

Clinical and genetic distinctions of pediatric FMF patients with erysipelas-like erythema: Clinical and genetic profile

Pediatric FMF hastalarında erizipel benzeri eritem: Klinik ve genetik ayrımlar

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Abstract

Objective: Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disease characterized by recurrent fever and serosal inflammation. Erysipelas-like erythema (ELE) is a pathognomonic but under-recognized skin manifestation. This study aimed to compare the clinical and genetic features of FMF patients with and without ELE.

Methods: We retrospectively analyzed 2,325 pediatric FMF patients who were followed from 2016 to 2024 at University of Health Sciences Türkiye, Ümraniye Training and Research Hospital. Patients were grouped based on the presence (Group 1) or absence (Group 2) of ELE. Demographics, clinical data, *MEFV* mutations, and treatment features were compared.

Results: ELE was present in 215 patients (9.25%). Group 1 had higher ages at symptom onset and at diagnosis ($p=0.003$). Musculoskeletal symptoms—including arthralgia (73.5%), arthritis (54.4%), myalgia (63.7%), leg pain (51.2%), and prolonged febrile myalgia (2.3%)—were significantly more frequent (all $p<0.001$). Chest pain and splenomegaly were also more common ($p<0.05$). No differences between groups were observed for fever and abdominal pain. Use of biologics (9.9% vs. 4.7%; $p=0.0049$) and colchicine doses ($p<0.001$) were higher in Group 1. Ankle arthritis was markedly more common (38.1% vs. 6.4%, $p<0.001$). M694V homozygosity was enriched in Group 1 (47.9% vs. 13.7%, $p<0.001$), whereas M694V/– and E148Q/– mutations were more common in Group 2.

Conclusion: ELE is associated with a more severe FMF phenotype, characterized by predominant musculoskeletal involvement, ankle arthritis, increased treatment requirements, and delayed diagnosis. Its early recognition may aid in timely and personalized FMF management.

Keywords: Familial Mediterranean fever, erysipelas-like erythema, *MEFV* mutation, ankle rash, FMF attacks

Özet

Amaç: Ailesel Akdeniz ateşi (AAA), tekrarlayan ateş ve seröz iltihaplanma ile seyreden otozomal resesif bir otoenflamatuvar hastalıktır. Erizipel-benzeri eritem (EBE), patognomonik ancak yeterince tanınmayan bir deri bulgusudur. Bu çalışmada, EBE varlığına göre AAA'lı hastaların klinik ve genetik özelliklerinin karşılaştırılması amaçlanmıştır.

Yöntem: 2016-2024 yılları arasında Sağlık Bilimleri Üniversitesi, Ümraniye Eğitim ve Araştırma Hastanesi'nde izlenen 2.325 pediatrik AAA hastası retrospektif olarak incelendi. Hastalar, EBE varlığına (Grup 1) ve yokluğuna (Grup 2) göre sınıflandırıldı. Demografik veriler, klinik özellikler, *MEFV* mutasyonları ve tedavi profilleri karşılaştırıldı.

Bulgular: EBE, 215 hastada (%9,25) saptandı. Grup 1'de semptom başlangıç yaşı ve tanı yaşı daha yüksekti ($p=0.003$). Kas-iskelet sistemi bulguları—artralji (%73,5), artrit (%54,4), miyalji (%63,7), bacak ağrısı (%51,2) ve uzamış febril miyalji (%2,3)—belirgin şekilde daha sık görüldü (tümü $p<0,001$). Göğüs ağrısı ve splenomegali de daha yaygındı ($p<0,05$). Ateş ve abdominal ağrı bakımından fark saptanmadı. Biyolojik ajan kullanımı (%9,9'a karşı %4,7; $p=0,0049$) ve kolşisin dozları ($p<0,001$) Grup 1'de daha yüksekti. Ayak bileği artrit belirgin oranda daha sık görüldü (%38,1'e karşı %6,4; $p<0,001$). M694V homozigotluğu Grup 1'de daha fazlaydı (%47,9'a karşı %13,7; $p<0,001$); buna karşın M694V/– ve E148Q/– mutasyonları Grup 2'de daha yaygındı.

Sonuç: EBE, daha şiddetli bir AAA fenotipi ile ilişkili olup kas-iskelet sistemi baskınlığı, ayak bileği artrit, artmış tedavi gereksinimi ve gecikmiş tanı ile karakterizedir. Erken tanınması, zamanında ve kişiselleştirilmiş AAA yönetimine katkı sağlayabilir.

Anahtar Kelimeler: Ailesel Akdeniz ateşi, erizipel-benzeri eritem, *MEFV* mutasyonu, ayak bileği kızarıklığı, AAA atakları

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Introduction

Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease, primarily affecting individuals from the Mediterranean region. It is characterized by recurrent, self-limited episodes of fever and serosal inflammation that typically begin in childhood or adolescence.^[1,2]

The disease is caused by mutations in the *MEFV* gene, which encodes the pyrin protein—an essential regulator of innate immunity. While over 300 mutations have been described, a small group of variants—especially *M694V*, *M680I*, *V726A*, and *M694I* in exon 10—are most commonly implicated in FMF. The *E148Q* variant in exon 2 is frequently observed but remains controversial in terms of its pathogenicity.^[3,4]

Among the cutaneous manifestations of FMF, erysipelas-like erythema (ELE) stands out due to its frequency and diagnostic relevance. ELE typically presents as sharply defined, tender, red plaques on the lower limbs, particularly the feet and ankles. Pathophysiologically, ELE is thought to result from dysregulation of the innate immune response driven by pyrin dysfunction in FMF. Mutations in *MEFV* enhance interleukin-1 β -mediated inflammatory signaling and impair apoptosis, resulting in exaggerated neutrophilic activation in the superficial dermis, which clinically manifests as ELE.^[5-8] Although observed in 25-47% of FMF patients, its prevalence differs across cohorts. However, when ELE is strictly defined as a pathognomonic finding, its frequency has been reported to be between 7% and 10%.^[9-11] Because it can resemble cellulitis or other inflammatory conditions, misdiagnosis is common, especially if ELE is the first or sole manifestation. Physical exertion and trauma often trigger these episodes, which usually resolve spontaneously within a few days.^[8,12-15]

Although ELE is only minimally represented in pediatric FMF criteria, several large-scale studies have indicated that it may be associated with a more severe disease profile. ELE has been reported to occur more frequently in colchicine-resistant patients and in individuals homozygous for *M694V*, suggesting a link to both treatment refractoriness and high-risk genetic background.^[16,17] Based on this, our central hypothesis was that FMF patients with ELE would differ meaningfully from those without ELE, demonstrating more pronounced musculoskeletal involvement, a higher prevalence of pathogenic *MEFV* variants—particularly *M694V* homozygosity—and greater treatment requirements. To test this hypothesis, we compared the clinical and genetic characteristics of ELE-positive and ELE-negative pediatric FMF patients within our cohort.

This study aims to investigate the clinical and genetic characteristics of FMF patients presenting with ELE compared to those without ELE. We specifically examine whether ELE

is associated with distinct demographic features, laboratory findings, and *MEFV* mutations. By clarifying these associations, we seek to improve diagnostic accuracy and facilitate more tailored management strategies in FMF.^[9,18]

Materials and Methods

This retrospective study was conducted using the medical records of pediatric patients diagnosed with FMF who were followed at the Pediatric Rheumatology Unit of University of Health Sciences Türkiye, Ümraniye Training and Research Hospital, between 2016 and 2024. A total of 2325 patients who met the diagnostic criteria and had at least 6 months of regular follow-up were included in the study. Patients older than 18 years at diagnosis and lacking genetic *MEFV* analysis reports were excluded. Follow-up duration, treatment protocols, and clinical data were obtained from patient records.

FMF diagnosis was established by pediatric rheumatologists based on clinical evaluation. All included patients fulfilled at least one of the established FMF classification criteria (Eurofever/PRINTO or Turkish pediatric FMF classification criteria).^[19,20]

Demographic information, clinical features, attack frequency, colchicine dosage, and treatment were recorded in detail. Patients were divided into two groups based on the presence or absence of ELE, and demographic, clinical and genetic differences between the groups were analyzed.

The study was conducted following approval by the University of Health Sciences Türkiye, Ümraniye Training and Research Hospital Ethics Committee (approval date: 26.12.2024; number: B.10.1TKH.4.34.H.GP.0.01/460). Informed consent was obtained from all patients or their legal guardians, as required by the institutional ethics committee. The study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Statistical Analysis

All statistical analyses were conducted using SPSS version 26.0 (IBM Corp., Released 2019. IBM SPSS Statistics for Windows, Version 26.0, Armonk, NY: IBM Corp.). Descriptive measures were calculated: means $\pm$ standard deviations for normally distributed quantitative variables and medians with interquartile ranges (IQRs) for non-normally distributed quantitative variables. Absolute frequencies and percentages were presented for qualitative variables. Normality was assessed using the Shapiro-Wilk test. Differences in categorical variables between groups were assessed using the chi-square test, while comparisons of continuous variables were made using the Mann-Whitney U test or the unpaired Student's t-test, depending on the distribution of the data. A p-value of less than 0.05 was considered statistically significant for all analyses.

Results

The study included 2,325 children diagnosed with FMF. The patient population consisted of 1,146 males (49.29%) and 1,179 females (50.71%) (Figure 1). The median age at symptom onset was 4.2 years (IQR, 2-7.8), and the median age at diagnosis was 6 years (IQR, 4-10). The median duration between attack onset and diagnosis was 12 months (IQR 6-24 months). Parental consanguinity was present in 19.6% of patients (n=449). A family history of FMF was documented in 51.2% of patients (n=1171), as was a history of amyloidosis in another 5.3% of patients (n=122) (Table 1).

ELE was detected in 215 patients (9.25%). The patients were divided into two groups based on the presence of ELE. Patients with ELE were assigned to Group 1, and patients without ELE were assigned to Group 2. Group 1 included 215 patients, while Group 2 included 2,110 patients. With respect to gender distribution, both groups exhibited almost equal proportions, with no statistically significant difference ($p=0.77$). The median age at symptom onset was earlier in Group 2 [4 (IQR 2-7.6)] than in Group 1 [5 (IQR 2.9-9)]; this difference was statistically significant ($p=0.003$). Similarly, the median age at diagnosis was significantly lower in Group 2 than in Group 1 [6 (IQR 4-9) vs. 7 (IQR 4.25-11); $p=0.003$].

In Group 1, inflammatory musculoskeletal symptoms were significantly more frequent than in Group 2. Specifically, arthralgia was reported in 158 patients (73.5%) in Group 1 compared with 1,083 patients (51.5%) in Group 2 ($p<0.001$); arthritis occurred in 117 patients (54.4%) in Group 1 compared

with 302 patients (14.4%) in Group 2 ($p<0.001$). Likewise, myalgia affected 137 patients (63.7%) in Group 1 versus 839 patients (39.9%) in Group 2, and leg pain or stiffness affected 110 patients (51.2%) in Group 1 versus 488 patients (23.2%) in Group 2 ($p=0.014$). Additionally, myalgia after exercise or walking was significantly more common in Group 1 (41.9%, $n=90$) than in Group 2 (18.5%, $n=389$) ($p<0.001$). Prolonged febrile myalgia, which was reported in 5 patients from Group 1 (2.3%) has been compared with 14 patients from Group 2 (0.7%) ($p=0.026$). Furthermore, chest pain (23.3% vs. 14.9%) and splenomegaly (5.6% vs. 1.3%) were significantly more common in the ELE-positive group ($p<0.001$). In contrast, no statistically significant differences were observed between the groups in terms of fever (Group 1: 78.1%, $n=168$; Group 2: 82.4%, $n=1732$; $p=0.135$) or abdominal pain (Group 1: 79.5%, $n=171$; Group 2: 83.7%, $n=1759$; $p=0.125$).

The last colchicine dose was significantly higher among patients with ELE. Group 1 had a median dose of 1 mg/day (IQR 1-1.5; $n=175$), while Group 2 had a median dose of 1 mg/day (IQR 1-1; $n=1664$); $p<0.001$. The use of biologic agents was significantly more frequent in Group 1 than in Group 2: 21 individuals (9.9%) versus 97 individuals (4.7%) ($p=0.005$) (Table 1).

Joint involvement during arthritis attacks differed between the groups. Ankle arthritis was observed in 82 (38.1%) of ELE-positive patients compared with 135 (6.4%) of ELE-negative patients ($p<0.0001$). Conversely, the absence of joint involvement was markedly more frequent among ELE-negative individuals ($p<0.0001$). No significant differences were observed for knee

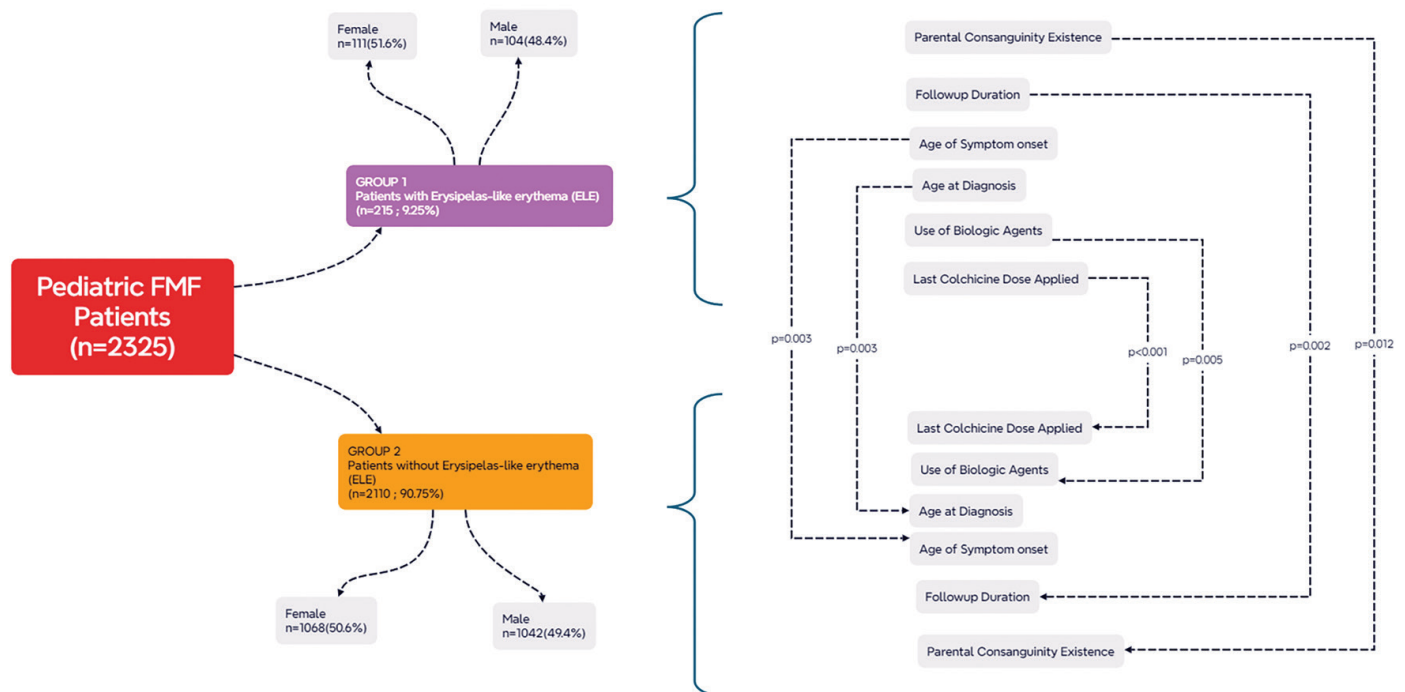


Figure 1. Schematization of the study for Familial Mediterranean fever patients grouped as with or without ELE and major clinical findings with statistical significance across these groups

involvement [43 (20.0%) vs. 366 (17.3%); $p=0.772$], elbow involvement [2 (0.9%) vs. 5 (0.2%); $p=0.534$], or hip, wrist, and small-joint involvement (all $p>0.05$) (Table 1).

A detailed comparison of *MEFV* genotype distributions is presented in Table 2. The *M694V/M694V* genotype was the most common, observed in 47.9% of patients (103/215) in Group 1, compared with 13.7% (290/2110) in Group 2 ($p<0.01$).

Conversely, heterozygous carriers were significantly less frequent in the ELE-positive group; specifically, the *M694V/-* genotype was found in 16.3% of Group 1 versus 25.4% of Group 2 ($p<0.01$), and the *E148Q/-* genotype was found in 6.0% of Group 1 versus 12.9% of Group 2 ($p<0.01$). Additionally, the compound heterozygous *M680I/V726A* genotype was absent in Group 1 but was present in 1.8% of Group 2 ($p=0.044$).

	Patients with ELE (n=215)	Patients without ELE (n=2110)	p-value
Demographic features			
Gender			
Female; [n (%)]	111 (51.63)	1068 (50.62)	0.77
Male; [n (%)]	104 (48.17)	1042 (49.38)	
Age of onset (years); [median (IQR Q1-Q3)]	5 (3-9)	4 (2-7.6)	0.003
Age of diagnosis (years); [median (IQR Q1-Q3)]	7 (4.25-11)	6 (4-9)	0.003
Duration between attack onset and diagnosis (months); [median (IQR Q1-Q3)]	12 (6-24)	12 (6-24)	0.084
Followup duration (months); [median (IQR Q1-Q3)]	40 (20-62)	34 (15-58)	0.002
Parental consanguinity existence; [n (%)]	56 (26.05)	393 (18.93)	0.012
Diagnosis of FMF in family; [n (%)]	113 (53.05)	1058 (51.01)	0.613
Diagnosis of amyloidosis in family; [n (%)]	13 (6.07)	109 (5.22)	0.826
Clinical features			
The annual number of attacks; [median (IQR Q1-Q3)]	12 (4-12)	12 (6-12)	0.382
Attack duration (days); [median (IQR Q1-Q3)]	3 (2-3)	3 (2-3)	0.345
Age at colchicine start (months); [median (IQR Q1-Q3)]	85 (55-132)	72 (44-108)	0.000
Fever; [n (%)]	168 (78.14)	1732 (82.4)	0.135
Abdominal pain; [n (%)]	171 (79.53)	1759 (83.68)	0.125
Chest pain; [n (%)]	50 (23.26)	314 (14.93)	0.002
Pleural effusion; [n (%)]	1 (0.47)	18 (0.86)	1
Vomiting; [n (%)]	15 (6.98)	266 (12.64)	0.015
Diarrhea; [n (%)]	40 (18.6)	275 (13.08)	0.028
Constipation; [n (%)]	6 (2.79)	116 (5.52)	0.107
Orchitis; [n (%)]	2 (0.95)	6 (0.29)	0.165
Splenomegaly; [n (%)]	12 (5.61)	27 (1.29)	0
Amyloidosis; [n (%)]	0 (0)	4 (0.19)	1.000
Headache; [n (%)]	18 (8.37)	202 (9.62)	0.626
Arthralgia; [n (%)]	158 (73.49)	1083 (51.47)	0
Arthritis; [n (%)]	117 (54.42)	302 (14.35)	0
Myalgia; [n (%)]	137 (63.72)	839 (39.86)	0
Myalgia after exercise/walking; [n (%)]	90 (41.86)	389 (18.48)	0
Prolonged febrile myalgia; [n (%)]	5 (2.33)	14 (0.67)	0.026
Non-erysipelas rash; [n (%)]	22 (10.23)	130 (6.18)	0.021
Leg pain/stiffness; [n (%)]	110 (51.16)	488 (23.22)	0.014
Treatment features			
Colchicine dose at last visit (mg/day); [median (IQR Q1-Q3)]	1.0 (1.0-1.5)	1.0 (1.0-1.0)	<0.001
Use of biologic agents; [n (%)]	21 (9.8)	97 (4.6)	0.005

ELE: Erysipelas-like erythema, FMF: Familial Mediterranean fever, IQR: Interquartile range

	Group1 (n=215)		Group2 (n=2110)		
Genotype	n	%	n	%	p-value
<i>M694V/M694V</i>	103	47.9	290	13.7	<0.001
<i>M694V/-</i>	35	16.3	535	25.4	<0.001
<i>M680I/M694V</i>	17	7.9	130	6.2	0.3
<i>E148Q/-</i>	13	6	272	12.9	<0.001
<i>E148Q/M694V</i>	10	4.7	67	3.2	0.23
<i>V726A/-</i>	8	3.7	145	6.9	0.08
<i>M694V/V726A</i>	8	3.7	117	5.5	0.34
<i>M680I/-</i>	7	3.3	105	5	0.32
<i>E148Q/E148Q</i>	4	1.9	29	1.4	0.54
<i>R761H/-</i>	1	0.5	44	2.1	0.12
<i>M680I/M680I</i>	1	0.5	36	1.7	0.25
<i>M694V/R761H</i>	1	0.5	36	1.7	0.25
<i>P369S/R408Q</i>	1	0.5	29	1.4	0.52
<i>E148Q/P369S</i>	1	0.5	27	1.3	0.51
<i>K695R/-</i>	1	0.5	17	0.8	1
<i>E148Q/M680I</i>	1	0.5	12	0.6	1
<i>M694V/ M694I</i>	1	0.5	4	0.2	0.38
<i>M694V/G632S</i>	1	0.5	1	0	0.18
<i>E148Q/K695R</i>	1	0.5	0	0	0.09
<i>M680I/V726A</i>	0	0	37	1.8	0.04
<i>A744S/-</i>	0	0	22	1	0.26
<i>V726A/V726A</i>	0	0	17	0.8	0.39
<i>E148Q/V726A</i>	0	0	12	0.6	0.62
<i>P369S/-</i>	0	0	11	0.5	0.61
Other genotypes	0	0	115	4	1

Discussion

This study contributes to the understanding of ELE, a distinct but underrecognized cutaneous manifestation in pediatric patients with FMF. ELE was observed in 9.25% of our cohort, consistent with previous reports, ranging from 7% to 10% in similar pediatric populations.^[9,11] Although ELE has traditionally been perceived as a minor skin manifestation, our findings affirm that ELE is not merely a dermatological feature but is intricately linked to a more severe inflammatory phenotype characterized by a distinct clinical presentation, delayed diagnosis, pronounced musculoskeletal involvement, and increased treatment needs.

Genetic analysis in our cohort revealed a significantly higher frequency of homozygosity for the *M694V* mutation among patients with ELE (47.9% vs. 13.7%, $p<0.001$), consistent with previous large-scale pediatric FMF studies reporting that ELE occurs more frequently in individuals homozygous for *M694V*. In parallel, ELE has been reported as a clinical feature enriched in colchicine-resistant patients in large registry-based analyses, supporting the view that ELE may be linked to both

genetic risk and treatment refractoriness.^[9,11,16,17] This striking genotype-phenotype correlation suggests that the observed clinical severity in the ELE group—such as increased frequency of arthritis and higher colchicine requirements—is likely driven by underlying genetic enrichment. Accordingly, ELE may be interpreted not merely as a cutaneous manifestation but as a visible surrogate marker for high-risk genotypes (particularly *M694V* homozygosity), signaling a predisposition to a more severe disease course.

Clinically, ELE-positive patients had a significantly higher prevalence of musculoskeletal symptoms, particularly arthralgia (87.5%), arthritis (52.7%), myalgia (82.4%), and exercise-induced leg pain (74.5%) than their ELE-negative counterparts ($p<0.001$ for all). These findings corroborate one of the prior observations which identified a musculoskeletal-predominant phenotype among ELE-positive patients.^[11] Moreover, our data indicate that classical FMF symptoms, such as fever and abdominal pain, did not differ significantly across groups, reinforcing the notion that ELE may delineate an alternative inflammatory axis less reliant on traditional diagnostic criteria.^[9,19]

Although splenomegaly is not considered a classical feature of FMF, it may appear as a reactive finding in the context of persistent systemic inflammation. Similar observations have been reported in large pediatric FMF cohorts, where splenomegaly has been described more prominently among individuals carrying high-risk *MEFV* genotypes, particularly *M694V* homozygosity.^[16] In the same analysis, splenomegaly was identified as an independent predictor of a more severe genetic profile. Within this framework, the splenomegaly observed in our study likely reflects an increased inflammatory burden and a phenotype aligned with genetically driven disease severity.

Notably, arthritis in ELE-positive patients exhibited a distinct predilection for specific anatomical sites. Ankle arthritis was significantly more common in ELE patients (38.1% vs. 6.4%, $p < 0.0001$), whereas other joints, such as the knees and hips, showed no significant differences in prevalence. This aligns with previous findings suggesting that ELE may reflect lower-extremity-dominant inflammation.^[11] Furthermore, our dataset revealed that patients with ELE had significantly higher colchicine requirements (median 2 tablets, IQR 2-3; $p < 0.001$) and increased use of biologics (9.9% vs. 4.7%; $p = 0.005$), suggesting a more treatment-resistant phenotype.

The observation that ELE often emerges as an early and sometimes sole clinical finding further complicates the diagnostic process. Patients with ELE were diagnosed significantly later notwithstanding their clinical symptoms, indicating a diagnostic delay (median age at diagnosis: 7 years vs. 6 years; $p < 0.01$), which may be attributed to non-specific or atypical presentations that fail to meet conventional FMF classification criteria.^[19] In our cohort, patients with ELE had a slightly older age at disease onset than those without ELE. Although this may appear counterintuitive in the context of a more severe clinical course, the finding is consistent with the inherent heterogeneity of FMF and aligns with previous reports. Recent Turkish studies similarly reported older age at diagnosis among patients with ELE.^[10,11,21] Moreover, the literature emphasizes that ELE tends to be a symptom observed more frequently at relatively later ages.^[9,21,22] When considered together, these converging data suggest that the somewhat higher age at onset seen in the ELE group reflects the marked clinical heterogeneity of FMF rather than contradicting the more severe phenotype associated with ELE. Given this, the presence of ELE should prompt clinicians to consider FMF even in the absence of hallmark features, particularly when supported by family history or elevated inflammatory markers.

Consistent with one study in the literature, we also noted that ELE is often localized to the lower extremities, unilateral and transient, and not always accompanied by fever-characteristics that distinguish it from infectious cellulitis or erysipelas.^[11] ELE may be misdiagnosed as infectious erysipelas

due to its sharply demarcated erythematous appearance; however, the absence of high fever, a background of FMF, a spontaneous, short-lived course (usually ≤ 4 days), a bilateral yet alternating presentation, absence of systemic toxicity, and rapid responsiveness to colchicine help distinguish it from infectious etiologies. Additional differential diagnoses include cellulitis, erysipelas, and acute septic arthritis; the latter is an important contributor to the wide range of reported prevalence (5-30%).^[22,23] Differentiation is critical, as misdiagnosis may lead to unnecessary antibiotic use or missed therapeutic opportunities in FMF management.

Finally, the importance of ELE as a predictor of disease severity and treatment escalation warrants inclusion in scoring systems for disease activity or colchicine resistance.^[11] While current FMF diagnostic and management algorithms do not universally incorporate ELE, our findings and those of others suggest that its inclusion may enhance phenotypic characterization and therapeutic stratification.

Study Limitations

This study has several limitations. Its retrospective design relies on routinely documented clinical data, which may limit the level of detail available for some variables. Conducting the study in a tertiary referral center may have resulted in a higher proportion of complex cases, potentially reducing generalizability. ELE was identified through expert clinical assessment rather than histopathology, a pragmatic choice to avoid unnecessary invasive procedures for a transient skin manifestation.

Conclusion

This study establishes that ELE is not merely a cutaneous manifestation of FMF but a distinct clinical marker indicating a severe disease phenotype. Our findings demonstrate a strong association between ELE and the *M694V* homozygous genotype, which is characterized by earlier symptom onset, pronounced musculoskeletal involvement—particularly ankle arthritis—and a significantly higher requirement for colchicine and biologic therapies. Consequently, the presence of ELE should be recognized as a “red flag” in pediatric FMF, prompting clinicians to suspect high-risk genotypes and to consider more aggressive management strategies early in the disease course to minimize long-term complications.

Ethics

Ethics Committee Approval: The study was conducted following approval by the University of Health Sciences Türkiye, Ümraniye Training and Research Hospital Ethics Committee (approval date: 26.12.2024; number: B.10.1TKH.4.34.H.GP.0.01/460).

Informed Consent: Informed consent was obtained from all patients or their legal guardians, as required by the institutional ethics committee.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.Ö.B., Concept: G.Ö.B., B.S., Design: G.Ö.B., B.S., Data Collection and Processing: G.Ö.B., Analysis or Interpretation: G.Ö.B., B.S., Literature Search: G.Ö.B., Writing: G.Ö.B., B.S.

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References

1. Arpacı A, Doğan S, Erdoğan HF, El Ç, Cura SE. Presentation of a new mutation in FMF and evaluating the frequency of distribution of the *MEFV* gene mutation in our region with clinical findings. *Mol Biol Rep*. 2021;48:2025-33.
2. Tufan A, Lachmann HJ. Familial Mediterranean fever, from pathogenesis to treatment: a contemporary review. *Turk J Med Sci*. 2020;50:1591-610.
3. Batu ED, Basaran O, Bilginer Y, Ozen S. Familial Mediterranean fever: how to interpret genetic results? How to treat? A quarter of a century after the association with the *mefv* gene. *Curr Rheumatol Rep*. 2022;24:206-12.
4. Van Gijn ME, Ceccherini I, Shinar Y, et al. New workflow for classification of genetic variants' pathogenicity applied to hereditary recurrent fevers by the International Study Group for Systemic Autoinflammatory Diseases (INSAID). *J Med Genet*. 2018;55:530-7.
5. Kolivras A, Provost P, Thompson CT. Erysipelas-like erythema of familial Mediterranean fever syndrome: a case report with emphasis on histopathologic diagnostic clues. *J Cutan Pathol*. 2013;40:585-90.
6. Guz G, Kanbay M, Ozturk MA. Current perspectives on familial Mediterranean fever. *Curr Opin Infect Dis*. 2009;22:309-15.
7. Rigante D, La Torraca I, Ansuini V, Compagnone A, Salli A, Stabile A. The multi-face expression of familial Mediterranean fever in the child. *Eur Rev Med Pharmacol Sci*. 2006;10:163-71.
8. Barzilai A, Langevitz P, Goldberg I, et al. Erysipelas-like erythema of familial Mediterranean fever: clinicopathologic correlation. *J Am Acad Dermatol*. 2000;42:791-5.
9. Yildirim DG, Seven MB, Gönen S, Söylemezoğlu O. Paediatric rheumatology erysipelas-like erythema in children with familial Mediterranean fever. *Clin Exp Rheumatol*. 2020;38:S101-4.
10. Çakmak F, Arık SD, Kavrut Kayaalp G, Çağlayan Ş, Ulu K, Coşkun T. Erysipelas-like erythema: a pathognomonic rash in children with familial Mediterranean fever. *Med J Bakirkoy*. 2023;19:217-21.
11. Coşkun S, Tanatar A. A unique pathognomic skin manifestation of familial Mediterranean fever: erysipelas-like erythema. *Harran Üniversitesi Tıp Fakültesi Dergisi*. 2025;22:154-8.
12. Long SS. Distinguishing among prolonged, recurrent, and periodic fever syndromes: approach of a pediatric infectious diseases subspecialist. *Pediatr Clin North Am*. 2005;52:811-35.
13. Turkish FMF Study Group. Familial Mediterranean fever (FMF) in Turkey. *Medicine* 2005;84:1-11.
14. Koné Paut I, Dubuc M, Sportouch J, Minodier P, Garnier JM, Touitou I. Phenotype-genotype correlation in 91 patients with familial Mediterranean fever reveals a high frequency of cutaneomucous features. *Rheumatology (Oxford)*. 2000;39:1275-9.
15. Barut K, Sahin S, Adrovic A, et al. Familial Mediterranean fever in childhood: a single-center experience. *Rheumatol Int*. 2018;38:67-74.
16. Tunc E, Atamyildiz Uçar SI, Polat MC, et al. Predicting homozygous M694V genotype in paediatric FMF: multicentre analysis and scoring system proposal. *Rheumatology (Oxford)*. 2025;64:4816-24.
17. Batu ED, Şener S, Aydın EA, et al. A score for predicting colchicine resistance at the time of diagnosis in familial Mediterranean fever: data from the TURPAID registry. *Rheumatology (Oxford)*. 2024;63:791-7.
18. Kasapcopur O, Arisoy N. Familial Mediterranean fever and other hereditary auto-inflammatory diseases. *Turk Arch Pediatr*. 2006;41:9-17.
19. Yalçinkaya F, Özen S, Özçakar ZB, et al. A new set of criteria for the diagnosis of familial Mediterranean fever in childhood. *Rheumatology (Oxford)*. 2009;48:395-8.
20. Ozen S, Sağ E, Oton T, et al. EULAR/PRÉS endorsed recommendations for the management of familial Mediterranean fever (FMF): 2024 update. *Ann Rheum Dis*. 2025;84:899-909.
21. Avar-Aydın PÖ, Özçakar ZB, Aydın F, Karakaş HD, Çakar N, Yalçinkaya F. Erysipelas-like erythema: a manifestation of severe disease phenotype in pediatric patients with familial Mediterranean fever. *Turk Arch Pediatr*. 2022;57:599-602.
22. Lidar M, Doron A, Barzilai A, et al. Erysipelas-like erythema as the presenting feature of familial Mediterranean fever. *J Eur Acad Dermatol Venereol*. 2013;27:912-5.
23. Schmit JL. Enquête prospective. Erysipèle et cellulites nécrosantes: quelle prise en charge en milieu hospitalier? [A prospective study on erysipelas and infectious cellulitis: how are they dealt within hospital?]. *Ann Dermatol Venereol*. 2001;128:334-7. French.