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# PERIODIC FEVER: A CASE REPORT

FLORIANA ADRAGNA, GIUSEPPE TAORMINA, AURELIO SEIDITA, ALBERTO D'ALCAMO, GIUSI RANDAZZO, GIOVAMBATTISTA RINI, PASQUALE MANSUETO
Internal Medicine, University of Palermo, Italy

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***ABSTRACT***

*In this report, we describe the case of a twenty-year-old woman, with recurrent fever, accompanied by shaking chills and followed by profuse sweating, bilateral diffuse arthralgia and evidence of focal myositis, associated with elevation of inflammatory markers, pancytopenia, hypocholesterolemia, and hepatosplenomegaly, unresponsive to antibiotic therapy. Subsequently to the exclusion of infectious, autoimmune and neoplastic causes, and because of clinical features and persistence of fever cycles unresponsive to antibiotic therapy, an autoinflammatory periodic fever was suspected. For this reason, the patient was tested for MEFV gene mutation, related to Familial Mediterranean Fever, the well-known and most studied autoinflammatory disease; the patient was negative and a treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) was started, with fever and symptom disappearance, normalization of inflammatory markers and cholesterol levels, and regression of leucopenia and thrombocytopenia. After 5 years of follow-up, the patient was in good general clinical condition with only periodic febrile episodes (2 times a year), with the same clinical and blood chemistry characteristics as before, successfully treated with NSAIDs within 1-2 weeks, and without any appearance of additional symptoms and/or signs of organ damage and/or deterioration of general clinical condition.*

***Key words:*** *Periodic fever, fever of unknown origin, Familial Mediterranean Fever, tumor necrosis factor receptor associated periodic syndrome.*

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## Introduction

There are a number of different conditions in the important field of monogenic autoinflammatory syndromes, including those provoked by mutations of gene coding for proteins that play a pivotal role in inflammatory response regulation[1].

Due to their genetic nature, most of these disorders have an early onset, ranging from the first hours to the second decade of life, and rarely occur in adulthood. Autoinflammatory syndromes are clinically characterized by recurrent flare of systemic inflammation, in the majority of cases appearing as sudden fever episodes associated with elevation of acute-phase reactants, with a number of clinical manifestations, such as rash, serositis (peritonitis, pleurisy), arthritis, myositis, lymphadenopathy and hepatosplenomegaly. Symptom-free intervals are characterized by complete wellbeing, normal growth and complete normalization of acute phase reactants[2].

In this report we describe the case of a twenty-year-old woman with recurrent fever unresponsive to antibiotic therapy. Subsequently to the exclusion of infectious, autoimmune and neoplastic causes, and because of clinical features and persistence of fever cycles unresponsive to antibiotic therapy, an autoinflammatory periodic fever was suspected. For this reason, a treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) was started, with fever and symptom disappearance, normalization of inflammatory markers and cholesterol levels, and regression of leucopenia and thrombocytopenia.

## Case presentation

A twenty-year-old female with nothing relevant in family and personal medical history until

the age of 15 years old, when night fever appeared, accompanied by shaking chills and followed by profuse sweating (axillary T. max: 39°C), treated with antibiotics (amoxicillin-clavulanic acid) with little benefit. Thereafter, because of the persistence of fever, she was admitted to the Division of Infectious Diseases of a Sicilian hospital. During hospitalization, pancytopenia, hyper-transaminasemia, increased alkaline fosfatasemia and γ-GT, and hyper-γ-globulinaemia were found. After isolation of Leishmania in marrow aspiration, she was diagnosed with "visceral leishmaniasis" and treatment started with N-methylglucamine antimoniate cycles, with apparent benefit (disappearance of fever). In July 2003, night fever (axillary T. max: 39°C) appeared again, not associated with other symptoms, resistant to antibiotic therapy (amoxicillin-clavulanic acid) and regressed spontaneously after 10 days. In July 2004, a further febrile episode (axillary T. max: 39°C), accompanied by asthenia, treated by family members with nimesulide as needed, with benefit (disappearance of fever in about a week.). In October 2004, there was a new onset of night fever (T. axillary max: 40°C), accompanied by chills and sweats, treated with antibiotics (moxifloxacin for 4 days, and then cefpodoxime for 6 days) and steroids (methylprednisolone for 5 days), without benefit.

The patient was readmitted to the same Division of Infectious Diseases, where the possibility of recurrence of visceral leishmaniasis was considered, and for this reason therapy was undertaken with liposomal amphotericin B and subsequently with N-methylglucamine antimoniate, but without benefit. During this hospitalization, in addition to fever, bilateral diffuse arthralgia appeared, with weight loss of about 10 kg. Thus the patient came to our Department for further investigation and treatment. On admission patient was lucid, cooperative, oriented in time and space, eupneic, pyretic. There was nothing relevant on physical examination, except for pale and dehydrated skin and mucous membranes, and mild hepatosplenomegaly.

There were no signs of local inflammation of the joints. Blood tests showed: pancytopenia (suspected iron deficiency anemia (hemoglobin, HGB, 6.9g/dl, ferritinemia 4ng/ml, serum iron 21mcg/ml), leucopenia (white blood cells, WBC, 2280 x mmc), with preservation of differential leukocyte count, mild thrombocytopenia (120,000 x mmc), elevation of inflammatory markers (erythrocyte sedimentation rate, ESR: 1st hour 91 mm, C-reactive protein, CRP: 6.4mg/dl, increase of alpha-globulins) and total hypocholesterolemia (99mg/dl). During hospitalization daily intermittent fever was observed, i.e. night fever with max temperature of 40°C confirmed in double (axillary and rectal) measurement, associated with diffuse bilateral arthralgia, without signs of local inflammation of the joints. Aware of the previous diagnosis of visceral leishmaniasis, the characteristics of the fever, and assuming an infectious etiology, we performed serology for Salmonella, Brucella, Toxoplasma and Leishmania, hepatitis serology markers (HBsAg, anti-HBs, anti-HBc, anti-HCV), Leishmania in peripheral blood and in the microscope slides supplied by the Hospital where the patient was previously hospitalized (without evidence of Leishmania promastigotes), serial blood cultures and, moreover, a Mantoux test, all proved negative. In addition we treated the patient with a parenteral broad-spectrum antibiotic therapy with vancomicin plus gentamicin, without benefit. Once we excluded the infectious nature of the disease, we then considered an autoimmune genesis and subsequently a neoplastic origin, leading to second and third level fever of unknown origin (FUO) investigations (see Table 1).

The following tests were all negative: assays of serum immunoglobulins (IgG, IgA and IgM), complement components 3 and 4, circulating immune complexes (CIC-IgG, IgA and IgM), evaluation of full autoreactive antibodies pattern (antinuclear, ANA, double strand anti-DNA, anti-dsDNA, anti-mitochondrial, AMA, anti-smooth muscle, ASMA, extractable nuclear antigen, ENA, anti-neutrophil cytoplasmic, ANCA antibodies) and rheumatoid factor, as well as direct and indirect Coombs test. Instrumental investigations: radiography of paranasal sinuses, dental orthopantomography, chest X-Ray, adbominal ultrasound, whole-body Computerized Tomography (CT scan) excluded expansive processes, confirmed mild hepatosplenomegaly and revealed a mild lateral cervical lymphadenopathy subsequently subjected to biopsy, with results of "reactive hyperplasia."

We also performed a whole-body positron emission tomography PET investigation, which detected an area of increased uptake in the right thigh (Figure 1), not confirmed by X-Ray examination and nuclear magnetic resonance NMR. After administration of NSAIDs, fever and arthralgia progressively disappeared, with recovery of kinesthesia and body weight, regression of leucopenia and thrombocytopenia, improvement of anemia (HGB

| **FIST LINE EXAMINATIONS** |
|---|
| Erythrocyte sedimentation rate |
| C reactive protein |
| Hemoglobin and mean cellular volume |
| Platelet count |
| Absolute and differential leukocyte count |
| Lactate dehydrogenase |
| Blood urea nitrogen and serum creatinine |
| Serum sodium |
| Serum potassium |
| Serum protein fractions |
| Serum alkaline phosphatase |
| Urine analysis |
| Fecal occult blood test (at least three times) |
| Antistreptolysin O antibodies |
| Tuberculin skin testing |
| Blood cultures (at least three times) |
| Urine cultures |
| Fecal cultures |
| Sputum cultures |
| Chest X-ray |
| Ultrasound of the abdomen |
| **SECOND LINE EXAMINATIONS** |
| Serology for *Cytomegalovirus, Epstein-Barr virus, hepatitis viruses, Mycoplasma, Chlamydia, Brucella, Salmonella, Toxoplasma and Leishmania* |
| Sputum for acid fast bacilli |
| Polymerase chain reaction for tuberculosis |
| Urine cultures for tuberculosis |
| Rheumatoid factor |
| Antinuclear antibodies |
| Serum levels of CH50, C3 and C4 |
| TSH, fT4, fT3, thyroglobulin and thyroperoxidase antibodies |
| Immunoelectrophoresis of serum |
| Radiography of paranasal sinuses |
| Dental orthopantomography |
| Echocardiography |
| Computed tomography of chest and abdomen |
| **THIRD LINE EXAMINATONS** |
| Esophagogastroduodenoscopy |
| Colonoscopy |
| Bone marrow aspiration or biopsy |
| Lymph node biopsy |
| Liver biopsy |

**Table 1**: First, second and third-line examinations for patients with fever of unknown origin.

9.6g/dl), and in serum markers of inflammation, and normalization of serum cholesterol. Therefore, it was assumed that the patient suffered from an autoinflammatory periodic fever and, for this reason, genetic testing was performed on the MEFV gene, related to Familial Mediterranean Fever (FMF), the well-known and most studied autoinflammatory disease[3]. However, the test results were negative. After 5 years of follow-up, the patient is in good general clinical condition with only periodic febrile episodes (2 times a year), with the same clinical and blood chemistry characteristics of the past, successfully treated with NSAIDs within 1-2 weeks and without any appearance of additional symptoms and/or signs of organ damage and/or deterioration of general clinical condition. Ultrasound examination of the right thigh, performed one year later, showed no significant morphological-structural alterations.

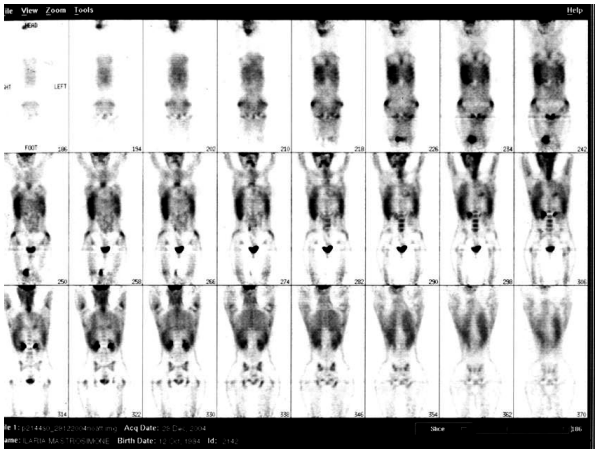

**Figure 1:** whole-body positron emission tomography (PET) investigation of the patient, detecting an area of increased uptake in the right thigh.

## Discussion

The correct approach to investigate a FUO is to examine the causes that may determine fever in the context of infectious, autoimmune or neoplastic diseases[4,5]. In our case, all the investigations carried out were negative, and led us to hypothesize that our patient was suffering from an autoinflammatory disease[6].

The term "autoinflammatory" refers to a group of diseases triggered by mutation of a single gene encoding regulatory proteins of inflammatory response[7]. The onset is typically early, during the first or second decade of life, rarely in adulthood. The clinical spectrum is very variable, but for simplicity they are divided into four groups: periodic fevers, cryopyrin-associated periodic syndromes (CAPS), granulomatous diseases, and pyogenic disorders (Table 2)[8].

Periodic fevers (such as FMF) are characterized by periodic episodes of systemic inflammation, with fever that may be associated with one or more symptoms and/or signs, such as rash, arthralgia, myalgia, pleurisy and pericarditis[9]. CAPS (such as Muckle-Wells syndrome) are characterized by fever and cutaneous rash[10]. Granulomatous diseases (such as Blau's syndrome) are characterized by the presence of granulomatous inflammatory infiltrate, with characteristic triad of dermatitis, arthritis and uveitis[11]. Pyogenic disorders (such as Pyogenic sterile Arthritis, Pyoderma gangrenosum, Acne, or PAPA syndrome), are characterized by sterile abscesses of joints, bones and skin[12].

Considering the previous diagnosis of visceral leishmaniasis based on marrow aspiration, we examined the microscope slides in our laboratory, and no Leishmania promastigotes were found, hence the diagnosis of leishmaniasis was excluded[13]. However, we considered a possible infectious origin of the patient's disease (mild hepatosplenomegaly and lateral cervical lymphoadenopathy), and for this reason the patient underwent serology for Salmonella, Brucella, Toxoplasma, hepatitis serology markers, Mantoux test and serial blood cultures (all were negative), and ex-adiuvantibus antibiotic treatment was unsuccessful. Because of fever pattern, elevation of inflammatory markers and associated arthralgias, we proceeded with immunological investigations, in particular dosage of immunoglobulins, complement factors and full pattern of non-organ specific autoantibodies. All results were normal.

Considering a potential neoplastic origin, the patient underwent a total-body CT, which only confirmed mild hepatosplenomegaly. Even though the CT did not detected any neoplasm, a whole-body PET investigation was carried out and it revealed the presence of increased uptake at the inner face of the right thigh, of possible inflammatory nature. Subsequently NMR investigation was performed and did not confirm the finding mentioned above. Due to the failure in determining fever origin and unresponsiveness to antibiotic therapy, during hospitalization the patient was treated with NSAID therapy, with progressive disappearance of fever and associated symptoms. Therefore, the patient was discharged with NSAID therapy at home, and a genetic test for MEFV gene mutations, responsible

| DENOMINATION | GENE |
|---|---|
| **PERIODIC FEVERS** | |
| Familial Mediterranean fever (FMF) | MEFV |
| Hyperimmunoglobulinemia D with recurrent fever (HIDS). Now defined (along with mevalonic aciduria) as mevalonate kinase deficiency | MVK |
| Tumor Necrosis Factor (TNF) receptor associated periodic syndrome (TRAPS) | TNFRSF1A |
| NALP12-associated periodic fever | NALP12 |
| **CRYOPYRIN-ASSOCIATED PERIODIC SYNDROMES (CAPS) or CRYOPYRINOPATHIES** | |
| Muckle-Wells syndrome (urticaria, sensorineural deafness and amyloidosis) | NLRP3 |
| Familial cold autoinflammatory syndrome (FCAS, formerly termed familial cold-induced urticaria) | NLRP3 |
| Neonatal-onset multisystem inflammatory disease (NOMID, also called chronic infantile neurologic cutaneous and articular syndrome or CINCA) | NLRP3 |
| **GRANULOMATOUS DISEASES** | |
| Periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA syndrome) | ? |
| Blau's syndrome | NOD2 |
| **PYOGENIC DISORDERS** | |
| Pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA syndrome) | PSTPIP1 |
| Deficiency of the interleukin-1 receptor antagonist (DIRA) | IL1RN |
| Majeed syndrome (chronic multifocal osteomyelitis, congenital dyserythropoietic anemia and neutrophilic dermatosis | LPIN2 |

**Table 2** Classification of autoinflammatory diseases.
*From Federici S, Caorsi R, Gattorno M. The autoinflammatory diseases. Swiss Med Wkly 2012; 142:w13602. doi:10.4414/smw.2012.13602. (modified)*

for FMF, was carried out[14] but it was negative. Nevertheless, this fact does not exclude the possibility that the patient suffers from another autoinflammatory disease, due to the clinical characteristics of fever and associated symptoms; and because the diagnosis of this kind of pathology remains clinical[15,16], despite the availability of genetic testing, there is a possibility of other autoinflammatory disease genetic variants yet to be demonstrated.

Considering clinical and biochemical patient features, it could be tumor necrosis factor receptor-associated periodic syndrome (TRAPS), the second most common inherited recurrent fever syndrome after FMF, caused by mutations in the tumor necrosis factor receptor 1 (TNFR1) gene (TNFRSF1A), with autosomal dominant pattern[17]. The majority of TRAPS-related mutations are missense mutations resulting in single amino acid substitutions in cysteine-rich domains, resulting in a TNFR1 protein folded into an improper 3-dimensional shape. These misfolded proteins are trapped within the cell and are not able to be exposed on the cell surface to interact with TNF. Inside the cell, these proteins are clustered and are thought to be able to initiate alternative pathways that trigger the inflammation, leading to an excessive activation of the latter in people with TRAPS. Moreover, because only one copy of TNFRSF1A gene is mutated, some normal TNFR1

proteins are synthesized and then stimulated by TNF, increasing inflammation. It is unclear if disruption of the apoptosis pathway plays an additional role in provoking the signs and symptoms of TRAPS. Fever episodes usually occur spontaneously, but sometimes they can be brought on by a variety of triggers, such as minor injury, infection, stress, exercise or hormonal changes. During episodes of fever, people with TRAPS can have further signs and symptoms. These include a spreading skin rash, typically found on the limbs, and abdominal and muscle pain. Affected individuals may also experience puffiness or swelling in the skin around the eyes (periorbital edema), joint pain and inflammation in various areas of the body including eyes, certain joints, skeletal muscles (especially of quadriceps), throat, or mucous membranes, such as the moist lining of the mouth and digestive tract (Table 3)[18].

| | |
|---|---|
| **Fever** | High, with chills<br>Onset: infancy or childhood<br>Attacks last: mean 2 to 3 weeks; range 3 to 75 days |
| **Abdominal pain** | Diffuse<br>Nausea and vomiting<br>Bowel obstruction: appendicitis-like<br>Diarrhea: occasional |
| **Pseudocellulitis** | Subcutaneous inflammation<br>Warm<br>Pitting edema |
| **Skin rash** | Macular; erysipela-like; erythematous<br>Onset after myalgias<br>Overlies areas of myalgia |
| **Myalgia** | Trunk or limbs<br>Focal<br>Starts proximally and moves distally<br>Deep cramping sensation |
| **Ocular** | Conjunctivitis<br>Periorbital edema: unilateral |
| **Other pain** | Chest<br>Testicular |
| **Course** | Chronic recurrences over many years |

**Table 3** Clinical features of tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS).

Occasionally, people with TRAPS develop amyloidosis, that can lead to kidney failure. It is estimated that 15 to 20 percent of people with TRAPS develop amyloidosis[19]. In this context, our patient showed, on whole-body PET, an area of increased uptake in the right thigh, not confirmed by X-Ray examination and NMR, suggesting asymptomatic focal myositis, not confirmed in a subsequent ultrasound exam[20].

After 5 years of follow-up, the patient is in good general clinical condition and has only periodic febrile episodes (2 times a year), with the same clinical characteristics and blood chemistry of the past, successfully treated with NSAIDs within 1-2 weeks and without any appearance of additional symptoms and/or signs of organ damage (i.e. renal function), and/or deterioration of general clinical condition[21].

In conclusion, we described the case of a young woman, with recurrent fever, unresponsive to antibiotic therapy, suspected of being autoinflammatory periodic fever (i.e. TRAPS), successfully treated with NSAIDs. Diagnosis of autoinflammatory disease, despite the availability of genetic testing, remains clinical.

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*Request reprints from:*
Prof. PASQUALE MANSUETO
Dipartimento di Medicina Interna e Specialistica
Azienda Ospedaliera Universitaria Policlinico 'P. Giaccone'
Via del Vespro, 141
90127 Palermo
*(Italy)*