



Thoracic and lung involvement in familial Mediterranean fever (FMF)

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Familial Mediterranean fever (FMF) is an episodic febrile disease with an autosomal recessive inheritance, prevalent in Sephardi Jews, Armenians, Turks, Arabs, Druzes, and other inhabitants of the Mediterranean basin [1–3]. It is characterized mainly by recurrent attacks of fever and serositis involving the peritoneum, pleura, synovial membrane, and tunica vaginalis [1,2]. The gravest consequence of FMF is kidney involvement by AA amyloidosis, which gradually leads to nephrotic syndrome and uremia [1,2,4]. Colchicine, in doses ranging between 1 to 3 mg/day, prevents acute attacks of FMF in the majority of the patients and ameliorates attack manifestations in most of the rest. In addition, it may fully prevent amyloidosis [1,5,6].

Genetic and pathogenetic background

The gene causing FMF (*MEFV*) was recently cloned from the short arm of chromosome 16 [7–11]. The gene is 10 KB long and includes 10 exons. The protein encoded by the gene was named pyrin by the International FMF Consortium, a term derived from the Greek word for fever and fire [10]. Pyrin is thought to be a down-regulator of inflammation. The finding that pyrin is almost exclusively expressed in the cytoplasm of mature granulocytes is consistent with the role of granulocytes as the major pathogenic cell involved in serosal inflammation during FMF

attacks. It has been inferred that pyrin itself holds a pathogenic role in the generation of FMF attacks [12]. More recently it was found that pyrin attaches to cytoplasmic microtubuli, which are also the site of action of colchicine, the mainstay of pharmacological intervention in FMF [13]. Finally, because several apoptotic proteins include a pyrin domain, it is assumed that pyrin exerts its anti-inflammatory effect by being involved in the apoptotic cascade [14].

To date, over 30 disease-associated mutations have been identified in the gene, most of which are located in its terminal 3' exon, exon 10 [15]. The most common mutation identified thus far is *M694V*, prevailing in North-African Jews. It is followed in frequency by *V726A*, occurring most commonly in Iraqi Jews and Arabs, and by *M694I* in Arabs and *E148Q* in Ashkenazi Jews. A recessive trait such as FMF requires that two mutations be clinically expressed. When an FMF patient population is screened for mutations, however, only 50% to 60% are found to carry two mutations. Thirty percent carry a single mutation and 20% have no identifiable mutations. The proportions between these three groups may vary depending on the number of screened mutations and the method of screening. The opposite occurs as well (ie, two mutations may be identified without bearing any FMF-related phenotypic expression [phenotype III]) [16].

While *MEFV* mutation carriers suffer no FMF manifestations under normal conditions, a recent publication described a man with pulmonary tuberculosis who began to suffer concurrent attacks of FMF [17]. He was found to carry only a single *M694V* mutation. The FMF attacks resolved sponta-

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neously once he was cured of tuberculosis. The authors suggested that an infectious or inflammatory condition might induce a typical FMF attack in carriers. Indeed, the authors showed that in a cohort of patients with Behcet's disease who had concurrent FMF, FMF was present despite the occurrence of only one *MEFV* mutation, as determined by sequence analysis [18].

The advent that followed FMF gene cloning was characterized by defining many genotype–phenotype correlates; the strongest was formed between disease severity and homozygosity for *M694V* [19,20]. Homozygosity for the *M694V* is also associated with amyloidosis and protracted febrile myalgia [21]. A negative association was found between this genotype and older age of FMF onset [22]. The elucidation of the genetic background of FMF has yet to define its role in the clinical work-up of FMF patients. Because mutations discovered so far recognize only about 60% of patients, diagnosis is still based on clinical criteria, which hold a sensitivity of 97% [23].

Pleuritis and pericarditis in FMF

Inflammation of the pleura, presenting as an attack of pleuritic chest pain associated with fever, occurs in 40% of FMF patients. It is one of the three most common manifestations of the disease, preceded only by abdominal attacks and arthritis [2]. A typical attack lasts between 1 and 4 days, similar to attacks in other locations. Physical examination and chest radiography are usually unrevealing, although occasionally the costo-phrenic angle may be blunted on the side of the attack and the recurrent attacks may sometimes result in pleural thickening and adhesions [2,24]. A minority of chest attacks is due to pericarditis rather than pleuritis [25]. While chart reviews of 4000 patients followed in the authors' clinic at the time of the study revealed a mere 27 patients (0.675%) with electrocardiograms, echocardiograms, or chest radiographs typical of pericarditis [27], a previous study found echocardiographic evidence of pericardial disease in 27% of FMF patients during the attack-free periods of the disease [26]. The discrepancy between the studies may be explained by a low index of suspicion for pericarditis in the authors' center or over-diagnosis and misinterpretation of the echocardiograms in the other center. Fortunately, pericardial attacks of FMF follow the same course as attacks at other sites (ie, they are of short duration, resolve spontaneously, and leave no sequela). Recurrent and chronic attacks are even

more rare because they are preventable by continuous colchicine treatment.

Recurrent pneumonia and FMF

While the FMF flaw is mainly located to neutrophils [2], neither deviation from normal leukocyte function [27] or predisposition to develop infection [28] were seen in FMF. Pleural inflammation, however, may result in an erroneous diagnosis of pneumonia, at times on a recurrent basis. The misdiagnosis may stem from the atelectasis that may accompany the pleural inflammation [29–31] or, more commonly, from misinterpretation of the symptoms. When chest attacks are the first—or, more rarely—the only manifestation of FMF, the correct diagnosis may be delayed for many years. In the meantime the patient receives recurrent courses of unnecessary antimicrobial therapy without colchicine. This exposes the patient to needless toxic effects on the one hand and unchecked amyloidogenesis on the other. Rarely, pulmonary infiltrates resulting from other FMF-related conditions, particularly vasculitides or thromboemboli, may occur, and therefore must be considered in the differential diagnosis.

FMF and chest malignancies

Over the years, several case reports of peritoneal mesothelioma in patients with recurrent abdominal attacks were published [32–35]. In the authors' patient cohort (which included at the time of the study 5000 FMF patients) there were no cases of peritoneal mesothelioma and only a single case of an elderly woman with rheumatoid arthritis and late onset FMF; this patient succumbed to a malignant pleural mesothelioma. It has been suggested that the wild-type FMF gene (*MEFV*) functions as a tumor suppressor gene and that a mutation in the gene causes both the FMF phenotype and the loss of anti-tumor activity [34]. The authors' experience does not support an association between mesothelioma and FMF, however. Furthermore, the Israeli Cancer Registry, which receives data on all patients with cancer in Israel, does not imply an increased incidence of malignancy in FMF patients.

FMF and protection from asthma

The frequency of carriers of mutated *MEFV* in populations at risk is very high, ranging from 1:5 to

1:16 [36–38]. This high rate implies the presence of a selection advantage for carriers. Initially, asthma served as a test case for this hypothesis. In one study the prevalence of asthma among 626,569 recruits of the Israeli Defense Forces was 2.96% compared to a mere 0.92% among 869 recruits with FMF ($P < 0.0005$) [39]. A second study reaffirmed these findings; asthma was absent among a group of 100 FMF patients despite the expected prevalence of 1% to 5% [40]. Two additional studies that searched for an advantage of *MEFV* carriers among North African [41] and Ashkenazi Jews [16] failed to find a statistically significant difference in the prevalence of asthma between heterozygotes and controls, however. These studies weaken the hypothesis that the carrier state entails protection from asthma, although homozygosity for *MEFV* does appear to confer such an effect.

Although the question of protection against asthma in FMF remains open, the possibility of a negative association between the two diseases is compelling. First, for a possible linkage disequilibrium, asthma-associated genes can be sought in the vicinity of *MEFV* on chromosome 16p13.3 [42]. Examples of such candidate genes are the tryptase genes, which are expressed highly in human mast cells that encode for serine proteases and are implicated in bronchial inflammation and constriction [43,44]. The IL-4 receptor alpha gene has also been examined recently as the 16p-linked susceptibility locus for asthma and atopy [45]. The findings suggest that it is indeed an atopy and asthma susceptibility locus, but that variations outside the coding region of the gene influence susceptibility. It may be postulated that the *MEFV* serves as such a modifier gene, exerting its influence through the IL-4 receptor alpha gene. Eosinophils may form an additional link between FMF and asthma because the pyrin protein, encoded by *MEFV*, is expressed not only in neutrophils but also in eosinophils [10–12]. It may be concluded that pyrin is essential for normal eosinophil function and that the mutated pyrin in patients with FMF attenuates eosinophil-mediated bronchial inflammation and constriction, resulting in a decreased frequency of asthma.

Serum eosinophil cationic protein levels were found to be higher in symptomatic patients with FMF than in healthy controls and patients with active asthma [46]. Eosinophil cationic protein is one of three specific eosinophil granule proteins of 21kd. It serves as an indicator of eosinophil activity and turnover, and is often elevated in patients with active asthma [47–50]. This fact, in addition to pyrin expression, suggests a role for eosinophils in the pathogenesis of FMF. The precise nature of this

association and how it affects the expression of asthma has not yet been elucidated, however.

Colchicine, the drug used on a continuous basis to prevent FMF attacks, may also ameliorate asthma with its anti-inflammatory effects [51,52]. Recent studies found no beneficial effect of colchicine compared to placebo in the treatment of asthma, however [53,54].

Lung involvement in amyloidosis of FMF

Amyloidosis of the AA type develops in most patients with untreated FMF and involves many tissues. Organ dysfunction is most prominent, however, and it is usually solely in the kidneys [1,2]. Kidney disease in amyloidosis of FMF develops from a subclinical stage onward through proteinuric, nephritic, and azotemic stages, culminating in uremia. Prolongation of life (by dialysis and kidney transplantation) in FMF patients with end stage renal disease due to amyloidosis allows further extrarenal amyloid deposition to continue, resulting in the development of overt gastrointestinal, thyroid, adrenal, heart, and lung diseases [55–58].

The appearance of clinically evident lung disease due to amyloidosis of FMF is uncommon, and is usually already associated with manifestations of other involved organs, as evidenced by the fact that it appears late in the course of the disease. In the first published series of FMF patients, autopsies performed in 42 of 470 cases revealed very fine amyloid deposits in the alveolar septa of the lung periphery. These deposits caused no symptoms in the patients [2].

In a recently published article of all cases of pulmonary amyloidosis seen at the Mayo clinic between 1980 and 1993, only one of 55 patients with pulmonary amyloidosis had FMF. This patient had diffuse interstitial lung infiltrates with bilateral adenopathy [59]. Extensive deposition of amyloid in the pulmonary vessels and alveolar capillary walls, resulting in pulmonary hypertension, was seen in the autopsy of another patient with FMF who presented with cough and progressive dyspnea associated with radiographic evidence of diffuse interstitial infiltrates. Pulmonary amyloidosis in this patient was part of a systemic amyloidosis involving the kidneys, spleen, liver, gastrointestinal tract, and heart. The patient died of ventricular fibrillation associated with amyloid cardiomyopathy [60]. Nevertheless, it should be noted that this AL-type clinical presentation is an extremely rare development in the AA amyloidosis of FMF.

Finally, homozygosity for the *M694V* mutation was found to be strongly associated with a more

severe disease characterized by earlier onset and multiple-site attacks, requiring a higher colchicine dose for control and a higher prevalence of amyloidosis [19]. Lung amyloidosis, as well as other pulmonary manifestations of FMF, should be sought primarily in this subset of patients.

Thromboembolism in FMF

The hypercoagulable state associated with the nephrotic phase of amyloid nephropathy predisposes to thromboembolism. Although the authors found no published reports of pulmonary embolism under these circumstances, their patient cohort includes at least six patients with amyloidosis who died due to thromboembolic phenomena, including one patient who had a massive pulmonary embolism.

One report describes an FMF patient with superior vena cava syndrome presenting with cough, hoarseness, exertional dyspnea, and neck swelling [61]. Because the patient had no evidence of nephrotic syndrome or amyloidosis, and since the patient's brother had been diagnosed with Behcet's disease, which is more common in FMF and in which thromboembolic phenomena are commonplace, the authors presume that the index patient had some form of an overlap syndrome between FMF and Behcet's disease that predisposed him to thrombosis.

Finally, FMF patients should be considered to be at a higher risk for cardiovascular disease (and thereby to arterial thromboembolic phenomena) because of the ongoing inflammation, increased serum CRP levels, and extensive use of COX-2 inhibition, all of which predispose patients to accelerated arterial plaque formation and rupture [62]. The authors found similar rates of cardiovascular disease amongst FMF patients and matched healthy controls, however [63]. A role for colchicine in counteracting the above risk factors has been suggested [63].

Pulmonary involvement in vasculitis of FMF

FMF is commonly associated with four vasculitides: polyarteritis nodosa (PAN), Henoch-Schoenlein Purpura (HSP), protracted febrile myalgia, and Behcet's disease. Although lung disease is uncommon in PAN, it may occur in the form of interstitial pneumonia, interstitial fibrosis, bronchiolitis obliterans, and pulmonary infiltrates, manifesting as severe dyspnea, cough, hemoptysis, chest pain, and fever [64–66]. Pulmonary involvement in HSP is rare as well, yet can include pulmonary hemorrhage and

interstitial pneumonitis; chest radiographs show alveolar and reticulonodular infiltrates, respectively [67,68]. Finally, Behcet's disease may involve the lung with arterial aneurysms, which may rupture and cause hemoptysis, major bleeding, or organizing pneumonia presenting with fever, infiltrate, hemoptysis, deep vein thrombosis, and emboli [69]. Theoretically, vasculitis of the above categories may manifest as lung disease in FMF. In addition, a case report of a patient with FMF and histologic and clinical findings compatible with lung infarction has been described. Isolated vasculitis of the lung was the supposed underlying mechanism in this case [7].

Summary

Lung involvement in FMF is limited mainly to transient pleuritis during acute attacks. Amyloidosis of the lung is rare and is associated with symptomatic involvement of other organs while remaining subclinical in itself. Vasculitis of the lung in FMF is possible because of the strong association between FMF and a variety of vasculitides. With the exception of one case of isolated pulmonary vasculitis, vasculitis of the lung in FMF has not been described. The claim that FMF protects against asthma has not been established, but this inverse association, if present, may be traced to linkage disequilibrium in which *MEFV* modifies the effect of asthma and atopic-related genes, or to eosinophil function. Mesothelioma has been reported in at least four patients with FMF and is related to chronic or recurrent stimulation of the serous membrane. Three patients had peritoneal mesothelioma, while one developed mesothelioma of the lung. Finally, thromboembolism should be considered, particularly in patients with FMF amyloidosis who present with respiratory distress.

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