrosis Factor Receptor-associated Periodic Syndrome: A 7-Year Follow-Up

Sir,

Tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) is an autosomal-dominant inherited periodic fever characterized by the prolonged episodes of periodic fever and localized inflammation related to mutations in the soluble TNF receptor super family 1A (TNFRSF1A).[1,2] Criteria to define TRAPS associate the clinical presentation and a plasma-soluble TNFRSF1A level measurement during the clinical attacks.[3,4]

A 40-year-old Caucasian male, working as a salesman in an office in the Paris region, was admitted for recurrent episodes of fever. He was completely healthy until the age of 35 years. At this time, he started to experience clinical episodes of high-grade fever (39°C), general weakness, headaches, abdominal and chest pain, arthralgia, myalgia, erythematous macules, periorbital edema, and conjunctivitis, but no weight loss. Each clinical episode lasted between 3 days and 1 week, occurring every month for the past 4 years. There was no family history of inflammatory or rheumatic disease. On admission, his laboratory tests showed a high level of C-reactive protein (100–350 mg/l, normal <5 mg/l) for each episode. Laboratory investigations for most likely infectious diseases were performed. Repeated screening included blood, urine, and stool cultures and laboratory tests for malaria and tuberculosis were negative. Serologic tests for human immunodeficiency virus, cytomegalovirus, Epstein–Barr virus, hepatitis B and C, West Nile virus, brucellosis, rickettsial infections, Lyme disease, salmonellosis, leptospirosis, *Coxiella burnetii*, syphilis, and toxoplasmosis were also negative. The possibility of an inflammatory or autoimmune disease was considered. Laboratory tests for rheumatoid factor, antinucleus antibodies, and ds-DNA antibodies were negative, and immunoglobulin serum level was normal. Human leukocyte antigen-B27 phenotype was absent. Serum ferritin level, especially the nonglycosylated form, was normal. The genetic test for familial Mediterranean fever (FMF) was negative. Chest, bone joint X-rays, thoracoabdominal computed tomography, transthoracic echocardiography, and gastrointestinal endoscopy were normal. Finally, all biological or medical imaging tests were negative.

After 5 years of recurrent similar clinical episodes, there was no confirmation of clinical diagnosis done definitively by pathology investigations. The patient presented with clinical signs compatible with and suggestive of TRAPS, but there was no available diagnostic test at the time.

However, symptoms were clinically suggestive of tick-borne infections such as relapsing fever or chronic Q fever. In view of the inability to make a definitive diagnosis for several years, despite many consultations and investigations in internal medicine, a chronic atypical infection was considered. It was decided, for the first time, to start an empirical antibiotic treatment known to be effective against these persistent infections. Antibiotic therapy was associated with hydroxychloroquine, the same way as reported for therapy of chronic Q fever.[5] The patient received amoxicillin (4 g/day), combined with hydroxychloroquine (200 mg/day). The clinical symptoms disappeared rapidly. One month later, the patient did not experience any expected clinical recurrence. It was decided to extend the duration of treatment to further 4 months. Years later, after the description of TRAPS in the literature, the laboratory which had performed the research of FMF mutation performed on an original frozen sample the molecular analysis of the TNFRSF1A gene and finally showed a R92Q mutation. The soluble type 1 TNF receptor (TNFR) could not be measured at this time, and the genetic diagnosis has been done years later.[4] The patient did not suffer from any further episodes of recurrent fever during a 7-year follow-up period.

This case report is the first one of TRAPS to be successfully treated with the association of amoxicillin and hydroxychloroquine. Clinical criteria include recurrent episodes of fever, abdominal and muscle and joint pain, skin rash, conjunctivitis, and periorbital edema. TRAPS is associated with mutations in the extracellular domain of the TNFR1 gene (TNFRSF1A). Patients presenting with TRAPS exhibit low serum levels of soluble TNFR1.

The penetrance of the R92Q mutation of the tumor necrosis factor superfamily 1A gene is incomplete; we thus hypothesize that the expression of the R92Q mutation is due to precipitating factors such as chronic infections. In this clinical setting, the rapid effective treatment of the triggering factor, a chronic infectious disease may explain why there were no further recurrent episodes of fever, in spite of the mutation responsible for TRAPS. However, immunomodulation due to hydroxychloroquine might have played a role in clinical improvement. Such infectious diseases could induce an excessive TNF-related inflammatory reaction in patients who carry this genetic mutation. The absence of clinical manifestation of TRAPS during the long follow-up period could have been due to the absence of new triggering factors such as infections. In this case, a triggering infectious factor

was successfully treated and no further episodes of clinical manifestations of TRAPS were reported till date. Antibiotic therapy for infectious diseases acting as precipitating factors for clinical episodes of TRAPS may be considered as an important measure in the management of TRAPS to be evaluated in the near future.

Key clinical message

The expression of the clinical signs and symptoms of the TRAPS could require both genetic factors (TNFRSF1A gene mutation) and precipitating factors such as chronic infectious diseases. Antibiotic therapy for infectious diseases acting as precipitating factors for clinical episodes of TRAPS may be considered as an important measure in the management of TRAPS. This needs to be evaluated in the near future. Successful management of recurrent clinical episodes of fever in TRAPS should involve timely identification of triggering factors and their treatment. This would prevent or abort the further clinical episodes of TRAPS. However, the absence of clinical manifestations of TRAPS during the long follow-up period does not claim the complete cure of a genetic disease such as TRAPS.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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