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CASE REPORT

Recurrent abdominal pain as the presentation of tumor necrosis factor receptor-associated periodic syndrome (TRAPS) in an Asian girl: A case report and review of the literature

Yun-Ju Chen [a], Hsin-Hui Yu [a], Yao-Hsu Yang [a], Yu-Lung Lau [b], Wen-I Lee [c], Bor-Luen Chiang [a,*]

[a] *Department of Medical Research, National Taiwan University Hospital, Taipei, Taiwan*
[b] *Department of Paediatrics and Adolescent Medicine, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong, China*
[c] *Department of Pediatric Allergy, Immunology, and Rheumatology, Chang Gung University and Children's Hospital, Taoyuan, Taiwan*

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Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is characterized by periodic fever, cutaneous rash, conjunctivitis, lymphadenopathy, abdominal pain, myalgia, and arthralgia. It is a rare autosomal dominant disease and strongly associated with heterozygous mutations in the tumor necrosis factor (TNF) receptor super family 1A (*TNFRSF1A*) gene. It is believed to be more common in Western countries than in Asian countries. Here, we present the case of a 14-year-old girl with periodic fever and abdominal pain with elevation of inflammatory markers for 2 years. After extensive work-up of infectious etiology with negative results, the diagnosis of TRAPS was made although no gene mutations were identified in the *TNFRSF1A* gene, *MVK* gene, and *NALP3/CIAS1* gene. She had partial clinical response to corticosteroids and immunomodulatory agents. However, the treatment response to TNF-α inhibitor etanercept was dramatic. She has remained symptom free under regular weekly to biweekly

* Corresponding author. Department of Pediatrics, National Taiwan University Hospital, Number 7, Chung-Shan South Road, Taipei 100, Taiwan.
E-mail address: gicmbor@ntu.edu.tw (B.-L. Chiang).

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etanercept treatment for 2 years. We also reviewed the related literature and summarized the data of 10 Asian cases of TRAPS.

Introduction

Hereditary periodic (recurrent) fever syndromes are a group of autoinflammatory diseases characterized by recurrent episodes of unprovoked inflammation without high-titer autoantibodies or autoreactive T cells. Seven diseases exhibit Mendelian patterns of inheritance with identified single gene defects.[1] They include familial Mediterranean fever (FMF), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), pyogenic sterile arthritis, pyoderma gangrenosum and acne (PAPA), hypergammaglobulinemia D with periodic fever syndrome (HIDS) and three overlapping conditions, the cryopyrinopathies, with common cryopyrin abnormalities: familial cold autoinflammatory syndrome (FCAS); Muckle-Wells syndrome (MWS); and neonatal-onset multisystem inflammatory disease (NOMID), also known as chronic infantile neurologic cutaneous articular syndrome (CINCA). Hereditary periodic fevers are characterized by recurrent flares of systemic inflammation presenting as sudden episodes of fever associated with a dramatic elevation of acute phase reactants and a number of clinical manifestations, such as rash, serositis (peritonitis, pleuritis), lymphadenopathy, and arthritis.[2] Disease flares are usually separated by symptom-free intervals of variable duration, characterized by complete well-being, normal growth, and complete normalization of acute phase reactants. The clinical spectrum of these disorders is also extremely variable.

TRAPS is characterized by periodic fever (duration of more than 1 week), migratory cutaneous rash, conjunctivitis, periorbital edema, lymphadenopathy, abdominal pain, myalgia, arthralgia, and serositis. It is an autosomal dominant disease that is related to heterozygous mutations in the tumor necrosis factor (TNF) receptor super family 1A (*TNFRSF1A*) gene encoding TNF receptor type 1 (TNFR1). Levels of acute-phase reactants are elevated during attacks and also during asymptomatic periods. TRAPS is the second most common disease among hereditary periodic fever syndromes following FMF. Although people of any ethnicity may be affected, there have been few reports to date with regards to patients from Asia. Here, we presented the case of a 14-year-old Asian girl with recurrent fever and abdominal pain for 2 years who was finally diagnosed with TRAPS, and had good response to etanercept, an anti-TNF-α agent.

Case report

A 14-year-old girl presented with ten periodic episodes of severe periumbilical abdominal pain with fever for nearly 2 years. The abdominal pain was not related to menstruation and was not associated with vomiting. The episodes lasted for 10—14 days and recurred at intervals of 1 month. The fever had a characteristic feature of the body temperature rising to 39°C or higher on a daily basis. Physical examination revealed diffuse tenderness and left rebound pain without hepatosplenomegaly. None of the episodes were associated with lymphadenopathy, skin rash, arthritis, arthralgia, conjunctivitis, or periorbital edema. She led a normal life during symptom-free days and had normal growth, and she did not have a family history of similar conditions. She had been diagnosed with acute abdomen or intra-abdominal infections without proven pathogens of bacteria, tuberculosis or parasites. Diagnostic laparoscopy was conducted several times and revealed only ascites. Abdominal computed tomography (CT) showed para-aortic and mesenteric lymphadenopathies. There was a marked acute phase response indicated by elevation of white blood cell (WBC) count (15,680/μl), C-reactive protein (CRP; 16.98 mg/dl), erythrocyte sedimentation rate (43 mm/hour), C3 (166 mg/dl), and C4 (32.9 mg/dl). Other laboratory investigations showed elevated serum TNF-α levels (61.7 pg/ml), negative antinuclear antibodies and normal serum immunoglobulin D concentrations. Gallium scan showed diffusely increased tracer uptake in the bone marrow of vertebral bones, however bone marrow study revealed normal findings. Repeated panendoscopy, small intestinal endoscopy, and colon fibroscopy revealed gastric, duodenal, small intestinal, and colon ulcerations. The pathologic findings of colon biopsies showed inflammatory infiltrates with IgM^+ plasma cells and diffuse $CD8^+$ cytotoxic T cells; however, there was an absence of $CD4^+$ T-helper cells. The epithelium was focally destructed by $CD8^+$ cytotoxic T cells.

Based on the patient's clinical history, TRAPS was highly suspected. After informed consent was obtained, sequence sequencing of the *TNFRSF1A gene*, *MVK* gene (for hyper-IgD syndrome), and *NALP3/CIAS1* gene (for familial cold-autoinflammatory syndrome or MWS) were performed. However, no mutations were found in the promoter or coding regions of these genes. She was treated with nonsteroidal anti-inflammatory drugs (NSAIDs), colchicines (0.5 mg twice per day); however, the response was poor. The abdominal pain and fever came under control after using a short course of intravenous methylprednisolone (2 mg/kg/day) for 5 days. The episodic clinical symptoms were only partially controlled by immunomodulatory drugs (azathioprine 1.6 mg/kg/day and mesalamine 30 mg/kg/day). However, the abdominal pain and fever had a dramatic response to a TNF-α inhibitor, etanercept (0.4 mg/kg/dose biweekly) monotherapy. Normalization of the inflammatory parameters such as WBC and CRP were found after etanercept usage. She has remained symptom free under regular weekly to biweekly etanercept therapy for 2 years. It is worth mentioning that severe abdominal pain without fever rapidly occurred after missing one dose of etanercept during these 2 years of treatment.

Table 1 Primers used for PCR sequencing of the TNFRSF1A gene, and RT-PCR of MVK gene, and NALP3/CIAS1 gene

Gene	Forward primer	Backward primer
MVK	CCAGGAGCCATGTTGTCAGA	GGTGTTGGTCAGCAGGAT
	CACGAAGTTGTGCCTACC	TGGCCAGCACAGAGTCGAAC
NALP3	AGCCACGCTAATGATCGACT	TATGCCAGTCAGTGCAGAGC
	GATCGTGAGAAAACCCTCCA	CTTCCTCCTTGGGCATGTTA
	GCTTCGACATCTCCTTGGTC	TCTGGCTGGAGGTCAGAAGT
	AACTGTCATCGGGTGGAGTC	ATGGATCGCAGCTCTCTC
TNFRSF1A	GGCTTATTGCCCCTTGGTGTT	TGGCTGAGGTTAGGACCTGCA
	GAATGTTTCACTGAGGAAGGAC	CACCAAAACACACACCTTCCTG
	GGACACTGCATGGATGTGAGT	CAGTAGGACCCTGAGCACTCT
	GATGTCCAACAATCTGTGTGGT	TCACCTCCCTCCACACATGTC
	TGAGGCATGTGACCACAAGTC	CGCCTCTCGTGGTCCCCTCT
	TTTCTCCCGCGGCTGGAGACGA	CGCAGGCAGCTGAGAAAAGCT

Sequencing of the *TNFRSF1A* gene

The genomic polymerase chain reaction (PCR) was performed using the HotStarTaq Plus PCR system (Qiagen GmbH, Hilden, Germany). Genomic DNA was amplified using the sense and antisense primers (Table 1) according to the manufacturer's protocol. PCR cycling was performed in a thermocycler as follows: 5 minutes of initial denaturation at 94°C, followed by 50 thermal cycles (denaturation for 30 seconds at 94°C, annealing for 1 minute at 60°C, and extension for 1 minute at 72°C), completed with 2 minutes of incubation at 72°C. The PCR product was analyzed by 1.5% agarose gel electrophoresis. DNA sequencing was performed on both strands using BigDye Terminator v3.1 Cycle Sequencing Kit and 3730xl DNA Analyzer (Applied Biosystems, Foster City, CA, USA).

Sequencing of the *MVK* and *NALP3/CIAS1* genes

Total RNA was isolated from peripheral blood mononuclear cells with TRIzol^{R} (Life Tech, Carlsbad, CA, USA). Reverse mRNA transcription followed by polymerase chain reaction (RT-PCR) was performed as previously described (Lee et al. 2005).[3] Briefly, 1 μg of RNA in a total volume of 20 μl was reverse-transcribed into cDNA using oligo-dT primers (Invitrogen, Carlsbad, CA, USA) and superscript RNaseH-reverse transcriptase (Qiagen, Chatsworth, CA, USA), and then amplified using 1 μl of cDNA in a total volume of 20 μl containing 0.5 U High Fidelity Taq DNA polymerase (Invitrogen), 1.875 mmol/L MgSO4, 200 μmol/L dNTP, and 500 nmol/L of one pair of oligonucleotide primers selected to cover the indicated coding region of the candidate genes (Table 1). The mutations identified from the cDNA were confirmed by sequence analysis of genomic DNA. Sequencing was performed using the BigDye Terminator kit and an ABI PRISM 3100 DNA Sequencer (Applied Biosystems, Foster City, CA, USA).

Discussion

In our case, the clinical features were compatible with TRAPS, including periodic attacks of fever lasting at least 1 week, abdominal pain, the presence of an acute-phase response when symptomatic, and a poor response to colchicines. Our patient lacked symptoms such as skin rash, conjunctivitis, arthralgia, or myalgia. Etanercept resulted in disease remission and prevented disease recurrence. Furthermore, discontinuing the drug caused disease flare-ups. The incidence of TRAPS varies among different ethnic groups. Most of the reported cases of TRAPS have involved individuals of northern European ancestry including Irish, Scottish, Finnish, French, and Dutch populations, and families of other ethnic groups such as Jewish, and Puerto-Rican have also been described. Reports involving Asian people are quite rare, and most reported cases have involved individuals from Japan. To the best of our knowledge, this is the first case reported in Taiwan.

No mutations in the *TNFRSF1A* gene, *MVK* gene (for HIDS) or *NALP3/CIAS1* gene (for FCAS, MWS, NOMID/CINCA) were found in our patient. TRAPS has been associated with at least 84 different mutations of the TNF receptor superfamily 1A gene (*TNFRSF1A*) encoding for the transmembrane TNFR1 protein, also known as p55 TNFR (INFEVERS TRAPS database: http://fmf.igh.cnrs.fr/infevers). *TNFRSF1A* mutations have been identified in a minority of patients, and mainly in association with a positive family history. In two families and in 90 sporadic cases that presented with TRAPS-like symptoms, Aksentijevich *et al.*[4] did not identify any TNFRSF1A mutations. Another large study by Aganna *et al.*[5] showed that only four of 176 patients with sporadic (non-familial) TRAPS-like symptoms were found to have TNFRSF1A mutations. Since TNFRSF1A mutations can not be identified in a proportion of patients with TRAPS-like phenotype, further studies to rule out the involvement in the pathogenesis of TRAPS of some of the genes known to regulate TNFR1 shedding, TNF-induced nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signal and transcription are needed. Unidentified genes remain to be investigated by a candidate gene approach in the TNF pathway or by applying the genome-wide function-free sequencing approach.[6]

The pathogenic mechanisms underlying TRAPS remain unresolved. Activation of TNFR1 by TNF causes cleavage and shedding of the extracellular part of TNFR1 from the cell surface into the circulation. The secreted form of TNF receptor acts as a natural inhibitor of TNF-α. *TNFRSF1A* mutations were formerly thought to cause inflammation by

Table 2 Summary of cases of Asian patients with TRAPS

Case	Age (y)/ Sex	Onset	Ethni -city	Fever	Myalgia	Arthralgia arthritis	Skin rash	Abdominal pain	LAP	Conjunctivitis	Fever		Laboratory data				TNFRSF1A Gene mutation[c]	Tx	Ref
											Duration (d)	Interval (m)	WBC (/μl)	CRP (mg/dl)	ESR (mm/hr)	sTNFRSF1A (pg/ml)	TNF-α (pg/ml)		
1	14F	I	Jap	+	−	+	+	−	−	+	14	2	46,570	28	128	461	<5	C70S	S	15
2	16M	I	Arab	+	+	+	+	+	+	−	10	1-2	—	>20	>100	627	—	C70R	Col, N	16
3	32M	C	Jap	+	−	−	+	−	−	−	5	Several	—	—	—	—	—	C70 G	N	17
4[a]	27F	A	Jap	+	+	+	+	−	−	+	—	—	200,00	5	—	2000+	369	T61I	—	18
5[b]	10M	I	Jap	+	+	+	+	+	−	−	14	1–2	25,400	4.8	68	378	<5	C30Y	S, N	19
6[b]	7F	C	Jap	+	−	+	−	+	−	−	<14	1–2	—	7.3	—	1660	—	C30Y	S, N	19
7[b]	14M	I	Jap	+	−	+	+	−	−	−	—	Several	—	—	—	435	—	C30R	S	20
8[b]	11M	C	Jap	+	−	−	−	−	−	−	—	Several	—	—	—	311.5	—	C30R	S	20
9[b]	F	A	Jap	+	−	−	+	−	+	−	—	Several	—	—	—	—	—	C30R	S	20
10[b]	17F	A	Jap	+	−	+	+	−	−	−	5–7	—	15,000	5.6	—	270	405	N101 K	S	8
11	14F	C	Taiw	+	−	−	−	+	−	−	10–14	1	15,680	16.98	43	—	61.7	Normal	S, E	d

A = adulthood; C = childhood; Col = colchicine; E = etanercept; N = NSAIDs; Jap = Japanese; LAP = lymphadenopathy; S = corticosteroids; Taiw = Taiwanese; Tx = treatment.

[a] She was diagnosed as having systemic lupus erythematosus (SLE) at the age of 21. Cases 5 and 6 were siblings. Cases 7, 8, and 9 were mother and sons.

[b] They were diagnosed with systemic juvenile idiopathic arthritis (JIA) or adult-onset Still disease (AOSD) before the current diagnosis.

[c] All gene mutations were missense mutations.

[d] Current case.

reduced TNFR1 shedding. However, defects in the shedding of TNFR1 by measuring serum soluble TNFR1 concentrations have been found to be inconsistent among patients.[5] *TNFRSF1A* mutations also affect receptor folding and trafficking. TNFR1 mutant proteins are retained and accumulate in the endoplasmic reticulum, activating mitogen-activated protein kinase (MAP) kinases and mitochondrial reactive oxygen species, resulting in constitutive inflammation through the secretion of proinflammatory cytokines such as Interleukin-1 (IL-1) and Interleukin-6 (IL-6).[7]

We summarized the clinical presentations, gene mutations, laboratory data, and treatment in 11 TRAPS cases including our patient from eastern Asia in Table 2. The onset age was typically young, with four cases in infancy and four in early childhood. The symptoms of the Japanese patients were milder than those reported in the Caucasian patients.[8] Chest pain was not observed in these patients. Abdominal pain is a hallmark of TRAPS, and is reported to occur in more than 90% of TRAPS patients. However, it was only reported in four of 11 (36.4%) of the Asian patients from our review (Table 2). Abdominal pain may reflect inflammation within the peritoneal cavity or the musculature of the abdominal wall. Signs of an acute abdomen often result in laparotomy and appendectomy, as in our patient. Serum TNF-α was low in two of 11 (18%) cases, and decreased *sTNFRSF1A* was seen in two of 11 (18%) patients.

As for the treatment for TRAPS, fever episodes usually respond to NSAIDs or corticosteroid treatment.[2] NSAIDs are generally unable to resolve musculoskeletal and abdominal symptoms. However, because of the possible long duration of fever attacks and the tendency to a chronic course, patients may become steroid-dependent. The use of other immunomodulatory drugs such as azathioprine, cyclosporin, thalidomide, cyclophosphamide, chlorambucil, intravenous immunoglobulin, dapsone, and methotrexate have been reported to be ineffective in TRAPS patients with regard to reducing the frequency and the intensity of the inflammatory episodes or in preventing the development of amyloidosis.[9] The hyperinflammatory response in TRAPS creates a rationale for TNF blockade in the treatment of TRAPS. Many reports have proved that infliximab, a chimeric monoclonal antibody that binds to human TNF-α, can induce the inflammatory attack,[10] while etanercept, a dimeric recombinant fusion protein of soluble TNFR linked by the Fc-fragment of IgG1, decreases the intensity and duration of inflammatory episodes.[11] In some TRAPS patients resistant to TNF-α inhibitor therapy, IL-1 receptor antagonist (anakinra) has been shown to control recurrent fever and prevent recurrence.[9,12]

The most devastating complication that clinicians should be concerned with in this kind of patient is reactive amyloidosis, which occurs in all kinds of hereditary periodic fever syndromes. The continuous elevation of serum amyloid A (SAA), one of the acute phase serum proteins, results in the development of AA systemic amyloidosis. The accumulation of AA amyloid fibrils in the extracellular spaces of various organs and tissues, most notably the kidneys (>90%), liver and spleen, and gastrointestinal involvement (20%), leads to organ failure in the middle age of life.[13] An estimated 14—25% of TRAPS patients develop reactive amyloidosis, but this has not been seen in Asian

cases (Table 2). It has been shown that certain *TNFRSF1A* gene mutations and duration and severity of inflammation confer increased risks for the development of AA amyloidosis; however, other genetic or environmental factors may also modulate the risk.[5] Etanercept has been shown to reduce not only the clinical symptoms and normalization of inflammatory parameters, but also SAA. In some reports, etanercept further reversed nephrotic syndrome.[14]

In conclusion, although periodic fever and abdominal pain are characteristic of TRAPS, there is usually a delay of diagnosis due to the extreme rarity of these disorders, especially in Asians. TRAPS should be considered in the differential diagnosis of recurrent fever cases. Most sporadic TRAPS cases have no *TNFRSF1A* gene mutations. Genetic heterogeneity with other genes effect exists in TRAPS patients. Regular etanercept usage can achieve resolution of symptoms and prevent systemic amyloidosis, and is recommended as the preferred treatment rather than corticosteroids. Although none of the patients in our review of Asian cases developed amyloidosis, we suggest continuously monitoring urinalysis and serum amyloid A concentrations during long-term follow-up of these patients.

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