Research Article / Araştırma Makalesi

A Unique Pathognomic Skin Manifestation of Familial Mediterranean Fever: Erysipelas-Like Erythema

Ailevi Akdeniz Ateşinin Eşsiz Patognomik Cilt Bulgusu: Erizipel Benzeri Eritem

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Abstract

Background: The present study aimed to describe the differences between patients with and without ELE in patients with Familial Mediterranean Fever (FMF) and to determine the relationship between erysipelas-like erythema (ELE) and demographic, clinical, genetic and treatment characteristics of the patients.
Materials and Methods: The medical files of patients who were followed up with a diagnosis of FMF in the Pediatric Rheumatology Department of Gaziantep City Hospital between October 2023 and October 2024 were retrospectively analysed.
Results: Of 409 patients with FMF, 205 (50.1%) were male. The median age at diagnosis was 6 (minimum:1-maximum:18) years. FMF attack was accompanied by fever in 325 (79.5%), abdominal pain in 302 (73.8%), arthralgia in 121 (29.6%), arthritis in 56 (13.7%), chest pain in 62 (15.6%) and ELE in 55 (13.4%) patients. When comparing patients with ELE to those without, the frequencies of chest pain, arthralgia, and arthritis were significantly higher in the ELE group (p=0.014, p<0.001, p<0.001, respectively).
Pathological mutations were significantly more common in FMF with ELE than those without one (p<0.001). Additionally, among FMF patients, the use of anti-interleukin-1 (anti-IL-1) treatment combinations due to colchicine resistance was significantly higher in those with ELE (p<0.001).
Conclusions: The present study showed that ELE may be associated with subclinical inflammation, arthritis, colchicine resistance, pathogenic mutations, and severe disease scores in FMF patients. Based on these findings and existing literature, we believe that the presence of ELE in FMF patients is significant in terms of diagnosis, prognosis, and predicting the course of the disease.

Keywords: Anti-interleukin-1, Colchicine resistance, Erysipelas-like erythema, Familial mediterranean fever

Öz

Amaç: Bu çalışmanın amacı erizipel benzeri eritemi olan ve olmayan Ailevi Akdeniz Ateşi (AAA) hastaları arasındaki farklılıkları tanımlamak ve erizipel benzeri eritem ile hastaların demografik, klinik, genetik ve tedavi özellikleri arasındaki ilişkiyi ortaya koymaktır.
Materyal ve Metod: Ekim 2023 ve Ekim 2024 tarihleri arasında Gaziantep Şehir Hastanesi Çocuk Romatoloji bölümünde AAA tanısıyla takip edilen hastaların dosyaları retrospektif olarak incelendi.
Bulgular: Ailevi Akdeniz Ateşi olan 409 hastanın 205'i (%50,1) erkekti. Hastaların tanı yaşı ortanca 6 (minimum:1-maksimum:18) yıldı. Hastaların 325'inde (%79,5) ateş, 302'sinde (%73,8) karın ağrısı, 121'inde (%29,6) artralji, 56'sında (%13,7) artrit, 62'sinde (%15,6) göğüs ağrısı ve 55'inde (%13,4) erizipel benzeri eritem FMF atağına eşlik ediyordu.
Erizipel benzeri eritemi olan hastalar olmayanlarla karşılaştırıldığında, göğüs ağrısı, artralji ve artrit sıklıkları erizipel benzeri eritemi olan grupta anlamlı olarak daha yüksekti (sırasıyla p=0.014, p<0.001, p<0.001).
Ailevi Akdeniz Ateşi hastalarında patolojik mutasyonlar ELE'si olanlarda ELE'si olmayanlardan daha yaygındı (p<0,001). Ayrıca AAA hastaları arasında kolşisin direnci nedeniyle anti-interlökin-1 tedavi kombinasyonlarının kullanımı erizipel benzeri eritemili hastalarda anlamlı derecede daha yüksekti (p<0.001).
Sonuç: Bu çalışma erizipel benzeri eritemin AAA hastalarında subklinik inflamasyon, artrit, kolşisin direnci, patojenik mutasyonlar ve ciddi hastalık skorları ile ilişkili olabileceğini göstermiştir. Bu bulgulara ve mevcut literatüre dayanarak AAA hastalarında erizipel benzeri eritem varlığının tanı, prognoz hem de hastalık seyrinin öngörülmesi açısından öneme sahip olduğana inanıyoruz.

Anahtar Kelimeler: Ailevi akdeniz ateşi, Anti-interlökin-1, Erizipel benzeri eritem, Kolşisin direnci

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Introduction

Familial Mediterranean Fever (FMF), an autoinflammatory disease characterized by fever, peritonitis, pleuritis, arthritis, and erysipelas-like erythema (ELE), is an autosomal recessive hereditary disease affecting ethnic groups, primarily those living in the Mediterranean region, such as Turkish, Armenian, Arab, and Jewish (1,2). Attacks are self-limiting and typically resolve within 1–3 days. FMF attacks usually begin in early childhood (3). Colchicine remains the mainstay of FMF treatment, aiming to prevent acute attacks and chronic inflammation (4). If left untreated, FMF patients are at risk of developing severe secondary amyloidosis, especially in the kidneys, and potentially renal failure.

Clinical manifestations of FMF are linked to mutations in the MEFV gene (2). More than 300 mutations of the MEFV gene that can lead to FMF have been identified (5). Detailed information about each mutation, including variant details, phenotype/genotype relationships, and pathogenicity, can be found in the InFevers database. M694V, M680I, V726A, and M694I are the most recognized and prevalent pathogenic mutations. While E148Q is a common mutation, its pathogenicity remains unknown (6).

The presence of mucocutaneous symptoms is clinically significant, as it may represent the first manifestation or the activation phase of autoinflammatory rheumatic diseases (7). Erysipelas-like erythema is a rare but essential and pathognomonic skin finding associated with FMF (7,8). The lesions are characterized by tender, erythematous plaques on the legs. These plaques can be triggered by physical exertion and usually resolve spontaneously after 48 to 72 hours of rest.

This study aimed to define the differences between FMF patients with and without ELE and to reveal the relationship between ELE and patients' demographic, clinical, genetic, and treatment characteristics.

Materials and Methods

Patients

The medical records of patients who were followed up with a diagnosis of FMF in the Pediatric Rheumatology Unit of Gaziantep City Hospital between October 2023 and October 2024 were retrospectively analyzed. Sixty-nine patients with incomplete file data, no regular follow-up, less than 6 months of follow-up, and eight patients with comorbid diseases were excluded from the study. The study included 409 patients who met Yalçınkaya and Özen's FMF diagnostic criteria (patients with at least three attacks lasting 6-72 hours; axillary fever above 38°C, abdominal pain, chest pain, arthritis, and at least two of the following criteria for FMF in the family) and re-evaluated by an expert (AT) and the diagnosis of FMF was confirmed (9,10).

Definitions

In this study, the PRAS disease severity score adapted to children (i.e., in terms of age and colchicine doses) by Özen and colleagues was used to determine the disease activity of FMF patients (11,12). For the calculation of the PRAS score, the age at presentation, the frequency of attacks in one month, arthritis, amyloidosis, and the dose of colchicine were recorded. ELE was removed from the score because it would affect the result. PRAS score was calculated as 2,3,4 points for 11 years, 6-10 years and under 6 years, respectively. 1 point for fewer than one attack per month, 2 points for 1-2 attacks per month, 3 points for more than two attacks per month, 2 points for acute arthritis, 3 points for chronic arthritis, and 3 points for amyloidosis. Colchicine dosage earns points: 1 point for less than 1 mg/day, 2 points for 1 to 1.5 mg/day, and 3 points for 2 mg/day.

All FMF patients included in the study were defined according to the International Study Group for Systemic Autoinflammatory Diseases (INSAID) classification criteria as MEFV variants a) pathogenic, b) likely pathogenic, c) variant of uncertain significance (VUS), d) likely benign, e) benign, f) unclassified (13).

One attack per month or persistence of subclinical inflammation despite colchicine use for at least 6 months was considered colchicine resistance (13-15). Elevated acute phase reactants in the absence of clinical symptoms were defined as subclinical inflammation (13).

Study Protocol

All FMF patients included in the study were analyzed by dividing them into two groups, those with and without ELE findings. It was investigated whether there were any differences between these two groups regarding demographic findings, clinical features, laboratory findings, genetic analyses, disease severity score, and treatments.

This study was evaluated and approved by the XXX ethics committee (Approval number/date: 94/2024-18.12.2024). All procedures performed during the study were fully compliant with ethical rules and the principles outlined in the Declaration of Helsinki.

Statistical Analysis

The data obtained were analyzed using version 22.0 of the Statistical Package for Social Sciences (SPSS). Chi-square (X^2) tests were conducted to compare categorical variables between groups. Categorical variables are presented as frequencies (n) and percentages, while continuous variables are presented as median values and minimum and maximum ranges. The Shapiro-Wilk test was employed to assess the normality of the data distribution. Independent-sample t-tests were used to compare two independent groups for normally distributed variables, whereas the Mann-Whitney U test was applied for non-normally distributed variables. The statistical significance level was accepted as $p < 0.05$.

Results

Of 409 patients with FMF, 205 (50.1%) were male. The median (minimum-maximum) age at disease onset was 5 (1-18) years, and the median age at diagnosis was 6 (1-18) years. The median delay in diagnosis was 1 year (0-13). FMF attack was accompanied by fever in 325 (79.5%), abdominal pain in 302 (73.8%), arthralgia in 121 (29.6%), arthritis in 56 (13.7%), chest pain in 62 (15.6%) and ELE in 55 (13.4%) patients (Table 1). Consanguinity was present in 102 (24.9%) patients. Family history of the patients: 97 patients had at least one history of FMF in their first, second, or third-degree relatives.

In the attack-free period, the mean ESR was 7.2 ± 5.3 mm/hour, and the mean CRP was 3 ± 2.5 mg/L. In the attack, the mean ESR was 28.1 ± 22.7 mm/hour, and the mean CRP was 41.1 ± 34.4 mg/L.

The most common MEFV mutation was M694V homozygous mutation detected in 73 (17.8%) patients.

During the last visit, 320 (78.2%) had mild disease activity (PRAS <6), 69 (16.9%) had moderate disease activity (PRAS= 6-8) and 20 (4.9%) had severe disease activity (PRAS ≥ 9). 382 (93.4%) patients were treated with colchicine only. Colchicine treatment was discontinued in 27 (2.3%) patients during follow-up. Colchicine resistance was present in 12 (2.9%) patients whose attacks could not be controlled despite colchicine treatment, and anti-interleukin-1 (Anti-IL-1) treatment was added to these patients in addition to colchicine treatment. Of the patients receiving anti-IL-1 treatment, 10 (83.3%) used canakinumab and 2 (16.7%) used anakinra.

Table 1. Demographic, clinical and laboratory characteristics of FMF

	All FMF n= 409	**FMF with ELE n= 55**	**FMF without ELE n= 354**	***p value***
Age at diagnosis, years, median (min-max)	6 (1-18)	7 (2-15)	6 (1-16)	0.426
Gender, n (%)				
Male	205 (50.3)	18 (32.7)	187 (52.8)	**0.004**
Female	204 (49.7)	37 (67.3)	167 (47.2)	
Fever, n (%)	325 (79.5)	39 (70.9)	286 (80.8)	0.320
Abdominal pain, n (%)	302 (73.8)	37 (67.24)	265 (74.9)	0.250
Chest pain, (%)	62 (15.6)	15 (27.2)	47 (13.3)	**0.014**
Arthralgia, n (%)	121 (29.6)	29 (52.7)	92 (26)	**<0.001**
Arthritis, n (%)	56 (13.7)	23 (41.8)	33 (9.3)	**<0.001**
WBC count, x10^9/L Median (min-max)	10.4 (5.9-15.9)	10.8 (5.9-15.9)	9.7 (6.1-14)	0.530
Hemoglobin, g/dL Median (min-max)	12.1 (10.1-16.4)	12.8 (10.1-15.3	11.8 (10.5-16.4)	0.860
Thrombocyte, x10^9/L Median (min-max)	383 (236-564)	386 (252-334)	363 (236-564)	0.617
PRAS score**,** mean±sd	6.3±0.5	9.2±18	5.9±1.1	**<0.001**
Anti-IL-1	12 (2.9)	8 (14.5)	4 (1.1)	**<0.001**

Anti-IL-1: anti-interleukin-1; ELE: erysipelas-like erythema; FMF: familial mediterranean fever; WBC: white blood cell; Bold values are p <0.05 is statistically significant.

Analysis of patients with and without ELE

Of the 55 patients with ELE, 37 (67.3%) were female, and it was found to be significantly more frequent in females (p=0.004).

Among these 55 patients, the following symptoms were observed: 39 patients (70.9%) experienced fever, 37 patients (67.2%) had abdominal pain, 15 patients (27.2%) reported chest pain, 29 patients (52.7%) experienced arthralgia, and 23 patients (41.8%) showed signs of arthritis. Out of the patients with arthritis accompanying ELE, 15 (65.2%) had arthritis in the ankle, 6 (26.1%) in the knee, and 2 (8.7%) had sacroiliitis.

When comparing patients with ELE to those without, the frequencies of chest pain, arthralgia, and arthritis were significantly higher in the ELE group (p=0.014, p< 0.001, p< 0.001, respectively). However, there were no significant differences in fever and abdominal pain (p =0.320, p =0.250, respectively).

FMF patients with ELE exhibited significantly higher frequent subclinical inflammation and/or attacks and higher PRAS scores at the last follow-up (p<0.001 for both).

The most frequently detected MEFV gene mutation in FMF patients with ELE was the homozygous M694V mutation, found in 30 (54.5%) patients. Pathological mutations were significantly more common in FMF patients with ELE than those without one (p<0.001). However, no significant differences were observed regarding the frequencies of possible pathological, benign, or clinically unknown mutations (p=0.230, p=0.560, p=0.220, respectively). In addition, among FMF patients, the use of anti-IL-1 treatment combinations due to colchicine resistance was significantly more common in ELE patients (p < 0.001).

Discussion

Familial Mediterranean fever, the most common hereditary periodic fever syndrome, is characterized by attacks of inflammation, although subclinical inflammation may persist during attack-free periods (16). The presence of mucocutaneous symptoms is of clinical importance as it may be part of the activation phase and a clue of autoinflammatory rheumatic diseases (8). ELE is a rare but pathognomonic finding of FMF and has been associated with subclinical inflammation and high disease activity (17,18). This study demonstrated that ELE is linked to a higher frequency of pathogenic mutations, increased subclinical inflammation, more severe disease, and a greater likelihood of colchicine resistance and anti-IL-1 treatment requirements in FMF patients. This study showed that the presentation of ELE in FMF is not only pathognomonic for the diagnosis but also an important and noteworthy finding for the course of the disease.

Mutations in the MEFV gene, which encodes the pyrin protein, cause the clinical picture in FMF patients (2). In a study evaluating pediatric FMF patients, Yildirim et al. reported that the M694V homozygous mutation was more frequent in FMF with pediatric FMF in whom there is ELE (7). In another study, Çakmak et al. reported that homozygous M694V mutation was statistically significantly more common in the FMF group with ELE (19). Similarly, Öztürk et al. reported that the frequency of ELE was significantly higher in patients with M694V homozygous mutations compared to other patients (20). Moradian et al. reported that exon 10 mutations, especially the M694V mutation, were more common in FMF patients with ELE (21). In contrast to these studies, Arpaci et al. reported that the mutation E148Q was the more frequent MEFV mutation in FMF patients with ELE (2). In the present study, the most common mutation in FMF patients with ELE was the homozygous M694V mutation, and pathological mutations were more common in the ELE group.

Subclinical inflammation is an important indicator, as it impacts the treatment and monitoring of FMF. Many studies have demonstrated that ELE is a key finding indicating subclinical inflammation.

Bayram et al. reported in their study evaluating pediatric FMF patients that ELE is an independent risk factor for subclinical inflammation in FMF patients (18). Yıldırım et al. reported in their study evaluating pediatric FMF patients that ELE may predict persistent inflammation in FMF patients (17). Avar-Aydın et al. reported that ELE indicates severe disease course and subclinical inflammation in pediatric FMF patients (22). Another study reported that FMF patients with ELE tend to have a more severe disease course (23). In this study, subclinical inflammation was found to be more common in patients with ELE than those without ELE, which is consistent with the literature.

Arthritis in children with FMF is usually monoarticular and affects primarily the lower extremities (hip, knee, ankle) (24). Yıldırım et al. reported that arthritis was more common in patients with ELE in their study evaluating pediatric FMF patients (7). In a similar study, Avar-Aydın et al. reported that arthritis was more common in patients with ELE (22). In this study, in agreement with the authors, more arthritis was observed in FMF with ELE than in FMF without ELE.

It was reported that colchicine could potentially prevent FMF attacks (25). Biologic agents such as anakinra, rilonacept, canakinumab, tocilizumab, etanercept, infliximab, or adalimumab may be helpful for individuals resistant or intolerant to colchicine (2). Mosa et al. reported that ELE was more common in colchicine-resistant patients in a study including pediatric FMF patients (26). Yıldırım et al. reported that higher doses of colchicine were required in pediatric FMF patients due to the severe disease course in patients with ELE (7). Batu et al. reported that ELE may be a clue for less colchicine response in a study evaluating pediatric FMF patients (27). Avar-Aydın et al. reported that anti-IL-1 therapy was used more frequently in pediatric FMF patients with ELE (28). In addition, Aktay Ayaz et al. developed a scoring system containing ELE to predict colchicine resistance in a study involving pediatric FMF patients (29). In this study, colchicine and colchicine resistance-associated anti-IL-1 use was more common in FMF patients with ELE than in the group without ELE.

The most important limitations of this study are the retrospective design and the single-center patients. Another limitation is the short follow-up period, which makes it impossible to observe whether patients will have ELE at follow-up. Despite this, a large number of patients from a single center were evaluated.

In conclusion, the present study showed that ELE may be associated with subclinical inflammation, arthritis, colchicine resistance, pathogenic mutations, and severe disease scores in FMF patients. Based on these findings and the existing literature, we believe that the presence of ELE in FMF is important not only for diagnosis but also for prognosis and prediction of disease course.

Ethical Approval: *The study was approved by the Gaziantep City Hospital, ethics committee before the study. (Approval number/date: 94/24-18.12.2024). Due to the retrospective design of the study, no patient consent was obtained.*

Author Contributions:
Concept: S.C.
Literature Review: S.C, A.T.
Design : S.C., A.T.
Data acquisition: S.C., A.T.
Analysis and interpretation: S.C.
Writing manuscript: S.C., A.T.
Critical revision of manuscript: S.C.

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