Case Report
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The First Case of a Korean Patient with a Mutation-Confirmed Tumor Necrosis Factor Receptor-Associated Periodic Syndrome

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Tumor necrosis factor receptor-associated periodic syndrome (TRAPS, OMIM: #142680) is a rare autoinflammatory disease (AID) with recurrent febrile episodes. To our knowledge, we report herein the first case of a patient with TRAPS in South Korea whose symptoms included fever, arthralgia, abdominal pain, rash, myalgia, cough, and lymphadenopathy. A pathogenic de novo mutation, c.175T>C (p.Cys59Arg), in the tumor necrosis factor receptor superfamily member 1A (*TNFRSF1A*) gene, was confirmed by gene sequencing. The patient has been with tocilizumab (an interleukin-6 inhibitor); tocilizumab administration every other week has completely alleviated the patient's symptoms. Our report further expands the clinical spectrum of patients with TRAPS and reaffirms the use of tocilizumab as a viable alternative treatment option for those patients who are unsatisfactorily responsive to other commonly used biologics, such as canakinumab, anakinra, infliximab, and etanercept. Furthermore, our report may aid in increasing awareness about the existence of mutation-confirmed TRAPS in South Korea in addition to emphasizing the importance of actively pursuing genetic testing to correctly diagnose rare AID.

Key Words: TRAPS, *TNFRSF1A*, tocilizumab, tumor necrosis factor receptor-associated periodic syndrome, autoinflammatory disease

INTRODUCTION

Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is an autosomal-dominant autoinflammatory disease (AID) caused by pathogenic variants in the tumor necrosis factor receptor superfamily member 1A (*TNFRSF1A*) gene.[1] Since the identification of pathogenic TRAPS-inducing mutations in 1999,[2] many variants in the *TNFRSF1A* gene, particularly in the region coding the extracellular domain of the receptor, have been reported.[1] The clinical manifestations of TRAPS include conjunctivitis, rash, myalgia, arthralgia, fever, abdominal pain, and amyloidosis.[1,3] In the previous Korean study where 1777 patients were analyzed for an AID, none was found to possess a pathogenic mutation in the *TNFRSF1A* gene.[4] Herein, we report the first case of a Korean patient with a pathogenic *TNFRSF1A* mutation who was initially diagnosed with systemic juvenile idiopathic arthritis (sJIA), but was then correctly diagnosed with TRAPS after 15 years.

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CASE REPORT

In 1993, an 18-month-old girl visited our tertiary referral hospital due to peanut aspiration, and fever was observed for the first time (Fig. 1). Five years later, she was diagnosed with Kawasaki disease. After 6 months, she had sustained a fever for 8 days, which was probably the beginning of recurrent febrile episodes. Hand-written accounts of her medical records before 2006 indicated that, at 6–13 years of age, she visited our hospital 1–3

times yearly due to fever. At 13 years of age, she was admitted due to fever and abdominal pain. Abdominal pelvic computed tomography (APCT) demonstrated mesenteric lymphadenitis with enteritis (Fig. 2A, Fig. 1-APCT[1]). Fever persisted for 8 days, and naproxen was administered for the first time. The diagnosis of sJIA–although arthritis was not apparent at the time–was then suspected clinically for the first time. After 1 year, the patient complained of pain in both knees. From 16 to 19 years of age, she experienced various episodes of shoulder and abdominal pain, fever, cough, and arthralgia, which were mostly controlled by naproxen. At 20 years of age, she was admitted due to fever, both wrist and shoulder pain, myalgia, headache, and rashes on both upper arms. These symptoms responded well to prednisolone and naproxen. From 20 to 22 years of age, she experienced episodes of fever, cough, rash, and arthralgia.

At 23 years of age, the patient experienced left ankle pain and developed swelling and rash on both ankles (Fig. 2C, Fig. 1-Rash[2]), which were regarded as a flare-up of sJIA. MRI of the left ankle revealed inflammatory arthritis (Fig. 2B, Fig. 1-MRI ankle[3]), which was treated with glucocorticoids, naproxen, and additionally methotrexate and sulfasalazine for the first time. After 3 months, although her ankle pain and swelling abated, recurrent episodes of epigastric and suprapubic pain followed. During this period, APCT revealed pelvic mesenteric haziness with peritoneal thickening and minimal pelvic ascites. Consultation for possible pelvic inflammatory disease and cystitis were inconclusive.

At 24 years of age, the patient visited our emergency department with unprecedented degree of epigastric pain, which she described as "twisting and tearing." APCT suggested a small bowel volvulus (Fig. 2D, Fig. 1-Volvulus[4]). Emergent exploratory laparotomy revealed the presence of adhesion band and proximal jejunal volvulus with bowel discoloration (Fig. 2E), which was restored after bandlysis. She developed a hypertrophic scar at the incision site (Fig. 2F).

Next year, after the appointment of a new primary physician, the patient presented with right knee pain and rash. Prednisolone, sulfasalazine, and naproxen were prescribed. However, after receiving treatment for 2 weeks, arthralgia at other joints, rash, and recurrent fever occurred more frequently. With a diag-

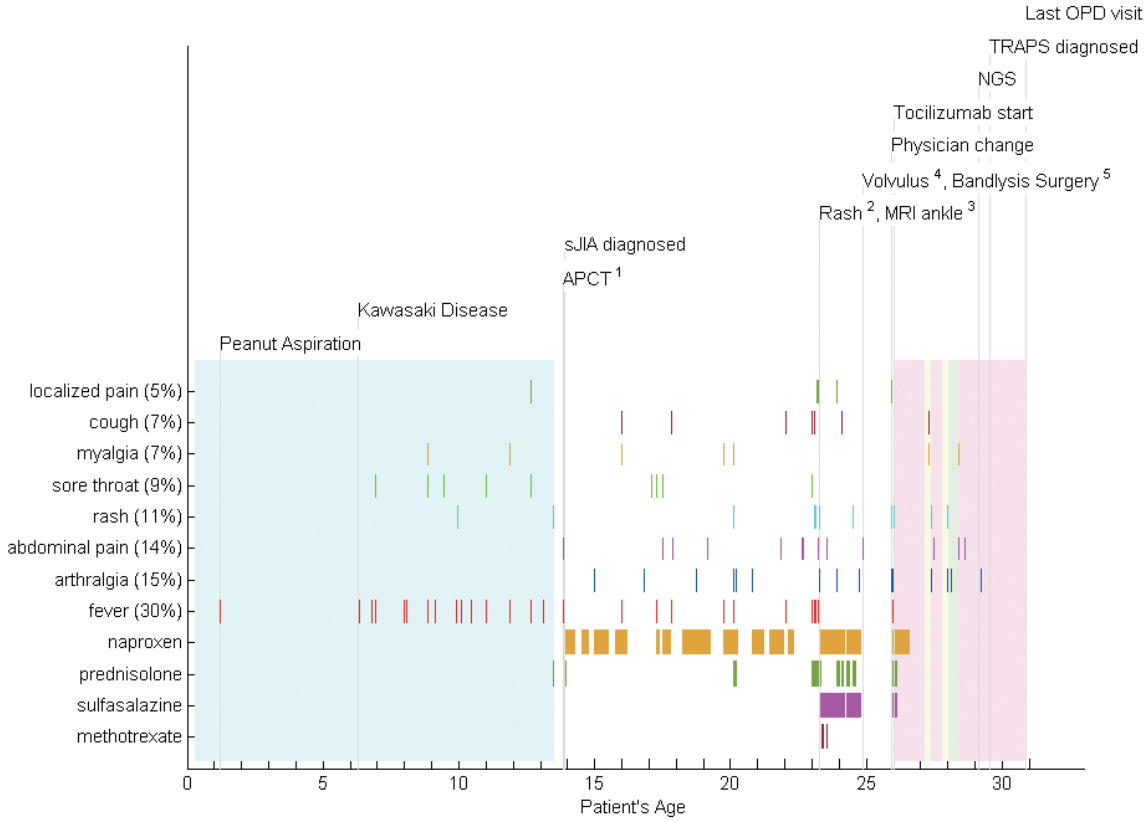

Fig. 1. Timeline of the patient's medical history. Major events are indicated in chronological order as gray lines connecting the patient's age and the corresponding event. X-axis: patient's age in years; Y-axis: from the bottom to the top. The first 4: the prescription dates for methotrexate, sulfasalazine, prednisolone, and naproxen are indicated as colored bars. The next 8: the 8 major symptoms of the patient are indicated as colored bars. The frequency of each symptom is indicated as a percentage within parentheses. Light-blue-shaded background: the period prior to the adoption of electronic medical record system in our hospital. Written medical accounts were reviewed for dates, symptoms, and major events. Medication history was not re-constituted. Pink-shaded background: tocilizumab administration every 2 weeks. Yellow-shaded background: tocilizumab-tapering period. Tocilizumab tapering was scheduled by delaying every subsequent tocilizumab injection for an additional 1 week. Light-green-shaded background: tocilizumab administration every 4 weeks. APCT[1] refers to Fig. 2A. Rash[2] refers to Fig. 2C. MRI ankle[3] refers to Fig. 2B. Volvulus[4] refers to Fig. 2D. Bandlysis surgery[5] refers to Fig. 2E. APCT, abdominal pelvic computed tomography; OPD, out-patient department; NGS, next-generation sequencing.

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nosis of sJIA, tocilizumab was initiated on an every-2-week dosing schedule for the first time at 25 years of age. Two weeks later, fever and rash disappeared, and arthralgia was improved. Even after prednisolone, sulfasalazine, and naproxen were tapered off, the patient reported no symptoms. After biweekly tocilizumab administration for 13 months, she proceeded with tocilizumab tapering, which was scheduled by delaying every subsequent tocilizumab injection for an additional 1 week. However, when dosing interval was prolonged to 5 weeks, she developed left elbow pain, swelling and rash. Her symptoms disappeared after returning to the biweekly tocilizumab administration. After 4 months, tocilizumab tapering was re-initiated and once again, when tocilizumab dosing interval was prolonged to 5 weeks, she developed right neck swelling and arthralgia. Every 4-week dosing also proved to be inadequate in preventing the symptoms. Thus, tocilizumab administration every 2 weeks was maintained without further tapering. The ESR, white blood cell count, platelet number, C-reactive protein, ferritin, SAA, and fibrinogen levels all strikingly responded to both tocilizumab administration and tocilizumab dosing interval (Fig. 3). Hemoglobin levels also gradually increased, which likely reflected recovery from anemia of chronic inflammation (Fig. 3).

In 2021, when the patient was 29 years old, next-generation sequencing was performed considering the patient's history and continued dependence on tocilizumab. A pathogenic variant of NM_001065.4:c.175T>C (p.Cys59Arg) in the *TNFRSF1A* gene was detected, and a subsequent trio test confirmed a de novo mutation. This mutation is one of the original six mutations reported in 1999,[2,5] and it has been experimentally demonstrated that the mutated receptors do not form soluble receptors and are retained in the endoplasmic reticulum due to protein misfolding and abnormal oligomerization.[6] The patient is still solely on a biweekly tocilizumab administration and remains without symptoms.

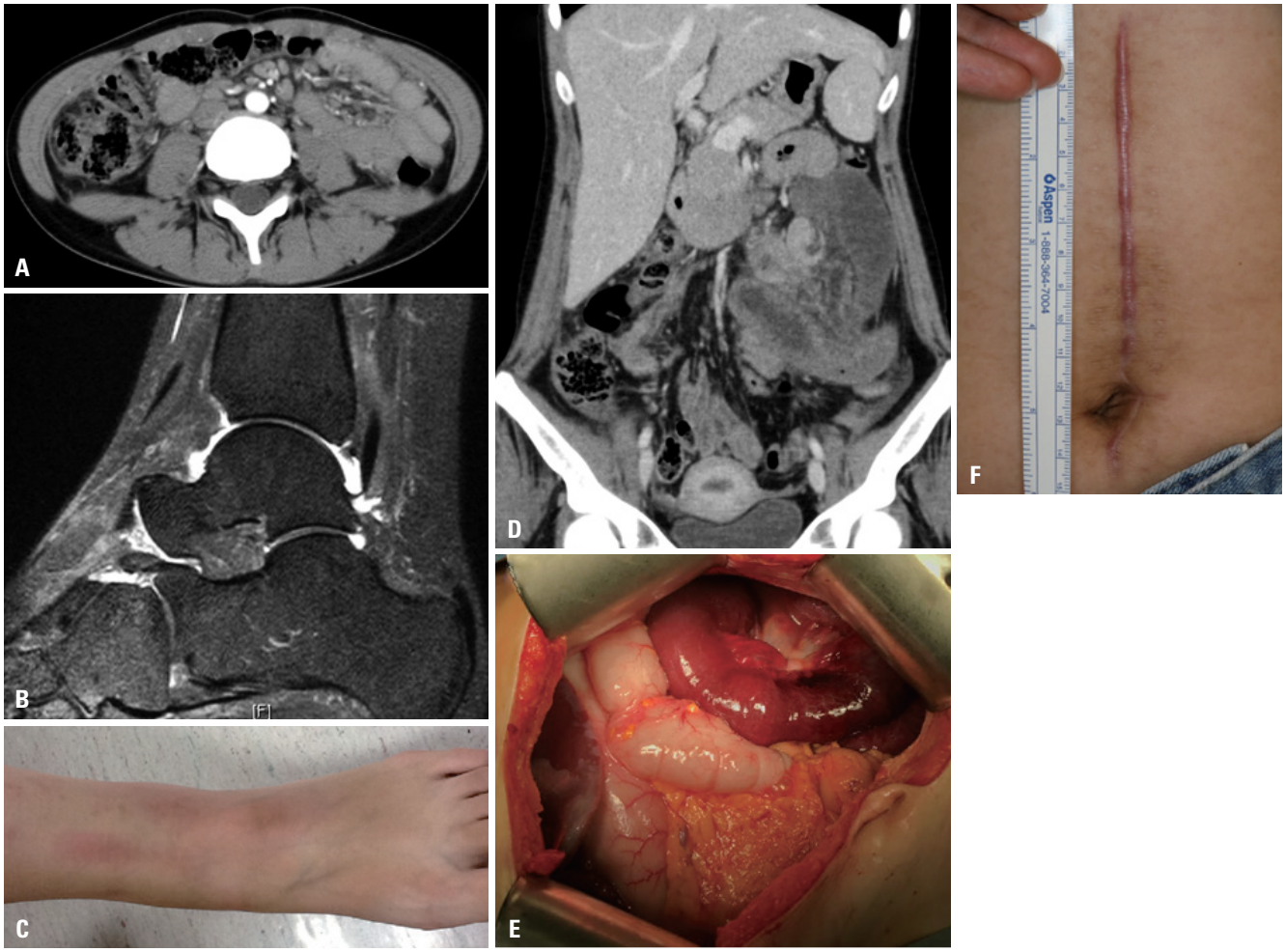

Fig. 2. Imaging data and pictures of the patient. (A) Abdominal pelvic computed tomography (APCT) of the patient corresponding to Fig. 1-APCT[1]. Note lymphadenopathy around the mesenteric vessels. (B) Magnetic resonance imaging of the left ankle corresponding to Fig. 1-MRI ankle[3]. Note joint effusion in the tibiotalar and subtalar joint with mild synovial enhancement, which indicated inflammatory arthritis. (C) Rash on the left ankle during a TRAPS flare-up corresponding to Fig. 1-Rash[2]. (D) APCT showing a small bowel volvulus corresponding to Fig. 1-Volvulus[4]. (E) Exploratory laparotomy corresponding to Fig. 1-Bandlysis surgery[5]. Note the small bowel discoloration. (F) A hypertrophic scar developed at the surgical incision site. Refer to the text for details. TRAPS, tumor necrosis factor receptor-associated periodic syndrome.

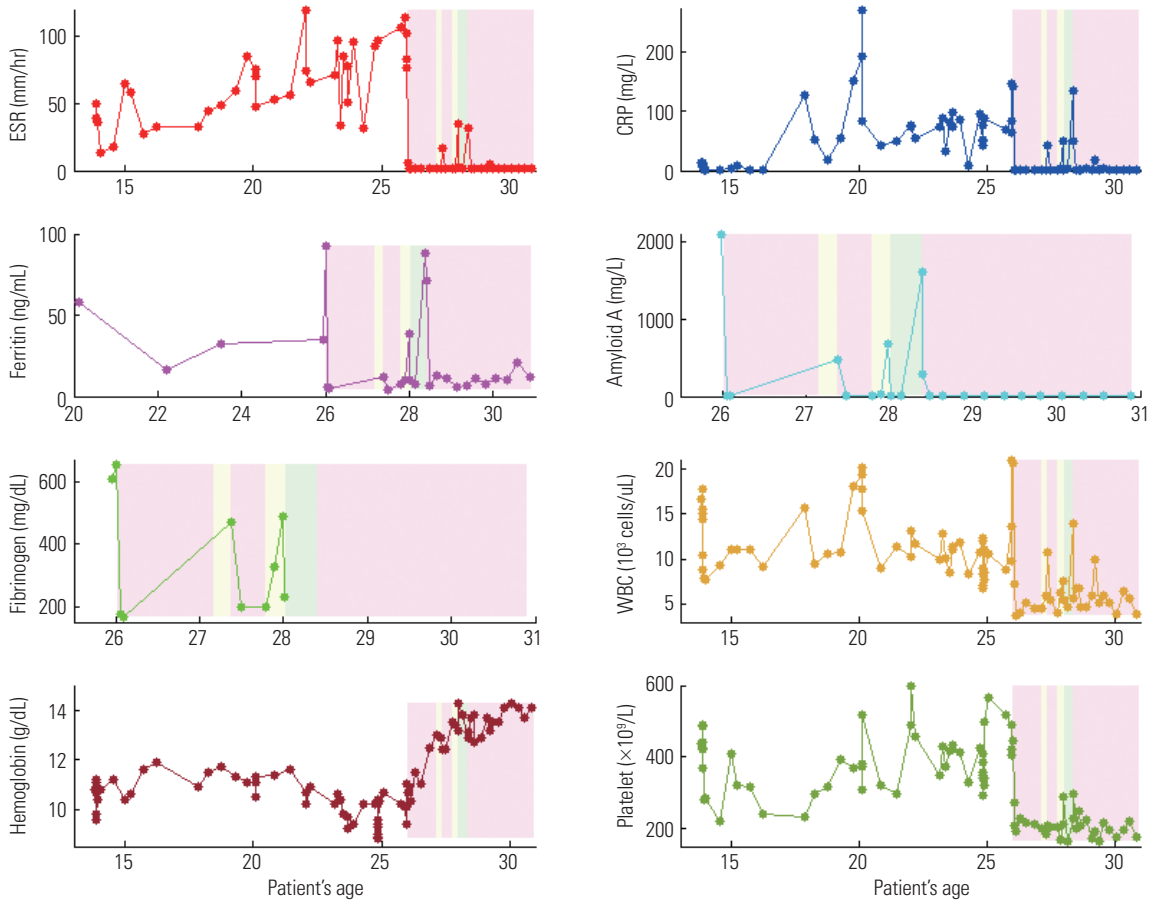

Fig. 3. Trends for the erythrocyte sedimentation rate (ESR), white blood cell count (WBC), platelet count, and levels of C-reactive protein (CRP), ferritin, serum amyloid A, fibrinogen, and hemoglobin in the patient. X-axis: the patient's age; Y-axis: the corresponding laboratory values. Pink-shaded background: tocilizumab administration every 2 weeks. Yellow-shaded background: tocilizumab-tapering period. Tocilizumab tapering was scheduled by delaying every subsequent tocilizumab injection for an additional 1 week. Light-green-shaded background: tocilizumab administration every 4 weeks. Note the rapid decrease in ESR, white blood cell count, platelet count, and levels of CRP, ferritin, serum amyloid A, and fibrinogen once tocilizumab administration (the first pink-shaded background) was initiated. When tapering was commenced (the first yellow-shaded background), the laboratory values started to increase. After tocilizumab administration returned to every-2-week administration (the second pink-shaded background), the laboratory values started to decrease again. Tapering was attempted once more (the second yellow-shaded background), and tocilizumab administration was prolonged to every 4 weeks (the green-shaded background). Eventually, every-2-week administration was necessary to control inflammation (the third pink-shaded background). Refer to the text for details.

DISCUSSION

This is the first reported case of a patient with TRAPS in South Korea who was successfully treated with tocilizumab. TRAPS and other AID, such as familial Mediterranean fever, mevalonate kinase deficiency, or cryopyrin-associated periodic syndrome, usually take years to be diagnosed as a clinician's keen suspicion based on a patient's history, physical examination, and exclusion of other possible diseases, such as infection, neoplasm, or autoimmune disease, are required.[1,7,8] Since the initial diagnosis of sJIA in 2006, it took another 15 years for the patient to be finally diagnosed with TRAPS, highlighting the importance of genetic testing for diagnosing AID.[7-9]

As the first-line therapy for TRAPS, canakinumab, anakinra, or infliximab is usually considered.[10] Since the involvement of interleukin-6-mediated cell signaling is well recognized in TRAPS, tocilizumab has been regarded as a treatment option.[11,12] Successful treatment with tocilizumab in patients with TRAPS have been reported in a few case reports where a patient unresponsive to anakinra and etanercept successfully responded to tocilizumab treatment,[12] a patient unresponsive to infliximab[13] and etanercept showed clinical improvement by tocilizumab treatment,[14] and a mutation-negative patient with TRAPS unresponsive to colchicine and etanercept was effectively treated by tocilizumab.[15] However, our case is the first in which tocilizumab was administered first without a previous trial of other biologics and was found to be effective for the longest duration–more than 5 years–documented so far in the literature. Our case report further strengthens the use of tocilizumab as a treatment option for TRAPS effective for a period of at least 5 years.

This study was approved by the IRB of Severance Hospital (2023-1642-001). The informed consent of the patient was obtained.

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AUTHOR CONTRIBUTIONS

Conceptualization: all authors. Data curation: all authors. Formal analysis: Seok-Jin Lee, Jee Yeon Baek, and Jong Gyun Ahn. Investigation: all authors. Methodology: Seok-Jin Lee, Jee Yeon Baek, Ji Young Lee, and Jong Gyun Ahn. Project administration: Seok-Jin Lee and Jong Gyun Ahn. Supervision: Jong Gyun Ahn. Validation: Ji-Man Kang and Jong Gyun Ahn. Visualization: Seok-Jin Lee and Jee Yeon Baek. Writing—original draft: Seok-Jin Lee. Writing—review & editing: Seok-Jin Lee and Jong Gyun Ahn. Approval of final manuscript: all authors.

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