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

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Hereditary periodic fever;
TNF-α inhibitor etanercept;
Tumor necrosis factor receptor-associated periodic syndrome (TRAPS)

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
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. 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 sity periodic fevers are characterized by recurrent flares of systemic inflammation presenting as sudden episodes of

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/C14 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.
DNA Sequencer (Applied Biosystems, Foster City, CA, USA).

formed using the BigDye Terminator kit and an ABI PRISM 3100 sequence analysis of genomic DNA. Sequencing was per-
mutations identified from the cDNA were confirmed by
indicated coding region of the candidate genes (Table 1). The
one pair of oligonucleotide primers selected to cover the
1.875 mmol/L MgSO4, 200

10 mmol/L dNTP, and 500 mmol/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 per-
formed using the BigDye Terminator kit and an ABI PRISM 3100 DNA Sequencer (Applied Biosystems, Foster City, CA, USA).

Sequencing of the TNFRSF1A gene

The genomic polymerase chain reaction (PCR) was per-
formed 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/CIA51 genes

Total RNA was isolated from peripheral blood mononuclear
cells with TRIzol® (Life Tech, Carlsbad, CA, USA). Reverse
mRNA transcription followed by polymerase chain reaction
(RT-PCR) was performed as previously described (Lee et al.
2005). Briefly, 1 µg of RNA in a total volume of 20 µl was
reverse-transcribed into cDNA using oligo-dT primers (Invi-
trogen, 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 con-
taining 0.5 U High Fidelity Taq DNA polymerase (Invitro-
gen, Carlsbad, CA, USA) and 100 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 per-
formed 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
dividuals from Japan. To the best of our knowl-
edge, this is the first case reported in Taiwan.

No mutations in the TNFRSF1A gene, MVK gene (for HIDS)
or NALP3/CIA51 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 super-
family 1A gene (TNFRSF1A) encoding for the trans-
membrane 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, Aksenti-
jevich et al. did not identify any TNFRSF1A mutations.
Another large study by Aganna et al. 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
symptoms were found to have TNFRSF1A mutations. Since
TNFRSF1A mutations cannot 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.

The pathogenic mechanisms underlying TRAPS remain
unresolved. Activation of TNFR1 by TNF causes cleavage
and shedding of the extracellular part of TNF1 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
Abdominal pain in TRAPS

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. 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. 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. 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, while etanercept, a dimeric recombinant fusion protein of soluble TNFR linked by the Fc-fragment of IgG1, decreases the intensity and the duration of inflammatory episodes. 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.

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. An estimated 14–25% of TRAPS patients develop reactive amyloidosis, but this has not been seen in Asian patients.

### Table 2

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (y)</th>
<th>Onset</th>
<th>Ethnity</th>
<th>Fever</th>
<th>Myalgia</th>
<th>Arthralgia</th>
<th>Skin rash</th>
<th>Abdominal pain</th>
<th>Laboratory data</th>
<th>TNFR1 mutation</th>
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<tbody>
<tr>
<td>1</td>
<td>14F I Jap</td>
<td>14 2</td>
<td>46,570</td>
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<td>461</td>
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<td>4.8</td>
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<td>378</td>
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### Notes
- **A**: adulthood; **C**: childhood; **Col**: colchicine; **E**: etanercept; **N**: NSAIDs; **Jap**: Japanese; **Taiw**: Taiwanese; **Tx**: treatment.
- **B**: They were diagnosed with systemic juvenile idiopathic arthritis (JIA) or adult-onset Still disease (AOSD) before the current diagnosis.
- **C**: Gene mutations were missense mutation.
- **D**: Current case.
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. 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.

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 cases.

References