A Case Presenting with the Clinical Characteristics of Tumor Necrosis Factor (TNF) Receptor-associated Periodic Syndrome (TRAPS) without TNFRSF1A Mutations Successfully Treated with Tocilizumab

Tadashi Hosoya1, Fumitaka Mizoguchi1, Hisanori Hasegawa1, Keiko Miura2, Ryuji Koike1,3, Tetsuo Kubota1,4, Nobuyuki Miyasaka1 and Hitoshi Kohsaka1

Abstract

A 30-year-old woman had suffered from recurrent and self-limiting fevers since childhood. Although she had no mutations in the exons or introns of the tumor necrosis factor (TNF) receptor superfamily member 1A gene, her clinical characteristics were consistent with those of TNF receptor-associated periodic syndrome (TRAPS). She did not respond to treatment with etanercept, although tocilizumab therapy was successful, subsequently ameliorating her symptoms and preventing further inflammatory attacks. Interleukin-6 blocking therapy should be considered as a new alternative treatment in patients with TRAPS who do not respond to etanercept.

Key words: autoinflammatory syndrome, mutation-negative patient, TNF receptor-associated periodic syndrome (TRAPS), tocilizumab

(DOI: 10.2169/internalmedicine.54.3371)

Introduction

Tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) is an autoinflammatory syndrome associated with mutations in the TNF receptor superfamily member 1A (TNFRSF1A) gene. It is inherited in an autosomal dominant pattern with incomplete penetrance characterized by recurrent episodes of remittent fevers accompanied by rashes, periorbital edema, abdominal pain, migratory myalgia and arthralgia. These episodes may last from a few days to several weeks and resolve spontaneously (1, 2). Although the pathogenesis of TRAPS remains uncertain, mutations in TNFRSF1A induce the overproduction of proinflammatory cytokines and increase sensitivity to inflammatory stimuli, such as toll-like receptor ligands (3, 4). Defective shedding of TNF receptor 1 (TNFR1) results in the insufficient neutralization of circulating TNF-α (1), and some mutations in the TNFR1 gene impair TNF-driven apoptosis (5). In addition, the accumulation of misfolded TNFR1 in the cytoplasm activates the nuclear factor (NF)-κB pathway and mitochondrial reactive oxygen species (ROS) generation (3, 4), while mutated TNFR1 downregulates autophagy, which further induces the accumulation of TNFR1 in the cytoplasm (6). These abnormalities may be responsible for the clinical features of TRAPS.

The diagnosis of TRAPS is confirmed based on the detection of mutations in TNFRSF1A. However, in a large-scale study of patients exhibiting symptoms compatible with TRAPS, mutations in TNFRSF1A were found in only 10 of 18 families, and four of 176 sporadic cases (7). Furthermore, patients without known mutations demonstrate abnormalities in TNF receptor-associated cellular functions similar to those observed in mutation-positive TRAPS subjects (8), and it has been revealed that some mutation-negative patients have mutations in the intron regions of

1Department of Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University (TMDU), Japan, 2Division of Surgical Pathology, Tokyo Medical and Dental University Hospital, Japan, 3Clinical Research Center, Tokyo Medical and Dental University Hospital, Japan and 4Graduate School of Health Care Sciences, Tokyo Medical and Dental University (TMDU), Japan

Received for publication May 28, 2014; Accepted for publication August 4, 2014
Correspondence to Dr. Hitoshi Kohsaka, kohsaka.rheu@tmd.ac.jp
accompanied by shaking chills, nausea, rashes, migratory episodes was admitted to our department with a high fever. The patient’s long history of recurrent and self-limiting inflammatory attacks since childhood suggested a diagnosis of TRAPS (2). We therefore started treatment with 15 mg/day of PSL, which had relieved the symptoms associated with her past inflammatory attacks, in addition to 1 mg/day of colchicine. However, these therapies did not decrease the severity of the attacks. Under a clinical diagnosis of TRAPS, we initiated treatment with ETN at a dose of 25 mg twice per week. However, neither the frequency nor severity of the attacks changed during the four weeks of treatment. Because the patient’s serum IL-6 level was elevated, we administered 8 mg/kg of TCZ; three days later, her fever and symptoms resolved. Ten days after the first TCZ infusion, a fever of 39°C with shaking chills, nausea and migratory myalgia recurred. The same dose of TCZ was again administered 14 days after the initial infusion, which immediately ameliorated the patient’s symptoms (Fig. 2). Subsequently, she experienced a symptom-free period for 104 weeks, after which the TCZ administration was terminated upon her request. Six months later, however, she developed a fever of 38°C with nausea and persistent macular rashes in the extremities that lasted for 12 days. The TCZ treatment was therefore resumed, which promptly ameliorated these symptoms. Thereafter, continuous TCZ infusions completely prevented any further recurrence of the inflammatory attacks.

In order to obtain a definitive diagnosis of TRAPS, we conducted a genetic analysis of the patient’s peripheral blood cells. However, DNA sequencing of all exons and introns of genomic TNFRSF1A revealed no mutations. In addition, she exhibited no mutations in the entire exons and introns of other autoinflammatory syndrome-associated genes.

Case Report

A 30-year-old woman without a family history of febrile episodes was admitted to our department with a high fever accompanied by shaking chills, nausea, rashes, migratory myalgia and large joint pain. She reported experiencing the same febrile episodes in a recurrent manner since 7 years of age. The inflammatory attacks lasted for approximately one month and resolved spontaneously without medication. She took high-dose aspirin or 15 to 30 mg/day of prednisolone (PSL) occasionally to relieve the symptoms and shorten the duration of the episodes, which occurred several times a year. At 29 years of age, the patient developed bilateral aseptic necrosis of the femoral head and discontinued all medications. One year later, a remittent fever accompanied by migratory myalgia and large joint pain recurred and gradually worsened. Two weeks later, she was referred to our department.

On admission, the patient’s temperature was 39°C. A physical examination revealed periorbital edema and erythematous patches on the extremities and trunk (Fig. 1). The erythema was migratory and accompanied by muscle pain and a high fever. The fever and associated symptoms lasted for a few hours, resolved spontaneously and developed again several times a day. Laboratory examinations revealed an elevated level of C-reactive protein (CRP: 67.3 mg/L) and accelerated erythrocyte sedimentation rate (81 mm/h). Tests for antinuclear antibodies, antineutrophil cytoplasmic antibodies and IgM rheumatoid factor were negative, and the levels of complement components C3, C4 and CH50 were all within the normal ranges. The serum level of ferritin was within the normal range; however, the serum levels of TNF-α (5.4 pg/mL) and IL-6 (47.1 pg/mL) were elevated, while the level of IL-1β was below the limit of detection of 10 pg/mL.

The patient’s long history of recurrent and self-limiting inflammatory attacks since childhood suggested a diagnosis of an autoinflammatory syndrome, and her clinical features were characteristic of TRAPS (2). We therefore started treatment with 15 mg/day of PSL, which had relieved the symptoms associated with her past inflammatory attacks, in addition to 1 mg/day of colchicine. However, these therapies did not decrease the severity of the attacks. Under a clinical diagnosis of TRAPS, we initiated treatment with ETN at a dose of 25 mg twice per week. However, neither the frequency nor severity of the attacks changed during the four weeks of treatment. Because the patient’s serum IL-6 level was elevated, we administered 8 mg/kg of TCZ; three days later, her fever and symptoms resolved. Ten days after the first TCZ infusion, a fever of 39°C with shaking chills, nausea and migratory myalgia recurred. The same dose of TCZ was again administered 14 days after the initial infusion, which immediately ameliorated the patient’s symptoms (Fig. 2). Subsequently, she experienced a symptom-free period for 104 weeks, after which the TCZ administration was terminated upon her request. Six months later, however, she developed a fever of 38°C with nausea and persistent macular rashes in the extremities that lasted for 12 days. The TCZ treatment was therefore resumed, which promptly ameliorated these symptoms. Thereafter, continuous TCZ infusions completely prevented any further recurrence of the inflammatory attacks.

In order to obtain a definitive diagnosis of TRAPS, we conducted a genetic analysis of the patient’s peripheral blood cells. However, DNA sequencing of all exons and introns of genomic TNFRSF1A revealed no mutations. In addition, she exhibited no mutations in the entire exons and introns of other autoinflammatory syndrome-associated genes.

Figure 1. Skin rashes observed during the inflammatory attacks. Diffuse, faint, nonpalpable sites of erythema were noted on the lower limbs during the patient’s inflammatory attacks. These symptoms migrated to other extremities or the trunk in association with muscle pain.

TNFRSF1A (9). However, the etiology of most cases of mutation-negative TRAPS remains unknown (7), and mutations in other unidentified molecules may be responsible for the pathogenesis of mutation-negative TRAPS.

The aim of treatment for TRAPS is to relieve symptoms and prevent inflammatory attacks, which eventually result in the development of secondary amyloidosis. Because abnormalities in TNF receptor-associated cellular functions are related to the pathology of TRAPS, etanercept (ETN), a recombinant human soluble TNF receptor fusion protein, is commonly used as a first-line therapy. However, some patients do not respond to ETN. Infliximab (IFX) and other monoclonal antibodies against TNF-α should not be used in such cases since they may induce inflammatory attacks in patients with TRAPS, although the exact mechanisms remain unknown (10, 11). In addition, high-dose corticosteroids suppress the severity of febrile episodes, although they are not usually tolerated as maintenance treatment due to their adverse effects (2). Therefore, the development of an effective treatment for TRAPS is required in order to ameliorate symptoms and prevent inflammatory attacks. We herein report a case of mutation-negative TRAPS that was successfully treated with tocilizumab (TCZ), an anti-interleukin (IL-6) receptor monoclonal antibody.
Our patient with mutation-negative TRAPS did not respond to treatment with ETN, although TCZ therapy was successful. This case suggests that TCZ can be used to effectively ameliorate symptoms and prevent inflammatory attacks in patients with TRAPS.

Genetic studies have demonstrated that the mutation of TNFRSF1A is critically involved in the etiology of TRAPS, and several anecdotal reports have described the favorable effects of ETN in TRAPS patients. In addition, a clinical trial revealed that ETN ameliorates the severity of acute inflammatory attacks by one-third and reduces the frequency of inflammatory attacks by half on average. These results confirm the involvement of TNF in the pathogenesis of TRAPS. However, ETN treatment has been found to be ineffective or insufficient to ameliorate symptoms and fails to prevent all inflammatory attacks in some patients. There are no common features among responders to ETN treatment, including the presence or position of mutations in TNFRSF1A and/or clinical symptoms. These results suggest that TNF is not the only cytokine to play a central role in the onset of TRAPS-related conditions.

Although ETN therapy may have been inadequate to suppress the patient’s febrile attacks in the present case, the favorable response to TCZ suggests that IL-6 plays a crucial role in the pathogenesis of TRAPS. Similarly, one case report described the efficacy of TCZ in a steroid-dependent and ETN-resistant patient with TRAPS. In addition, IL-1 blocking therapy has been reported to be effective in patients resistant to ETN. These results indicate that TNF is not the only critical target in the treatment of TRAPS. Therefore, IL-6 blocking therapy should be considered as a new alternative treatment option in patients with TRAPS who do not respond to ETN.

TCZ has been reported to prevent amyloidosis in the setting of several chronic inflammatory diseases, including rheumatoid arthritis and Castleman’s disease. TCZ may also be effective in preventing the development of amyloidosis in patients with TRAPS, one of the most severe complications of this disorder.

The present patient exhibited clinical manifestations characteristic of TRAPS, without any identified mutations in the TNFRSF1A gene. Somatic mosaicism may account for this discrepancy, as reported in cases of chronic infantile neurological cutaneous and articular (CINCA) syndrome and Muckle-Wells syndrome. In addition, the lack of mutations in this case may be due to the presence of mutations in other genes related to the aberrant regulation of cytokine production and/or initiation of inflammation.

In conclusion, IL-6 blocking therapy may be a useful treatment for TRAPS. However, further clinical investigations are required to confirm its efficacy in both mutation-positive and -negative TRAPS patients.

**Discussion**

Our patient with mutation-negative TRAPS did not respond to treatment with ETN, although TCZ therapy was successful. This case suggests that TCZ can be used to effectively ameliorate symptoms and prevent inflammatory attacks in patients with TRAPS.

Genetic studies have demonstrated that the mutation of TNFRSF1A is critically involved in the etiology of TRAPS, and several anecdotal reports have described the favorable effects of ETN in TRAPS patients. In addition, a clinical trial revealed that ETN ameliorates the severity of acute inflammatory attacks by one-third and reduces the frequency of inflammatory attacks by half on average. These results confirm the involvement of TNF in the pathogenesis of TRAPS. However, ETN treatment has been found to be ineffective or insufficient to ameliorate symptoms and fails to prevent all inflammatory attacks in some patients. There are no common features among responders to ETN treatment, including the presence or position of mutations in TNFRSF1A and/or clinical symptoms. These results suggest that TNF is not the only cytokine to play a central role in the onset of TRAPS-related conditions.

Although ETN therapy may have been inadequate to suppress the patient’s febrile attacks in the present case, the favorable response to TCZ suggests that IL-6 plays a crucial role in the pathogenesis of TRAPS. Similarly, one case report described the efficacy of TCZ in a steroid-dependent and ETN-resistant patient with TRAPS. In addition, IL-1 blocking therapy has been reported to be effective in patients resistant to ETN. These results indicate that TNF is not the only critical target in the treatment of TRAPS. Therefore, IL-6 blocking therapy should be considered as a new alternative treatment option in patients with TRAPS who do not respond to ETN.

TCZ has been reported to prevent amyloidosis in the setting of several chronic inflammatory diseases, including rheumatoid arthritis and Castleman’s disease. TCZ may also be effective in preventing the development of amyloidosis in patients with TRAPS, one of the most severe complications of this disorder.

The present patient exhibited clinical manifestations characteristic of TRAPS, without any identified mutations in the TNFRSF1A gene. Somatic mosaicism may account for this discrepancy, as reported in cases of chronic infantile neurological cutaneous and articular (CINCA) syndrome and Muckle-Wells syndrome. In addition, the lack of mutations in this case may be due to the presence of mutations in other genes related to the aberrant regulation of cytokine production and/or initiation of inflammation.

In conclusion, IL-6 blocking therapy may be a useful treatment for TRAPS. However, further clinical investigations are required to confirm its efficacy in both mutation-positive and -negative TRAPS patients.

**Author’s disclosure of potential Conflicts of Interest (COI).**


**Acknowledgement**

The authors thank Drs. Daniel L. Kastner and Ivona Aksentijevich (Inflammatory Disease Section, National Human Genome Research Institute), Dr. Hiroaki Ida (First Department of Internal Medicine, Nagasaki University Hospital of Medicine and Dentistry) and Dr. Tomohiro Morio (Department of Pediatrics and Developmental Biology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University) for performing the genetic analyses.

**References**

1. McDermott MF, Aksentijevich I, Galon J, et al. Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory