EVALUATION OF FAMILIAL MEDITERRANEAN FEVER WITH PLEURAL EFFUSIONS

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ABSTRACT

***Objective**: We aimed to evaluate the frequency of Familial Mediterranean Fever (FMF) related pleural effusions in the patients who hospitalized for pleural effusion.*

***Methods**: 123 adult patients with pleural effusion were included in the study. In addition to demographic data clinical, radiological/scintigraphic imaging , bronchoscopical findings, cytological, histopathological, biochemical analysis of the pleural fluid and pleural tissue were evaluated.*

***Results**: Female/male ratio was 11/112 and mean-age was 46.57 (16-75). 69.9% of the effusion was benign (n=86) and 22.7% was malignant (n=28). The most frequent etiological factor was tuberculosis (30.1%). However 5.6% (n=7) of pleural effusions were undiagnosed. FMF was the cause of pleuritis in two (1.6%) male patients. Case I was 35 years old and Case II was 59 years old. Although, in the Case I amyloidosis was detected previously in his renal biopsy, colchicine treatment hadn't been started. Case II had been hospitalized in our hospital four-times in the past, FMF was firstly diagnosed in his last hospitalization. Their sedimentation rates were 120 and 110 mm/hr, respectively. Fibrinogen levels were 1125 mg/dl in Case I and 690 mg/dl in Case II during attack and 260 mg/dl and 150 mg/dl after attack, respectively.*

***Conclusion**: Undiagnosed pleural effusions are problematic cases for the physicians. However, FMF should be kept in mind in case of undiagnosed and/or recurrent pleuritis, particularly in the areas where disease is prevelant. The early diagnosis will prevent the patients from further invasive diagnostic procedures.*

***Key words**: Amyloidosis, Familial Mediterranean fever, pleural effusion, pleuritis.*

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Introduction

Pleural effusion is an important sign which is frequently encountered by chest or internal medicine specialists. Some cases can be diagnosed easily by medical history, physical examination and routine laboratory tests while some others require many invasive procedures including surgery. But sometimes, diagnosis can not be achieved despite all the efforts and these cases constitute a problem for the physician and require long term follow-up.

Familial Mediterranean Fever (FMF) is a chronic inflammatory disease which favors certain ethnic groups (Armenian, Jewish, Arabic and Turkish)[1]. FMF also called "recurrent polyserositis" is a periodic febrile disease with an autosomal recessive inheritance affecting mostly individuals of Mediterranean descent[2]. It is characterized by recurrent abdominal pain, fever, chest pain in pleuritic type and pleural effusion, and its etiology is not clearly known[1, 3]. FMF prevalence is reported to be 9.3/10.000 in Turkey[4]. It makes this disease difficult to be diagnosed in adulthood period, while the diagnosis is generally made in childhood and adolescence. Normally favoring ethnical background, today in a globalizing world, this disease can be seen in every population.

Pleural effusion or pleuritis is one of the most important signs of FMF[1,3]. But, if the patient has no former diagnosis or pleural effusion was the first symptom, it may be occasionally difficult to establish the diagnosis of FMF. The incidence of pleuritis is reported to be 40% related to this disease[1], but no data could be found concerning the incidence of FMF pleuritis among all causes of pleurisy. We aimed to evaluate the frequency of FMF related pleural effusions in the patients hospitalized for pleural effusion investigation.

Matherials and methods

In this study we retrospectively evaluated data of 123 patients with pleurisy. Clinical findings, routine hematological tests, fibrinogen levels if it was measured, were noted. For the diagnosis, pleural fluid analysis (biochemistry, bacteriology, cytology), ventilation/perfusion scanning, bronchoscopy and open pleural biopsy methods were used gradually if necessary, along with radiological and bacteriological tests. Additional tests regarding FMF diagnosis were requested from the patients whose diagnosis was not made but a doubt concerning FMF was present. Pleural effusion diagnosis was established according to following criteria[5-8];

Malignant effusion: If malignant cells are demonstrated in pleural fluid cytology or pleural biopsy.

Paramalign effusion: Exudative fluid in which no malignant cells can be demonstrated with pleural fluid cytology or pleural biopsy, despite the presence of a known malignancy.

Pleural tuberculosis: Presence of parenchymal lesions in chest X-ray, positivity of *Mycobacterium tuberculosis* in sputum and/or pleural fluid, increasing of adenosine deaminase level in pleural fluid or presence of granulomatous inflammation with caseating necrosis in pleural biopsy.

Pulmonary embolism: Along with clinical findings, medium or high probability in ventilation/perfusion scanning or multidetector pulmonary arterial computed tomography angiography, presence of deep venous thrombosis in venous Doppler ultrasonography of lower extremities.

Parapneumonic effusion: Pleural effusions those accompany with bacterial pneumonitis, abscess of the lung or bronchiectasis, are diagnosed as "parapneumonic", while the ones in which directly pus was aspirated and leukocytosis or bacterial proliferation in culture were demonstrated are diagnosed as "empyema".

Effusion due to Familial Mediterranean Fever: The diagnosis was established according to the criteria described by Livneh et al. and the response to colchicine treatment (Table 1)[7].

Effusion due to heart failure: The diagnosis was made upon clinical findings of congestive heart failure and presence of transudative pleural effusion.

Malignant mesothelioma: It was diagnosed by pleural biopsy.

Chylothorax: If the effusion was white colored and odorless, and the triglyceride level in it exceeds 110 mg/dl.

Effusion due to by-pass: Presence of any by-pass operation in the last 6 months and effusion which could not be explained with other reasons.

Undiagnosed effusion: All other cases of pleuritis, when the diagnosis could not be established, despite all invasive or noninvasive procedures.

The statistical analysis of this study was given in percentages.

Major criteria
Recurrent febrile episodes accompanied by peritonitis, synovitis or pleuritis
-Amyloidosis of AA-type without predisposing disease
Favorable response to continuous colchicine treatment
Minor criteria
Recurrent febrile episodes
Erysipelas-like erythema
FMF in first degree relative
Definitive diagnosis: 2 major or 1 minor and 2 major
Probable diagnosis: 1 major and 1 minor

Table 1: Criteria for the diagnosis of familial Mediterranean fever[7].

Results

The majority of the patients were male (M:112/F:11); mean age was 46.5 years[16-75]. 69.9% of the pleural effusion was benign, 22.7% was malignant, and in 5.6% (seven subjects) any etiological cause was not found. The most common reasons of the pleurisy in this study were tuberculosis, parapneumonic effusions, and malign pleurisy, respectively (Table 2). Diagnoses were frequently elicited with closed needle biopsy with Abram's needle. Open pleural biopsy was performed in three of seven subjects, who were undiagnosed; remaining four did not accept further invasive procedures. Fibrinogen had been requested from the seven patients who were undiagnosed and/or a doubt of FMF. Even though obtained high levels in four cases, FMF was not considered because of the absence of the other diagnostic findings. Progress of the disease was good in these patients except one who died during follow-up, and effusions regressed in chest X-rays. It was concluded that the effusions in these patients can be related to benign reasons except one. We showed that the main symptoms and clinical and laboratory findings in table 3 and table 4.

Diagnose* n	Clinically	Pleural Biopsy With Abram's needle	Fluid analysis	Doppler/V/P scintigraphy	Transthoracic aspiration biopsy	Bronchoscopy	Open pleural biopsy
Tuberculosis pleurisy (n=38)	-	28	7	-	-	-	3
Pleuropneumonia (n=24)	19	-	5	-	-	-	-
Malign pleurisy (n=22)	-	6	7	-	2	7	-
Congestive heart failure (n=11)	11	-	-	-	-	-	-
Pulmonary embolisation (n=8)	-	-	-	8	-	-	-
Malign mesothelioma (n=6)	-	5	-	-	-	-	1
After coronary by-pass (n=3)	-	-	3				
FMF (n=2)	2	-	-	-	-	-	-
Empyema (n=1)	-	-	1	-	-	-	-
Chylothorax (n=1)	-	-	1	-	-	-	-
Total (n=116)	32	39	24	8	2	7	4

Table 2: The causes of pleurisy and applied diagnostic procedures are shown in the table. Diagnoses were elicited by clinical assessment vast majority of the patients.
** Seven patients whose pleural effusion etiologies were not known are not show. We show diagnostic procedure percentage in 116 patients, and diagnoses percentage in 123 patients.*

Symptoms (n= 123)	Malign (n=28)	Benign (n=86)	FMF (n=2)	Undiagnosed (n=7)
Chest pain (n=75)	16	54	11	4
Cough (n=46)	14	31	-	1
Dyspnea (n=43)	9	31	2	1
Fever (n=39)	2	34	2	2
Appetite, weakness, weight loss(n=26)	11	15	-	-
Colored sputum and hemoptysis (n=19)	7	12	-	-
Night sweet (n=12)	2	9	1	-
Recurrence of pleurisy (n=3)	-	-	1	2
Abdominal pain (n=3)	-	1	2	-

Table 3: Symptoms of the cases with pleuritis. Chest pain was the most frequent symptom especially in the benign pleurisy patients.

FMF was the cause of pleuritis in two (1.6%) male patients. Although, in the Case I amyloidosis was detected previously in his renal biopsy, colchicine treatment hadn't been started. Other patient had been hospitalized in our hospital four-times in the past, and he had been diagnosed both with chronic obstructive pulmonary disease and pleuropneumonitis. Case II was firstly diagnosed as FMF in his last hospitalization. Their sedimentation rates were 120 and 110 mm/hr, respectively. Fibrinogen levels were 1125 mg/dl in Case I and 690 mg/dl in Case II during attack and 260 mg/dl and 150 mg/dl after attack, respectively (Table 5). FMF had been diagnosed based on their responses to the clinical specialty and colchicine treatment[6]. During four years of follow up with colchicine treatment, they had no FMF attack.

Discussion

Differential diagnosis of pleural effusions are common and important clinical problems for both chest physicians and thoracic surgeons[9-12]. Generally, the incidence rate of pleural effusion is indicated as 4/1000 in a year[13]. The causes of pleural effusions

n=123	Malign	Benign	FMF*	Undiagnosed
Effusion side Right (n=76) (61.8%)	25%	69.73%	1.31%	3.94%
Left (n=36) (29.2%)	22.22%	72.22%	- -	5.55%
Bilaterally (n=11) (9%)	9%	63.63%	9%	18.2%
Analysis of effusion (mean)				
Glucose (mg/dl)	123.9	101.25	-	99.5
LDH (U/l)	649.9	783.66	-	651.60
T. Protein (mg/dl)	4.89	4.99		5.23
Albumin (mg/dl)	2.82	2.89		3.26
Sedimentation rate (n=123)				
20 mm/hr> (n=15)	2.43%	6.5%	-	3.25%
21-100 mm/hr	13%	53.65%	-	2.43%
101 mm/hr <	7,31%	9.75%		1.62%
PPD (n=47)				
10 mm≥ (n=8)	4.25%	4.25%	2.12%	6.38%
10 mm< (n=29)	4.25%	53.2%	2.12%	2.12%
Fibrinogen (n=7)				
400 mg/l %↓	-	-	-	57.14%
400 mg/l %↑	-	14.28%	28.75%	-

Table 4: Radiological and laboratory findings of all the cases. Right sided pleural effusions frequently was determined both malign and benign pleural effusions.
•*Pleural fluid could not be aspirated from the FMF patients.*

	Case I	Case II
Gender	Male	Male
Age (years)	35	59
Family history	Brother?	No
Sedimentation rate (mm/h)	120	110
CRP	(-)	(-)
RF	(-)	(-)
ANA	(-)	(-)
Fibrinogen (mg/dl)	690	1125
Amyloidosis	(+)	(-)
Treatment	Colchicine	Colchicine

Table 5: Data about FMF cases.

differ among countries and geographical regions and depend on the local incidence of disease which was associated with the pleural effusion. In developed countries the common causes of pleural effusions in adults are right heart failure, malignancies and pneumonia, however in developing countries where infectious disease related effusions are more prevalent[10,14]. The most common cause was tuberculosis in our patient group as reported in some other countries[15,16]. In FMF cases the incidence of pleural effusions were demonstrated as 18% in a study conducted in our country[17]. Differently Sayarlioglu et al. reported that pleuritis rate was 53% in the 401 adult FMF patients[18]. However, we could not be found any data concerning the frequency of FMF among the all causes of pleuritis. In recent study, we analyzed with different perspective and found that pleuritis due to FMF was 1.62 % among all causes of pleuritis.

Determination of the etiology of pleural effusion is crucial for the treatment and prognosis[10]. Despite all the efforts to elucidate the etiology of the pleural fluid, 15-20% of cases had been reported as undiagnosed[11,13]. Davies et al. showed that about 31% of the pleural effusions were undiagnosed despite the implementation of medical thoracoscopy[19]. In recent study, 5.6% of our patients remained undiagnosed. Clinical symptoms were substantially similar common symptoms were chest pain, cough and dyspnea. It was interesting that in both of the FMF patients had dyspnea, despite the low volume of pleural fluid. In FMF patients restrictive or obstructive disorders can be present in pulmonary function tests, like as the Case II whose lung function test was obstructive pattern[20]. Clinical and genetic findings of FMF may be variable in different populations. Environmental factors may also affect clinical features of FMF[21,22]. FMF related chest attacks are characterized by unilateral pleuritic chest pain, shortness of breath and high body temperature (38- 40ºC)[1,2]. Among the manifestations of FMF, pleuritis is the third common findings, coming after peritonitis and arthritis. Its frequency was found to be 18% in a study carried out by Özel et al. in 105 adult FMF subjects[23]. The frequency of pleuritis as a single initial symptom was reported to be 7.6%, in the same study. Tunca et al. found that the most frequent clinical findings of patients were peritonitis (93.7%), fever (92.5%), arthritis (47.4%), pleuritis (31.2%)[2].

The first step to diagnose of pleurisy is pleural fluid analysis. It is important whether it is exudates or transudates[10]. Exudative fluid rate was very high in benign pleurisy group in our study because of the tuberculosis. Characteristics of FMF related effusion are sterile and contains many mononuclear or polymorphonuclear leukocytes[1]. But the amount of the pleural effusion is considerably small and generally no fluid can be obtained by puncture. In both of our patients, pleural fluid aspiration had been tried but fluid couldn't be obtained.

In FMF patients pleural fluid appears in equal rates on both right and left chest sides and costophrenic angle may be blunted on chest X-ray[24,25]. In this study, in Case I minimal pleural effusion was present on the right side on his chest X-ray. When we examined the hospital data of other patient, it was realized that there had been present some degree of bilateral effusions on the chest X-rays every time of his hospitalization, which soon had been disappeared. On the last hospitalization, there was minimal pleural

effusion bilaterally. Most of the pleuritic attacks heal without any sequel, but in some patients pleural thickening can occur after recurrent attacks[24]. In our patients all the symptoms were disappeared in 1 to 3 days of follow-up without requiring any treatment.

Although, we were not able to perform a genetic test in our cases, we made the diagnosis in the first patient by clinical findings and the presence of amyloidosis in the biopsy, and in second patient only by strong clinical findings. The regression of pleural effusion in several days without any treatment in both patients supported the diagnoses. Amyloidosis is the main complication of the disease and its development dependents on environmental and genetic factors, and delay in the diagnosis. Amyloidosis as well as the attacks can be prevented with colchicine treatment[26,27].

In conclusion, although we found low rate of FMF among all of the pleural effusions, FMF should be kept in mind in a case of undiagnosed and/or recurrent pleuritis, particularly in the areas where the prevalence of the disease is high or high risk ethnical population live.

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