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Case Report

Genotype-Phenotype Correlation Expressed as Cardiac Amyloidosis in "FMF-like" Disease

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Abstract

Familial Mediterranean Fever, the most common autoinflammatory disease, is inherited in an autosomal recessive pattern. During the recent years, a new phenotype has been described concerning heterozygous carriers of Mediterranean Fever (MEFV) mutations that express typical clinical features of Familial Mediterranean Fever (FMF). This new pattern of genotype-phenotype correlation is called "FMF-like" disease.

Herein, we describe the case of a heterozygous M694V carrier, presented with clinical characteristics similar to "FMF-like" disease complicated with cardiac amyloidosis.

Keywords: FMF, Familial Mediterranean fever, Amyloidosis, "FMF-like" disease

Introduction

Familial Mediterranean Fever (FMF) is hereditary autoinflammatory disorder associated with mutations in MEFV gene. FMF homozygous patients are characterized by recurrent bouts of fever and serositis, manifested as abdominal or chest pain and arthralgias. They can also develop renal and rarely cardiac amyloidosis. During the recent years, it has been observed that heterozygous MEFV mutation carriers can suffer from a mild or incomplete form of FMF, characterized by episodic arthritis without fever or chronic fibromyalgic pain, which is often misdiagnosed [1].

Herein, we delineate the case of a heterozygous FMF patient that developed cardiac amyloidosis in the absence of renal impairment. To our knowledge, this is the first case of a patient with "FMF-like" disease complicated with cardiac amyloidosis.

Case Presentation

A 53-years-old female patient, presented to our Outpatient Clinic, complaining about arthralgias of both knees and elbows, general muscle weakness, fatigue and a ten-day history of heart palpitations. Her medical history involved diabetes mellitus type II and a thyroid goiter while her medication included vindagliptin, metformin and levothyroxine sodium respectively. The patient had been identified as heterozygous of M694V mutation of FMF. Her sister was homozygous for the same mutation, yet free of FMF long-lasting complications since she was under colchicine therapy throughout the last 20 years.

On admittance, patient's vital signs were within normal ranges: blood pressure was 140/70 mmHg, temperature up to 36.8 ^{o}C, saturation of 97%, apart from heart rate that was mild elevated. No orthostatic hypotension was observed. Otherwise, physical examination did not reveal any pathological findings as lung and heart aspiration, abdominal and neurological examination was normal. Furthermore, no joint swelling was noticed. Finally, the electrocardiography examination revealed supraventricular arrhythmia.

Afterwards, the patient underwent extended laboratory examinations. Hematological and biochemical tests revealed no anemia, renal insufficiency, electrolyte disturbances or thyroid dysfunction. Urine tests were also negative. However, prominent inflammatory reaction was observed since C - reactive protein (CRP) and Erythrocyte Sedimentation Rate (ESR) levels were elevated (Table 1). Further immunological tests were performed, excluding the possibility of connective tissue disorders (Table 2). Due

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WBC count (x 10^3/ μL)	7510	Ca (mg/dL)	10,16
Neutrophils/ Lymphocytes (%) Hct (%)	69/25 42,3	P (mg/dL) K (mmol/L)	3,33 4,7
Hb (g/dL)	14,3	Na (mmol/L)	142
ESR* (mm/h)	51	CRP* (mg/ dL)	8,2
Urea (mg/dL)	28	TSH/ FT4 (μIU/mL)	1,120/ 0,98
Serum Creatinine (mg/dL)	0,59	RF	0,0
Uric Acid (mg/dL)	5,6	IgG	1162
SGOT/ SGPT (U/L)	12/ 15	IgA	145
γGT (U/dL)	12	IgM	94

**Values above normal limits.*

Hct = hematocrit; Hb = hemoglobulin; ESR = erythrocyte sedimentation rate; SGOT = serum glutamicoxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; γGT = gamma-glutamyl transferase; Ca = calcium; P = phosphorus; K = potassium; Na = sodium; CRP = c - reactive protein; TSH = thyroid stimulating hormone; FT4 = free T4; RF = rheumatoid factor; IgG = Immunoglobulin G; IgA = Immunoglobulin A; IgM = Immunoglobulin

Table 1: Laboratory findings (1) – Hematological & Biochemical tests.

ANA	negative	anti-Sm	negative
anti-dsDNA	negative	anti-SSA (Ro)	negative
ANCA-MPO	negative	anti-SSB (La)	negative
ANCA-PR3	negative	anti-CCP	negative
C3	125.5	SAA* (mg/dL)	77.3 (normal ranges 0-6,8)
C4	37	Anti-HCV	negative
anti-Jol 1	negative	HbsAg	negative
anti-RNP	negative	Anti-HBc	negative
anti-Scl 70	negative	Anti-HIV I/II	negative
Serum Immunofixation Assays		no detection of monoclonal immunoglobulins	
Urine Immunofixation Assays		no detection of monoclonal immunoglobulins	

**Values above normal limits.*

ANA = antinuclear antibodies; ANCA = antineutrophil cytoplasmic antibodies; ANCA-MPO = myeloperoxidase antibodies; ANCA-PR3 = proteinase 3 antibodies; C3 = complement component 3; C4 = complement component 4; anti-Sm = anti – Smith antibody; anti-CCP = anti -cyclic citrullinated peptide antibodies; anti-HCV = hepatitis C virus antibodies; HbsAg = surface antigen of the hepatitis B virus ; anti – Hbc = antibodies against core antigen of hepatitis B virus; anti-HIV = human immunodeficiency virus antibodies.

Table 2: Laboratory tests (2) - Immunological Tests.

to patient's family history of FMF serum amyloid levels (SAA) were measured to be high (Table 2) leading to high suspicion of "FMF-like" disease. Concurrently, the patient underwent chest X-ray, radiological images of upper and lower extremities and an abdominal ultrasound that did not reveal any pathological findings. In order to investigate the leading cause of arrhythmias, a 24h-Holter electrocardiography was performed indicating mean heart rate of 87 beats per minute with sinus rhythm and few paroxysmal supraventricular tachyarrhythmias. Transthoracic echocardiography detected impaired left ventricular function with normal ejection fraction, elevated values of intraventricular diameter and left atrium diameter and "granular sparkling" myocardium appearance without pericardial effusion (Figure 1). Additionally, heart Magnetic Resonance Imaging highlighted characteristic patterns of subendocardial depositions of amyloid extending in varying degrees into the myocardium (Figure 2). Those findings in conjunction with elevated Serum Amyloid A (SAA) levels led to the diagnosis of cardiac amyloidosis.

After initiation of colchicine therapy and within six months constitutional symptoms were resolved while SAA levels were gradually reduced. Subsequently, the patient received treatment with colchicine 1mg, twice daily. The patient's clinical course satisfied Tel Hashomer's criteria of FMF: 2 major – AA amyloidosis and response to colchicine treatment, 1 minor – first degree relative with homozygous mutation of M694V of FMF. Thus, cardiac amyloidosis was attributed to FMF disease.

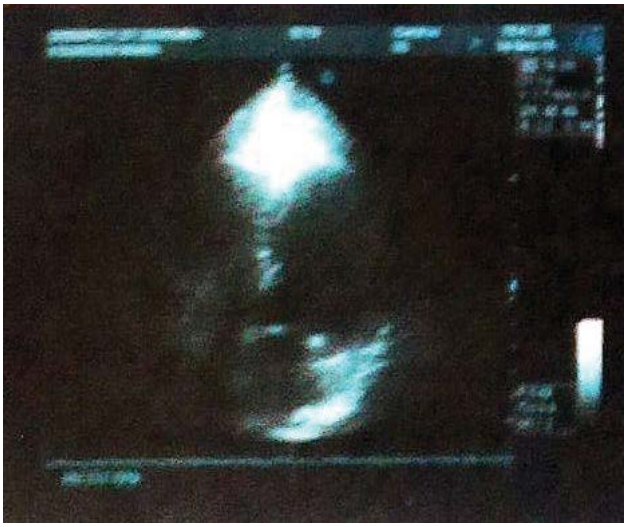

Figure 1: Heart echocardiogram - "granular sparkling" myocardium appearance.

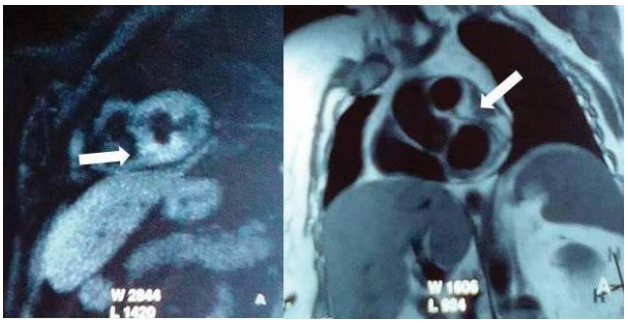

Figure 2: Heart MRI - The arrows show amyloid depositions.

Discussion

Familial Mediterranean fever (FMF) is regarded as the most common periodic syndrome. It represents an inherited autoinflammatory disorder which is characterized by recurrent self-limited attacks of fever and serosal inflammation resulting in pain in the abdomen, chest or joints [2-4].

FMF is caused by a mutation in the Mediterranean FeVer (MEFV) gene which encodes a protein called manestrin/ pyrin. MEFV gene was identified in 1977 [5,6]. It is located on chromosome 16p13.3 and is composed of 10 exons. As yet, more than 300 mutations in MEFV gene have been identified [7] while the most common and severe is M694V [8].

FMF is inherited as autosomal recessive disease, although features of autosomal dominant pattern of transmission have been demonstrated in several families [9]. In any case, the diagnosis of FMF is clinical, based on the Tel-Hashomer criteria [10,11]. Recent studies have shown that patients diagnosed with clinical picture of FMF are proven to be carriers of a single heterozygous mutation [1, 8], suggesting a new pattern of genotype-phenotype correlation that is called "FMF-like" disease. Studies show that

in 20-25% of patients with clinical presence of FMF and/ or a positive response to colchicine therapy, no mutation in the second allele is demonstrated [1].

The presence of a high number of heterozygote patients with typical symptoms of the disease has driven a number of alternative aetiopathogenic hypotheses during the last years [12]. In 2009, Booty, et al. showed that Turkish children, who are born and live in Turkey, have a higher disease severity score compared with Turkish children living in Germany. This study demonstrated that infections act as triggers of a weak innate immune pathway via pathogen-recognition factors and can influence the expression of the phenotype [13]. In parallel, other environmental factors have been investigated in relation to the disease severity of FMF [14]. Changes in pyrin sequence can be caused by selective pressures driven from environmental agents. For example, microbes such as *Clostridium difficile* and Yersinia, that modify the RhoGTPases, are able to stimulate pyrin inflammasome and can result in clinical patterns of FMF even with an incomplete phenotype [15].

Furthermore, it has been proved that certain mutations/ polymorphisms influence the phenotype in different ways. For example, amyloidosis, a severe complication in patients with clinical diagnosis of FMF, has been mostly correlated to M694V mutation [16] since the methionine residue in codon 694 plays a crucial role in the pyrin function [9]. Finally, recent investigations have recognized that some specific micro-RNA such as miR-4520a can play a key-role to genotype-phenotype correlation. More specifically miR-4520a is predicted to target genes implicated in autophagy through regulation of RHEB/mTOR signaling pathway. Latsoudis, et al. compared FMF patients bearing the M694V mutation to healthy controls showed a significant increase in miR-4520a expression levels suggesting a role of deregulated autophagy in the pathogenesis of FMF [12].

One of the most devastating complications observed in FMF patients is AA amyloidosis [17]. It represents a potentially life-threatening aftermath which results from the extracellular deposition of serum A amyloid, an acute phase reactant that is usually produced in hereditary autoinflammatory syndromes such as FMF. The spectrum of organ involvement usually includes the kidneys, the liver and less commonly the autonomic nervous system, the testes and the heart of untreated patients [18].

FMF is characterized by a vigorous increase in SAA levels during inflammatory paroxysms, which often persist between the attacks period. In FMF, arthritis and homozygosity for the M694V variant are additional independent risk factors for development of amyloidosis [19]. Early recognition and effective treatment of this condition is therefore of crucial importance in order to prevent the occurrence of AA amyloidosis [18].

FMF, particularly at a progressive stage, is associated with heart rate variability abnormalities suggestive either of cardiac amyloidosis or of the presence of autonomic nervous system dysfunction [20]. Both situations are rather rare. Cardiac amyloidosis as a part of systemic disease in FMF was firstly recognized in 1982 by Dabestani, et al. [21]. Amyloid deposition in the heart is a devastating and progressive process that leads to congestive heart failure (CHF), arrhythmias and sudden death. By implication, in patients with amyloidosis, infiltration of the heart confers the worst prognosis.

The golden standard of treatment for FMF is colchicine [22]. In 1972, Zemer, et al. suggested that daily use of colchicine is able to prevent both FMF attacks and secondary amyloidosis by reducing the level of subclinical inflammation [23]. The mechanisms of action are based on its ability to reorganize the actin cytoskeleton and down-regulate MEFV gene expression [22]. Studies have shown that not only homozygous but also symptomatic heterozygous with MEFV mutation may benefit from a trial of colchicine in a median dose of 1-2 mg daily [24].

Regarding our patient, she presented with arthralgias and constitutional symptoms surprisingly in advanced age. Inflammatory markers such as CRP and ESR were raised. Due to her family medical history of FMF, we suspected systemic inflammation that was confirmed by SAA elevated levels. She also referred heart palpitations which were identified as paroxysmal supraventricular arrhythmias through a 24-h Holter electrocardiographic monitoring. Unexpectedly, both heart echocardiography and MRI unraveled the image of "sparkling myocardium" due to subendocardial amyloid deposits. The patient received treatment with colchicine therapy (1mg, twice daily) and she remains stable until today while her constitutional symptoms gradually resolved. The response to colchicine therapy represented an additional element of FMF diagnosis according to Tel - Hashomer criteria, despite the fact that our patient was a heterozygous M694V carrier.

Conclusions

FMF diagnosis is mainly clinical. In recent times, a mild or incomplete form of FMF, known as "FMF-like" disease, has been identified. "FMF-like" disease is regarded as a new entity concerning heterozygous carriers of MEFV mutations. Candidate patients with clinical features either complication similar to FMF should be investigated thoroughly via precise clinical history recording and inflammatory markers' levels evaluation. Especially, assessment of SAA levels is crucial in those patients since they can develop AA amyloidosis leading to destructive repercussions such as cardiac amyloidosis. Since it is difficult to determine the variable penetrance and expressivity of the disease, it is highly recommended that clinicians should be of great awareness with FMF heterozygous carriers.

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