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Unilateral Lymphocytic Pleuritis as a Manifestation of Familial Mediterranean Fever*

Stamatis Katsenos, MD; Charalampos Mermigkis, MD; Kostas Psathakis, MD; Kostas Tsintiris, MD; Vlassios Polychronopoulos, MD, FCCP; Panagiotis Panagou, MD; Kostas Ritis, MD; and Richard W. Light, MD, FCCP

Familial Mediterranean fever (FMF) is an autosomal recessive disease affecting predominantly populations surrounding the Mediterranean basin. It is the most prevalent hereditary periodic fever syndrome characterized mainly by recurrent and short attacks of fever and serositis (pleuritis, arthritis, peritonitis). Unilateral polymorphonuclear exudative pleuritis associated with fever has been reported as the solitary manifestation of the first FMF attack, in <10% of patients. This case study describes a 30-year-old Greek man with recurrent episodes of lymphocytic exudative pleuritis associated with fever. After a thorough workup (clinical criteria and molecular genetic testing identifying homozygosity polymorphisms of the FMF gene), the diagnosis of FMF was established. Treatment with colchicine, 2 mg/d, eliminated FMF attacks. To our knowledge, this is the first well-documented case report of a patient with FMF presenting with a lymphocytic exudative pleural effusion. (CHEST 2008; 133:999–1001)

Key words: familial Mediterranean fever; fever; lymphocytic pleural effusion

Abbreviation: FMF = familial Mediterranean fever

Familial Mediterranean fever (FMF) is an episodic febrile disease with an autosomal recessive inheritance affecting predominantly people from the Mediterranean basin.1,2 It is characterized chiefly by short and periodic attacks of fever and serositis involving the pleura, peritoneum, synovial membrane, and tunica vaginalis.3 The initial attack usually occurs before the age of 20 years and typically has peritoneal symptoms and signs. Unilateral polymorphonuclear pleuritis associated with fever has been described as the primary attack of FMF in <10% of patients, but approximately 30 to 40% manifest an attack of febrile pleurisy during the evolution of the disease.4 In this article, we present a patient with FMF and recurrent febrile unilateral lymphocytic pleuritis who was treated satisfactorily with colchicine. This is the first case report in the literature of a patient presenting with a lymphocytic exudative pleuritis due to FMF.

Case Reports

A 30-year-old Greek man with a 20-pack-year smoking history was admitted to our department because of fever (38.8°C), dry cough, and left-sided chest pain. His symptoms appeared a week before hospital admission. The patient received a course of antibiotics (cefotaxime plus clarithromycin orally) without any improvement. He had been in good health previously, without remarkable findings obtained by family, travel, or occupational and environmental exposure history. There was no history of FMF in first-degree relatives.

Physical examination of the chest showed dullness on percussion at the base of the left hemithorax as well as decreased breath sounds. The rest of the clinical examination was unremarkable.

Standard laboratory studies demonstrated mild leukocytosis (WBC count, 11,400/μL) and slightly increased erythrocyte sedimentation rate (50 mm/h) and C-reactive protein (5.7 mg/L). Serum biochemistry test results were within normal limits. The result of tuberculin skin test performed with 2 IU of purified protein derivative BT-23 tuberculin was positive (17 mm). Arterial blood gas levels on room air were within normal range. Further laboratory investigation including serum complement analysis, rheumatoid factor, antinuclear antibodies, antineutrophilic cytoplasmatic antibodies, Ig levels, serologic tests for hepatitis A, B, and C, as well as for common viruses and atypical infectious agents disclosed no apparent pathologies. An enzyme-linked immunsorbent assay for anti-HIV antibodies was also negative. The pattern of serum protein on electrophoretic analysis was normal. Similar findings were observed by serum concentration analysis of thyroid hormones, as well as thyroid and heart ultrasound examinations.

A posteroanterior chest radiograph performed on the day of hospital admission showed blunting of the left lateral costophrenic angle. Contrast-enhanced CT of the chest performed a day later revealed pleural fluid accumulation on the left pleural cavity, while spiral CT pulmonary arterial angiography obtained simultaneously was negative for emboli in pulmonary arterial trunk and the following branching system (Fig 1).

Diagnostic thoracentesis was performed showing an exudative pleural effusion with a high percentage of lymphocytes (90%) [Table 1]. Adenosine deaminase level was normal (28 U/L).
Additionally, cytologic examination of the pleural fluid, flow cytometry, Gram-stained and cultured pleural fluid, and polymerase chain reaction for Mycobacterium tuberculosis did not reveal abnormal findings. Afterwards, the patient underwent fiberoptic bronchoscopy. No intraluminal lesions or other abnormal findings were observed. Microbiologic examination of samples obtained by bronchial washings and BAL for mycobacteria and other common pathogens as well as cytologic examination were negative.

Subsequently, direct examination of the pleura via medical thoracoscopy showed abnormal pleura with increased vascularization and thickening especially in the lower third of the hemithorax and the posterior costophrenic angle (findings compatible with chronic nonspecific inflammation). Microscopic examination of the biopsy samples obtained during the procedure disclosed nonspecific chronic inflammation.

The patient received empirical antituberculous chemotherapy comprising isoniazid, rifampicin, and pyrazinamide based mostly on persistent clinical features, positive tuberculin skin reaction, and pleural fluid lymphocytosis. This treatment regimen was discontinued a month later because the patient had no clinical or radiologic improvements.

Recurrent pleuritis was observed two more times during the subsequent 3 months until the final diagnosis was established. All of these episodes were associated with a low-grade fever with a duration of approximately 7 to 10 days. Thoracentesis was performed in all cases, and the pleural fluid futures did not differ compared to those obtained by the first thoracentesis (Table 1). Chest radiograph findings were normal between the episodes of fever and pleural effusion, while C-reactive protein values were mild elevated.

Additional workup for other unusual causes of pleuritis revealed that the patient had FMF. Particularly, molecular testing using the nonisotopic ribonuclease cleavage assay as a method for screening of the entire coding sequence of MEFV (the gene responsible for FMF) identified homozygosity polymorphisms (D102D/D102D, A1656T/A1656T, and R202Q/R202Q) in exon 2. These features taken together with the clinical findings of recurrent episodes of febrile pleuritis and also the favorable response to colchicine treatment (as described below) established the final diagnosis of FMF.

Treatment with colchicine was started at a dose of 1 mg/d. Because there was only a slight response of the main symptoms at the above-recommended dosage, a dose escalation up to 2 mg/d was decided. Our patient tolerated this dose regimen well enough. Episodes of fever and chest pain subsided after 1 month of continuous treatment with the new dosage. At this time, 15 months after the colchicine was started, the patient remains in stable condition, without further episodes of fever, chest pain, or pleuritis, while he continues colchicine at 2 mg/d.

**DISCUSSION**

FMF, also called recurrent polyserositis, is a periodic febrile disease with an autosomal recessive inheritance affecting mostly individuals of Mediterranean descent. The salient features of this disease include brief recurrent episodes of peritonitis, pleuritis, and arthritis, which are usually associated with fever. The majority of patients exhibit the first attack before the age of 20 years.

The most frequent initial attack is abdominal pain presenting in 95% of patients. Pleuritic chest pain and fever as manifestations of the first attack are observed in < 10% of patients, but approximately 40% have an episode of febrile pleurisy during the course of the disease. Approximately 25% of all FMF patients may present with fever alone.

The gene responsible for the development of FMF (MEFV) was recently cloned from the short arm of chromosome 16. It consists of 10 exons (coding regions) and encodes a protein, named pyrin or marenostrin, that takes cardinal part in the generation of FMF attacks. Strictly speaking, the pyrin is expressed in the cytoplasm of mature neutrophils and monocytes and is thought to trigger the biosynthesis of a chemotactic factor inactivator. Without this functional use of pyrin due to genetic mutation, no inactivator is produced leading to attacks.

Exons 2 and 10 are the most frequent mutation regions of

**Table 1—Pleural Fluid Features**

<table>
<thead>
<tr>
<th>Thoracentesis</th>
<th>WBC Count, Cells/μL</th>
<th>Pleural Fluid LDH, U/L</th>
<th>Pleural Fluid LDH/Serum LDH Ratio</th>
<th>Pleural Fluid Protein, g/dL</th>
<th>Pleural Fluid Protein/Serum Protein Ratio</th>
<th>Adenosine Deaminase, U/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>3,400 (80)</td>
<td>1,041</td>
<td>4.2</td>
<td>5.5</td>
<td>0.75</td>
<td>28</td>
</tr>
<tr>
<td>Second</td>
<td>2,400 (70)</td>
<td>833</td>
<td>3.4</td>
<td>5.3</td>
<td>0.71</td>
<td>25</td>
</tr>
<tr>
<td>Third</td>
<td>2,900 (76)</td>
<td>396</td>
<td>1.7</td>
<td>4.8</td>
<td>0.67</td>
<td>30</td>
</tr>
</tbody>
</table>

*LDH = lactate dehydrogenase.
†Serum lactate dehydrogenase upper normal limit = 460 U/L.
the \textit{MEFV} gene. Half of the FMF population carries two mutations, while 30% and 20% carry a single mutation and no identifiable mutation, respectively. Nonisotopic ribonuclease cleavage assay is the most reliable method for rapid screening of the coding sequence of the \textit{MEFV} gene, and this test result was positive in our patient.\textsuperscript{5}

Plural inflammation is one of the three most common manifestations of the disease. Physical examination and imaging findings are usually nondiagnostic.\textsuperscript{3} The characteristics of pleural fluid have not been described in detail, but an older study\textsuperscript{10} stated that the pleural fluid contains predominantly polymorphonuclear leukocytes. To the best of our knowledge, pleural fluid lymphocytosis due to FMF has not been reported. The diagnosis of this entity was established in our patient through the exclusion of all recognized causes of lymphocytic pleural effusions, using all the appropriate diagnostic tests including medical thoracoscopy. Furthermore, the diagnosis was supported by clinical criteria, which hold a sensitivity and specificity of 97%, as well as molecular testing.\textsuperscript{11} The diagnosis of FMF has until recently relied on clinical signs only (Table 2), thus making it difficult to establish a correct diagnosis in patients with mild or atypical manifestations of the disease. The isolation of the \textit{MEFV} gene and the identification of the mutations causing FMF opened the way for direct molecular diagnosis. Genetic diagnosis has still limitations because the mutations detected hitherto identify only approximately 60% of patients.\textsuperscript{15} However, molecular assay can be used as a confirmatory test in suspicious cases of FMF. More specifically, at the inception of the disease when the clinical features are not distinctive or when the family history is missing, genetic testing is of fundamental importance.\textsuperscript{13}

A sufficiently plausible and convincing explanation for the predominance of lymphocytes in the pleural fluid would be a chronic process affecting the pleural surfaces. In corroboration of disease chronicity was the fact that the patient sought medical assistance only when the related symptomatology was very intense. Additional support for this hypothesis is the chronic inflammation seen on pleural biopsy.

Colchicine has been established as a mainstay of therapeutic intervention in FMF for several years.\textsuperscript{14} It eliminates the acute FMF attacks in the majority of patients, diminishes appreciably the number of attacks in most of the rest, and averts the development of amyloidosis.\textsuperscript{15,16}

\textbf{CONCLUSION}

This case describes a unilateral lymphocytic pleural effusion presenting as the major feature of FMF. The pleuritis and the lymphocytic effusion were eliminated with continuous colchicine administration. FMF should be taken into account in the differential diagnosis of a patient presenting with periodic episodes of fever and painful manifestations in the abdomen, chest, joints, skin, and scrotum. The diagnosis depends mostly on clinical criteria, supported recently by molecular genetic testing.

\textbf{REFERENCES}


\textbf{Table 2—Tel-Hashomer Criteria for Diagnosis of FMF*}

<table>
<thead>
<tr>
<th>Major criteria</th>
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</thead>
<tbody>
<tr>
<td>Recurrent febrile episodes accompanied by serositis or synovitis</td>
</tr>
<tr>
<td>Amyloid A amyloidosis without a predisposing cause</td>
</tr>
<tr>
<td>Response to continuous colchicine prophylaxis</td>
</tr>
<tr>
<td>Minor criteria</td>
</tr>
<tr>
<td>Recurrent febrile episodes</td>
</tr>
<tr>
<td>Erysipelas-like erythema</td>
</tr>
<tr>
<td>FMF in a first-degree relative</td>
</tr>
<tr>
<td>Definite diagnosis</td>
</tr>
<tr>
<td>Two major or one major and two minor criteria</td>
</tr>
<tr>
<td>Probable diagnosis</td>
</tr>
<tr>
<td>One major and one minor criteria</td>
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*Adapted from Pras.\textsuperscript{11}
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