

**CASE PRESENTATION – STUDIUL DE CAZ – PRESENTATION DE CAS
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**CHALLENGING DIAGNOSIS: COEXISTENCE OF TWO RARE DISEASES –
FAMILIAL MEDITERRANEAN FEVER AND LOYEZ-DIETZ SYNDROME TYPE 3**

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Introduction. *Autoinflammatory diseases are a group of genetically inherited disorders and familial Mediterranean fever is the most common of this group. It is rare in other than Middle East populations. Clinical manifestations of FMF are attacks of fever usually shorter than 24 hours, associated with arthritis, pleuritic chest pain, and abdominal pain.*

Case presentation. *A 15-year-old female patient was included in the study. She complained of recurrent episodes of fever associated with arthritis and abdominal pain. Moreover, the patient presented dysmorphic features like hyperthelorum, prognathia, scoliosis, pectus carinatum, and hypermobility syndrome. The laboratory exam revealed mutations in both MEVF and SMAD 3.*

Conclusions. *An autoinflammatory disorder should be suspected in any patient who has a history of recurrent fever. The attack patterns of FMF varies not just in different patients, but also in the same patient. Mainstay of treatment is colchicine that significantly improves the prognosis of patients with FMF.*

Cuvinte cheie: *boli autoinflamatorii, febră mediteraneană familială, copii.*

DIFICULTĂȚI DIAGNOSTICE: COEXISTENȚA A DOUĂ BOLI RARE – FEBRA MEDITERANEANA FAMILIALĂ ȘI SINDROMUL LOEYS-DIETZ TIP 3

Introducere. *Bolile autoinflamatorii constituie un grup de maladii determinate de activarea aberantă a căilor inflamatorii. FMF este cea mai frecventă afecțiune autoinflamatorie. Cu excepția țărilor din Orientul Mijlociu, FMF se întâlnește rar. Manifestările clinice includ episoade febrile cu o durată ce nu depășește 24 ore, fiind asociate cu artrită, durere abdominală și de tip pleuritic.*

Prezentarea cazului. *Pacientă de 15 ani, inclusă în studiu. S-a adresat cu acuze de episoade febrile recurente, asociate cu artrită și dureri abdominale. La examenul clinic pacienta prezenta dismorfisme: hipertelorism, prognatie, pectus carinatum, sindrom de hipermobilitate. La examenul de laborator au fost depistate mutații în genele MEVF și SMAD 3.*

Concluzii. *Un sindrom autoinflamator va fi suspectat la pacienții cu istoric de febră recurentă. Patternul atacurilor în FMF este variabil nu doar la diferiți pacienți, ci și în cazul aceluiași bolnav. Baza terapiei este colchicina, care a ameliorat substanțial prognosticul pacienților cu FMF.*

INTRODUCTION

Autoinflammatory diseases are a group of genetically inherited disorders, caused by inadequate activation of inflammatory pathways in the absence of antigen directed autoimmunity. Periodic fever is the most common manifestation (1, 2).

An autoinflammatory disorder should be suspected in any patient who presents a history of recurrent fever over years and months. Most patients present first symptoms in early childhood. The clinical picture includes fever, rashes, serositis, arthritis, meningitis, and uveitis. Clinical patterns should be evaluated to check if it refers to an autoinflammatory condition [2]. Next, genetic tests should be carried out in order to confirm the presumptive diagnosis (3).

Familial Mediterranean fever is the most common autoinflammatory disease. Its prevalence is 1:250-1:1000 in Middle East population, but rare in other populations. The cause is the mutation in MEVF gene located on chromosome 16 (4).

The attack lasts 12-72, showing the following characteristics: fever, aseptic peritonitis, pleuritic thoracic pain, erysipel-like rash, headache (rare), orchitis (rare), and arthralgia/arthritis (children - oligoarthritis). During the febrile episode, a high number of neutrophils and acute phase reactants can be noted. The diagnosis is confirmed by genetic testing, although it remains a clinical one. It is based on a history of recurrent, self-limited attacks of fever and serositis that are prevented by colchicine (2, 4, 5).

CASE PRESENTATION

A 15-year-old female was admitted to the Rheumatology unit, complaining of a recurrent fever (2-6 times per month), up to 40°C, associated with nausea, vomiting, sometimes abdominal pain; fever commonly lasts no more than 24 hours and does not respond to fever medication. In addition, she complained of non-inflammatory joint pain, myalgia after mild physical exertion, fatigability and migraine.

The disease history revealed that the first febrile episode of unknown etiology and increased levels of acute phase reactants occurred during infancy. She had many episodes, interpreted as upper respiratory tract infections and urinary tract infections. Moreover, at the age of 4, the patient had the first episode of arthritis. At the age of 8 she was admitted to hospital for being

suspected of peritonitis. At the age of 8, she was diagnosed with juvenile oligoarthritis, but the patient did not return for follow-up monitoring. At the age of 15, the patient presented again at the rheumatologist and a diagnostic plan was set up.

The patient was born from uneventful pregnancy, breastfed until 1 year of age and vaccinated according to the national schedule. Patient did not report any allergies.

Family history was negative for autoimmune, immunodeficiency or genetic diseases. Patient's mother was diagnosed with migraine.

The patient was clinically and paraclinically examined within the Rheumatology unit.

Patient's clinical examination revealed that she was underweight (BMI 16.6, -1.61 SDS), having astenic constitution and deformities of the thorax - pectus carinatum and thoracolumbar scoliosis. On the lower limbs - multiple excoriations and bruises (according to patient's mother the girl presented a delayed wound healing). On inspection, hypertelorism and prognathia were also revealed. Patient wore braces for orthodontic treatment. Musculoskeletal system exam revealed hypermobility syndrome (Beighton score of 8 points) and pes planus. Respiratory and cardiovascular examination were normal (including blood pressure - percentile 50 for age and height). No hepatomegaly or splenomegaly were revealed on abdominal exam.

The laboratory exam recorded normal values of differential CBC, biochemical test (renal function, liver panel, metabolic panel), and urine test. C-reactive protein was positive (6 mg/dL). Serum amyloid was 24 mg/L (normal value <10mg/L). The internal organ ultrasound imaging of kidneys and heart was normal. Antinuclear antibody screening test, as well as immunoblot for autoimmune disease were negative. Also, the immunoglobulin levels were assessed, and flow-cytometry was performed. The study findings are presented in Table 1.

Due to multiple stigma, a genetic test for connective tissue diseases was carried out. Also, considering the recurrent fever, the autoinflammatory panel was added. Finally, the patient was found positive to mutations Chr16:3293407T>C, p. Met694Val and Chr16:3293405T>C, p. Met694Ile on gene MEVF, both having pathologic significance.

Table 1. Immunoglobuline levels and flow-cytometry results.

	Prior to the treatment	After 3 months of treatment	Reference	Units
SAA	24	20	<10	mg/L
Lymphocytes	31.8	29.1	36-43	
CD3+	78.98	78	66-76	
CD4+	54.61	54	33-41	
CD8+	19.79	20	27-35	%
CD16+	3.71	6	9.9-22.9	
Monocytes	9.1	7.9	4-8	
Lymphocytes	1749	1775	2000-2700	
CD3+	1381.4	1384	1400-2000	
CD8+	346.1	355	600-1900	cells/uL
CD19+	243.5	284	300-500	
CD16+	64.8	106	100-500	
CD4/CD8	2.76	2.7		

Furthermore, a pathologically significant mutation in gene SMAD 3 – Chr15: 67477068G>C was revealed.

Therefore, based on EUROFEVER/PRINTO a diagnosis of familial Mediterranean fever was made. Furthermore, based on the presence of confirmatory mutation on the gene SMAD 3, a diagnosis of Loyez-Dietz syndrome was also established.

Treatment with colchicine 1 mg/24h was initiated. Over half a year, the attack intensity of markedly decreased, as well as their frequency.

DISCUSSIONS

Autoinflammatory diseases are a group of genetically inherited disorders, caused by inadequate activation of inflammatory pathways in the absence of antigen directed autoimmunity. Periodic fever is the most common manifestation. The spectrum of the autoinflammatory disorders is extending continuously, and now include not just Il-1 mediated diseases but also those that don't include fever as a major sign (1, 2).

An autoinflammatory disorder should be suspected in any patient who presents with a history of recurrent fever over years and months. Most patients present first symptoms in early childhood. The clinical picture include fever, rashes, serositis, arthritis, meningitis, uveitis. Clinical patterns should be evaluated to check if it is related to an autoinflammatory condition. Next, a genetic test should be ordered in order to confirm the presumptive diagnosis (1, 2, 3, 6).

Differential will include recurrent fever, mali-

gnancies, systemic onset juvenile idiopathic arthritis.

Familial Mediterranean fever is the most common autoinflammatory disease. Its prevalence is 1:250-1:1000 in the Middle East population, but rarely occurs in other populations. The cause is the mutation in MEVF gene located on chromosome 16. This mutation is a gain of function mutation, so it stimulates uncontrolled production of Il-1. It has both, autosomal recessive and autosomal dominant transmission (1, 3, 4).

Nowadays, there are around 300 mutations described; all of them are registered in the INFEVERS database. Not all the mutations are associated with FMF phenotype and its significance is not clear. The most common mutations that are associated with FMF are p.M694V, M694I, M680I and V726A. Mutations localized on 10th exon are considered to be the most severe. In our patient's case, there are two different mutations – p.M694V (Ancestry – Jewish Non Ashkenasi), M694I (Ancestry – Maghrebian), both located on 10th exon. Therefore, is expected to have a severe disease, with a chance not to respond to colchicine treatment (4, 6).

Clinical features. Usually, a patient with FMF presents the first symptom by the age of 20. The duration of the attack is 12-72 hours, showing the following characteristics: fever, aseptic peritonitis, pleuritic thoracic pain, erysipel-like rash, headache (rare), orchitis (rare), and arthralgia/arthritis (children – oligoarthritis). During the febrile episode, a high number of neutrophils and acute phase reactants can be noted. The attack patterns vary not just in different patients,



but also in the same patient. The mechanism that triggers the attack is unknown, but many patients complain of physical and psychological

exhaustion, associated with the onset of the attack (2,4).

**Eurofever/PRINTO
Familial Mediterranean Fever criteria**

Presence of a confirmatory MEVF genotype and at least one of the above:

- Duration of febrile episodes 1-3 days
- Arthritis
- Pleuritic pain
- Abdominal pain

OR

Presence of a nonconfirmatory MEVF genotype and at least two of the above:

- Duration of febrile episodes 1-3 days
- Arthritis
- Pleuritic pain
- Abdominal pain

Sensitivity 0.94

Specificity 0.95

Accuracy 0.98

The diagnosis is confirmed by genetic testing but mostly remains a clinical one. It is based on a history of recurrent, self-limited attacks of fever and serositis that are prevented by colchicine.

Treatment. Colchicine licenced by FDA is used for prophylactic use in case of FMF from the age of 4. Continuous use of colchicine prevents or reduces substantially the symptoms of FMF in at least 95% and almost completely excludes the risk of amiloidosis. The mechanism of action of colchicine is unknown, but most of patients have a good clinical response to doses 250 mg-2g/24h (7, 8).

Complications. The treatment is necessary to be

continued throughout the whole life, and the prognosis is favorable, having a good life expectancy. Prior to use of colchicine, 60% of patients with FMF develop amiloidosis. Destructive arthritis is rare. Growth and fertility are nearly normal for both sexes (in case of treatment adherence) (5, 7, 8).

The described case is unique – there are no registered patients with FMF in the Republic of Moldova. Furthermore, our patient exhibited clinical features not just of an autoinflammatory syndrome, but also of a hereditary connective tissue disease, that made the clinical diagnosis even more complicated.

CONCLUSIONS

1. Autoinflammatory diseases are a group of genetically inherited disorders, caused by inadequate activation of inflammatory pathways. Familial Mediterranean fever is the most common autoinflammatory disease, with the highest prevalence among Middle East population that rarely occur in other populations.
2. Clinical manifestations of FMF are attacks of fever usually shorter than 24 hours, associated with arthritis, pleuritic chest pain, and abdominal pain. Pattern of attacks varies not just in different patients, but also in the same patient. The mainstay of treatment is colchicine that significantly improves the prognosis of patients with FMF.

CONFLICT OF INTERESTS

All authors declare no competing interests.

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