Joint Bone Spine 84 (2017) 159–162

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

Concise Report

Association of hidradenitis suppurativa and familial Mediterranean fever: A case series of 6 patients

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ARTICLE INFO

Article history:
Accepted 7 February 2016
Available online 26 May 2016

Keywords:
Familial Mediterranean fever
Hidradenitis suppurativa
Autoinflammatory syndrome
Colchicine
Interleukin-1 inhibitors
MEFV

ABSTRACT

Objectives: Familial mediterranean fever (FMF) is the most common monogenic autoinflammatory disease. Hidradenitis suppurativa (HS) is an inflammatory cutaneous disease. Those diseases can occur simultaneously among the same individual. Our objective was to describe the features of patients displaying both FMF and HS.
Methods: We screened the French adult FMF reference center for FMF patients with HS.
Results: Six patients out of 151 (4%) with a median age of 36 years old were concerned. Among them, FMF was symptomatic at a median age of 11.5 years old and colchicine was introduced at a median age of 20.5 years old. HS was diagnosed at a median age of 31.5 years old. An elderly patient displayed AA amyloidosis in the outcome of FMF, with a late diagnosis of HS, with response to anakinra. There was no temporal relation between FMF and HS attacks. Some patients had a persistent inflammatory syndrome under treatment.
Conclusion: FMF and HS are both inflammatory diseases involving young patients, with HS possibly being an autoinflammatory disease. Although their association seems to be fortuitous, both can induce an important inflammation state that could lead to AA amyloidosis and require a close monitoring of clinical signs and acute-phase reactants. Anakinra was successful in treating the only patient with both HS, FMF and amyloidosis.

1. Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disorder caused by mutations in the *MEFV* gene, mainly p.M694V in exon 10 [1]. It is the commonest hereditary autoinflammatory syndrome [1] with recurrent episodes of fever accompanied by abdominal, chest and joint pain. *MEFV* encodes pyrin, a protein expressed in neutrophils and monocytes and involved in the regulation of inflammation [2]. Daily colchicine administration can prevent both attacks and occurrence of AA amyloidosis [2]. Ex vivo studies performed with monocytes from FMF patients demonstrated the importance of increased secretion of the potent pyrogenic cytokine interleukin-1 beta (IL-1 beta). Subsequently, IL-1 inhibitors have been suggested as an alternative or a supplementary treatment in colchicine-resistant patients [2].

Hidradenitis suppurativa is an inflammatory skin disease characterized by recurrent painful nodules and abscesses in sites of

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http://dx.doi.org/10.1016/j.jbspin.2016.02.021
1297-319X/

apocrine sweat glands and mechanical friction, mainly the inguinal and axillary areas, leading to sinus tracts and scars [3]. It could affect 1 to 4% of the general population, and is associated with genetic susceptibility, hormonal factors, obesity and smoking [3]. Theoretical and clinical evidence tend to show that dysregulation of innate immunity plays a major role in its partially-understood pathogenesis, resulting in a systemic inflammation state that can even lead to complications like inflammatory amyloidosis [4].

We report 6 patients with a proven FMF who displayed HS and discuss the significance and consequences of this particular association.

2. Methods

We screened the French adult FMF reference center for patients with HS. The diagnosis of FMF was made according to the Tel Hashomer's diagnostic criteria [5]. The diagnosis of HS was made when recurrent inflammation of the inverse regions of the body, presenting with nodules, sinus tracts and/or scars occurred more than 2 times each 6 months [6] and was validated by a dermatologist's examination. We had access to the complete medical file. The following data were recorded:

- family history;
- tobacco use;
- Body Mass Index (BMI) in kg/m^2;
- age at diagnosis of FMF and HS;
- presence or absence of *MEFV* mutation;
- age at beginning of colchicine;
- mean colchicine dose;
- current colchicine dose;
- history of treatment for FMF and HS;
- clinical control of FMF under colchicine and of HS;
- existence of amyloidosis;
- renal insufficiency;
- CRP and SAA variation under treatment.

The *MEFV* mutation was searched as previously described [7]. CRP and SAA measurements were centralized in a single laboratory. High sensitive (Hs)-CRP and SAA were measured by immunonephelometry on an IMMAGE® analyzer (Beckman-Coulter, Villepinte, France). The sensitivity of the assays were 0.11 and 6 mg/L for Hs-CRP and SAA, respectively.

3. Results

We report 6 patients (4 men, 2 women) with a median age of 36 years, ranging from 27 to 70 and displaying both HS and FMF out of the cohort of 151 patients with FMF followed in the French adult reference center for FMF (Table 1). Their FMF was symptomatic at a median age of 11.5, ranging from 3 to 30 years old; colchicine was introduced at a median age of 20.5 years old, ranging from 4 to 34, with a mean current dosage of 1.25 mg per day [1,2]. HS was diagnosed at a median age of 31.5 years old, ranging from 13 to 63. Four of our six patient's families displayed cases of inflammatory diseases: FMF, Ankylosing spondylitis (AS) and Crohn. Patient 6's son carried a homozygous M694 V *MEFV* mutation and had both an FMF and an AS. None of our patients displayed symptoms of other inflammatory diseases, including AS. Patient 5 displayed severe acne. None displayed other cutaneous signs like psoriasis or pustulosis. Two of our patients were homozygous for M694 V *MEFV* mutation (patient 1 and 4). One of our patients carried a pathogenic homozygous mutation V726A *MEFV* mutation (patient 2). Each one of patients 5 and 6 carried a single pathogenic allele. There seemed to be no difference in the clinical presentation of FMF and HS, or the delay between the apparition of the two diseases, depending on the *MEFV* genotype and the patient's family history. Most of our patients displayed factors associated to HS including tobacco use and/or overweight.

All of our patients were treated by colchicine for their FMF. Patient 2 was the only one with no treatment for his HS despite an active disease. Half of our patients had an inflammatory syndrome despite treatment due to their FMF and/or HS. One of them had both an active FMF despite 1.5 mg of daily colchicine and an active HS (patient 1) so colchicine was increased to 2 mg daily; another one had both an active FMF under 2 mg of daily colchicine and an active HS (patient 2); one had an inactive FMF with an irregular intake of 1 mg per day of colchicine and an active HS (patient 3). On the contrary, one of our patients (patient 5) had a negative CRP despite an active HS, with no recurrent FMF crisis.

The oldest patient (patient 4) was the only one to display an AA amyloidosis revealed by a nephrotic syndrome at the age of 69, and

Table 1
Main features of the 6 FMF patients with HS.

	1	2	3	4	5	6
Sex	M	M	M	M	F	F
Age at inclusion (years)	27	36	50	70	28	36
Body mass index (kg/m^2)	23	29	27	25	24	31
Tobacco use	No	Yes	Yes	Yes	No	Yes
Family history	Crohn's disease in several family members		FMF in a cousin	Renal failure in two brothers FMF in one nephew		FMF mutation M694V/M694V and AS in one son FMF with mutation M694V/– in two sons, one of them treated by colchicine
MEFV mutation	M694V/M694V	V726A/V726A	ND	M694V/M694V	V726A/F479L/E148Q	M694V/–
Age at diagnosis of FMF (years)	3	20	4	10	13	30
Age at introduction of colchicine (years)	4	20	15	34	21	31
Age at diagnosis of HS (years)	23	36	45	63	27	13
Mean colchicine daily dose (mg)	1,5	2	1	1	1.5	1
HS treatment	AB + surgery	Nothing	AB + surgery	AB + surgery	AB	AB
Inactive FMF	No	No	Yes	Yes	Yes	Yes
Inactive HS	No	No	No	Yes	No	Yes
CRP/SAA at inclusion (mg/L)	68/557	21,5/19,2	12/ND	<5/<6	<5/<6	<5/<6

ND: not done; M: male; F: female; FMF: Familial Mediterranean Fever; AS: ankylosing spondylitis; HS: hidradenitis suppurativa; AB: antibiotics.