Abdominal pain and fever in a patient with familial periodic fever: an extremely rare mutation of the TNF receptor superfamily member 1A gene

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Abstract

Periodic fever syndromes (PFSs) are a clinically inhomogeneous group of diseases based on peculiar genetic mutations. PFSs have to be suspected in young patients presenting with recurrent attacks of abdominal pain, skin rashes, arthritis, myalgia and fever as soon as more prevalent diseases have been excluded. An unconsidered hypothesis of PFSs may lead to delaying the diagnosis and unnecessary medical and surgical treatments.

In this article, we described the case of a young man presented to our attention due to recurrent abdominal pain and fever caused by TNF-receptor-associated periodic syndrome (TRAPS) sustained by the TNFRSF1A gene mutation.

Introduction

Periodic fever syndromes (PFSs) are a clinically inhomoge-
On admission, patient was hemodynamically and respiratory stable, fever was up to 39.5°C, the abdomen was mildly distended with diffuse tenderness and guarding on physical examination. Blood tests were within normal range except for leucocytosis (WBC 14.2x10^9/L) and increased level of C-reactive protein (21.2 mg/dL).

On plain abdominal X-ray no abnormalities were described. A contrast computed tomography scan showed the presence of distended small bowel loops with fluid levels, mesenteric thickness, reactive lymph nodes and free intra-abdominal fluid (Figure 1).

According to the clinical and radiological findings no emergency surgery was required and the patient was admitted to our department for further investigations and medical treatment.

Patient was treated with empiric antibiotic therapy (intravenous amoxicillin/clavulanic acid 2.2 g three times a day) and intravenous fluids with prompt clinical improvement and a significant reduction in inflammatory markers. An ultrasound of the small bowel loops documented the presence of intra-abdominal free fluid with diffuse mesenteritis without gross pathology of the hollow organs.

According to patient’s family history, also his brother has suffered from similar symptoms and was hospitalized several times without a conclusive diagnosis.

In suspicious of a PFS, a multidisciplinary panel of specialists, including internal medicine doctors, gastroenterologists and surgeons, reviewed the case and a diagnostic work up was established in order to rule out further potential diagnoses (Table 1). Finally, patient underwent a genetic test which showed the presence in the heterozygous state of the pathologic alteration c.305G>A localized in the TNFRSF1A gene that is in keeping with FPF (familiar periodic fever), a rare form of PFSs. Genetic testing performed among family members were consistent with FPF with a maternal lineage inheritance (Figure 2).

**Discussion and Conclusions**

We described the case of a young man presented to our attention due to recurrent abdominal pain and fever caused by the FPF, which is an extremely rare disease. This autoinflammatory disorder is also known as TNF-receptor associated periodic syndrome (TRAPS) and is an idiopathic recurrent fever with autosomal dominant inheritance. FPF was first described in Irish family in 1982 and since then more than twenty families affected by FPF have been described in Australia, South America, United States and Europe. In FPF, clinical manifestation may vary significantly as well as the symptom-free intervals duration. The median age at onset is 10 years old. Frequently, patients refer to the Emergency Department for musculoskeletal and abdominal pain, high fever and, less commonly, painful erythematous macules and patches which might migrate to the extremities.

Laboratory tests show leucocytosis and increased level of C-reactive protein. Because of the lack of specificity of C-reactive protein and leucocytosis as inflammatory markers, physicians are

![Image](https://example.com/image1.png)

**Figure 1.** Abdomen computed tomography scan with contrast. A contrast computed tomography scan with evidence of distended small bowel loops, mesenteric thickness, reactive lymph nodes and free intra-abdominal fluid in a patient affected by TRAPS (TNF-receptor associated periodic syndrome).

![Image](https://example.com/image2.png)

**Figure 2.** Genetic tree showing autosomic dominant inheritance with maternal lineage of a patient affected by TRAPS (TNF-receptor associated periodic syndrome). *Patient described.

**Table 1. Differential diagnosis work-up and laboratory tests.**

<table>
<thead>
<tr>
<th>Test Description</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool culture (Shigella spp, Salmonella spp, Yersinia spp, Campylobacter spp)</td>
<td>Negative</td>
</tr>
<tr>
<td>CMV antibodies (IgG/IgM)</td>
<td>Negative</td>
</tr>
<tr>
<td>EBV antibodies (IgG/IgM)</td>
<td>Negative</td>
</tr>
<tr>
<td>HIV 1/2 antibodies</td>
<td>Negative</td>
</tr>
<tr>
<td>Celiac testing*</td>
<td>Negative</td>
</tr>
<tr>
<td>Autoimmune screening (ANA, ENA, ANCA)</td>
<td>Negative</td>
</tr>
</tbody>
</table>

CMV, citomegalovirus; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus type 1 and 2; ANA, antinuclear antibodies; ENA, extractable nuclear antigens; ANCA, antineutrophil cytoplasmic antibodies. *IgA anti-tissue transglutaminase antibody, total IgA, IgG deamidated gliadin peptides.
inclined to consider more common diseases (e.g., acute appendicitis, acute pancreatitis, acute biliary disorders, intestinal obstruction or urolologic pathologies) rather than PFSs. Moreover, especially in the young population, this signs and symptoms can be related to a number of systemic disorders such as chronic infectious disease, HIV, autoimmune disorders and inflammatory bowel diseases.

A further step in diagnosis is represented by radiological investigations such as abdominal ultrasound and CT scan whose finding may mimic surgical abdominal emergencies.

The patient referred to our attention complained for severe abdominal pain with guarding and high fever with increased levels of leucocytosis and C-reactive protein. Acute appendicitis was excluded because of past appendectomy. The CT scan performed in the emergency department showed intra-abdominal free fluid without overt signs of intestinal obstruction or perforation. The presence of mesenteritis with lymph nodes increased in volume was considered a non-specific finding.

A more detailed anamnestic interview revealed the periodic nature of the fever. Besides the family history showed that the patient’s brother has suffered from recurrent episodes of acute abdominal pain and unknown origin fever for which was hospitalized several times. In consideration to the clinical presentation and the relevance of the family history, a PFS was finally suspected. Differential diagnosis work-up and tests are listed in Table 1.

To date, two main different forms of PFSs have been described: MFM and FPF. MFM is a genetic disease with an autosomal recessive inheritance. It is caused by mutations in the MEV gene and it is characterized by periodic fever attacks with abdominal, thoracic, articular pain and cutaneous rashes. Amyloidosis and chronic renal insufficiency are well known long term complications. Colchicine is the first line treatment and prevents febrile attacks in 60% of patients; additionally it reduces the risk of amyloidosis deposition.

FPF, also known as TNF-receptor associated periodic syndrome (TRAPS), is a genetic disorder with an autosomal dominant inheritance sustained by an alteration in TNFRSF1A gene. The onset of this medical condition usually occurs during the childhood and the most common clinical features include high fever which can even last for three weeks, diffuse abdominal pain, nausea and vomiting, localized myalgia and painful periarticular erythema. High-dosage corticosteroids are advised during the acute phases. Etanercept, a dimeric recombinant protein that binds effectively TNF-α receptors and attenuates its biologic effect, is considered first line therapy. More recently Anankira, a recombinant human interleukin (IL)-1 antagonist receptor, has been proved to be an effective weapon in TRAPS complicated by severe renal failure due to amyloidosis. Colchicine is supposed to be ineffective in treating this syndrome, even though it seems to mitigate symptoms in this patient.

We conducted a molecular analysis on genomic DNA of patient’s leucocytes by amplification and direct sequencing of the coding regions of MEV (NM_000243) and TNFRSF1A (NM_001065), genes. Molecular testing showed no pathologic variations in the coding regions of MEV gene and the diagnosis of FMF was excluded. Surprisingly, a pathologic alteration in exon 3 of the TNFRSF1A gene was identified consisting in a substitution of a cysteine residue with a tyrosine residue at codon 102 (c.305G>A; pCys102Tyr). This genetic variant is extremely rare in the population and it is consistent with the diagnosis of FPF. Results of family genetic testing are shown in Figure 2.

FPF is a rare clinical entity with a challenging diagnostic work-up. Family history and an accurate anamnestic record are essential for diagnosis. Clinicians should maintain a high index of suspicion as a delay in the diagnosis can lead to unnecessary medical and surgical treatments. Furthermore, as soon as the diagnosis of PFS has confirmed by genetic testing, a screening of family members has to be encouraged in order to ensure best treatment available.

References