Erysipelas-Like Erythema: A Manifestation of Severe Disease Phenotype in Pediatric Patients with Familial Mediterranean Fever

Pınar Özge Avar-Aydın, Zeynep Birsin Özçakar, Fatma Aydin, Hatice Dilara Karakaş, Nilgün Çakar, Fatoş Yalçınkaya

Department of Pediatric Rheumatology, Ankara University Faculty of Medicine, Ankara, Turkey

ABSTRACT

Objective: Erysipelas-like erythema is the pathognomonic skin manifestation of familial Mediterranean fever although not frequently seen in the pediatric population. This study aims to describe the differences between patients presenting with and without erysipelas-like erythema and to examine the relation of erysipelas-like erythema with subclinical inflammation in a large pediatric cohort of familial Mediterranean fever patients.

Materials and Methods: This retrospective study from a single pediatric rheumatology referral center included familial Mediterranean fever patients with a follow-up for at least 6 months in the last 5 years. Patients were grouped according to the presence of erysipelas-like erythema and subclinical inflammation.

Results: Among 515 patients with familial Mediterranean fever, 35 patients (6.8%) were found to present with erysipelas-like erythema, and the earliest age for erysipelas-like erythema was 2.9 years. All erysipelas-like erythema lesions were defined on lower extremities with concurrent arthritis in 21 patients (60.0%). Compared to other patients in the cohort, patients presented with erysipelas-like erythema had significantly higher frequencies of acute arthritis, subclinical inflammation, and biallelic exon 10 mutations, and they used significantly higher doses of colchicine at the latest visits (all \( P \leq 0.002 \)). Patients with subclinical inflammation more frequently presented with erysipelas-like erythema compared to others without subclinical inflammation (21.7% vs. 2.9%, \( P < 0.001 \)).

Conclusion: Erysipelas-like erythema is an uncommon but important finding that can be a sign of severe disease course and subclinical inflammation in the pediatric population with familial Mediterranean fever.

Keywords: Familial Mediterranean fever, erysipelas-like erythema, subclinical inflammation

INTRODUCTION

Familial Mediterranean fever (FMF) is the most frequent inherited autoinflammatory disease. Clinical inflammatory attacks include recurrent fever and polyserositis lasting for 1-3 days with elevated acute phase reactants (APRs), whereas subclinical inflammation can be seen in between clinical attacks. Colchicine and anti-interleukin-1 (anti-IL-1) therapies used in colchicine resistance or intolerance are current medications used in FMF.

Erysipelas-like erythema (ELE) is a well-known, but uncommon, skin manifestation of FMF. The estimated frequency of ELE has been reported to be between 3% and 46% in patients with FMF with decreasing rates in children. It is mostly triggered by physical activity and is seen as an erythematous, warm, and tender rash usually on the dorsum of the feet and ankles. Acute arthritis can accompany ELE, particularly when seen on the ankles. The ELE lesions usually resolve within 2-3 days. Rarely, it can be the first and sole manifestation...
ELE in Pediatric FMF

Turk Arch Pediatr 2022; 57(6): 599-602

of FMF.\textsuperscript{10} Although the histopathological examination is not necessary for the diagnosis, neutrophilic infiltrates and edema in the superficial dermis and perivascular area, perivascular C3 deposition, and the absence of vasculitis are typical histopathological findings.\textsuperscript{3}

This study aims to describe the differences between patients presenting with and without ELE in a large pediatric cohort of FMF patients. Further, the relation of ELE with subclinical inflammation was examined.

MATERIALS AND METHODS

The study included patients from a single pediatric rheumatology referral center who were followed between October 2016 and October 2021. Electronic medical charts of the patients with a diagnosis of FMF and a follow-up for more than 6 months were reviewed. Turkish pediatric criteria of FMF had been used to diagnose FMF.\textsuperscript{4} Demographic, clinical, and laboratory features, treatments, and genetic results of MEditerranean FeVer gene mutations were recorded. Exon 10 and exon 2 mutations of the MEFV gene analyzed by polymerase-chain-reaction and included at least six mutations (M694V, M680I, M694I, V726A, K695R, and E148Q) had been examined for all patients in the cohort.

Increased APRs during attack-free periods under regular colchicine treatment defined subclinical inflammation.\textsuperscript{2} After other reasons that increase APRs had been excluded, the presence of subclinical inflammation in 3 consecutive visits at least 2 months apart was accepted as positive. Patients were grouped according to the presence of ELE and subclinical inflammation.

The Statistical Package for Social Sciences version 21.0 software (IBM Corp.; Armonk, NY, USA) was used for statistical analysis. Continuous variables were presented with mean ± standard deviation or median (interquartile range) according to the distribution of the data analyzed by the Shapiro–Wilk test and distribution graphs. The independent-samples t-test was applied for parametric and Mann–Whitney U test for non-parametric data. The odds ratio with 95% CI was calculated. Categorical variables were shown with frequency (n) and percentage (%), and their comparison was done by the chi-square or Fisher’s exact test. The correlation between categorical variables was analyzed by Phi and Cramer’s correlation coefficients. The correlation was considered important if the correlation coefficient was >0.20. The correlation coefficient was accepted as mild if between 0.20 and 0.40, moderate between 0.40 and 0.60, and significant if >0.60. The statistical significance level was accepted at \( P < .05.\)

RESULTS

A total of 515 patients with a mean follow-up of 6.60 ± 4.08 years were included in the study. The female-to-male ratio was 1.12. The mean disease onset of FMF was 3.66 ± 3.55 years, whereas the median diagnostic delay was 2.08 years (3.60).

Thirty-five patients (6.8\%) were found to present with ELE. The earliest age for the presentation of ELE was 2.9 years. Erysipelas-like erythema was seen on the ankles and the dorsum of the foot in 91.4\% (n = 32) of the patients, and all was defined on lower extremities. Two patients (5.7\%) had bilateral ELE. Twenty-one patients (60.0\%) experienced ELE with concurrent arthritis. In the presence of ELE, the risk of acute arthritis was 9.38 (95\% CI: 4.36–20.17). One patient had a skin biopsy from the lesion with ELE because of relapsing and remitting course with a suspect of vasculitis. Histopathological examination revealed perivascular and interstitial inflammation with neutrophilic infiltrates without any immune deposits or evidence of vasculitis. The comparison of demographic, clinical, and genetic features of patients presenting with ELE and other patients in the cohort is shown in Table 1.

Subclinical inflammation was present in 106 patients (20.6\%). Patients with subclinical inflammation more frequently presented with ELE compared to others without subclinical inflammation (21.7\% vs. 2.9\%, \( P < .001).\) Considering patients carrying biallelic

| Table 1. The Comparison of Demographic and Clinical Characteristics of Patients Presenting with Erysipelas-Like Erythema and Other Patients in the Cohort of Familial Mediterranean Fever | Patients Presenting with ELE (n = 35) | Other Patients (n = 480) | \( P \) |
| --- | --- | --- | --- |
| Female gender | 24 (68.6) | 248 (51.7) | .053\* |
| Age at onset of FMF, years | 3.73 ± 3.28 | 3.66 ± 3.57 | .900\* |
| Age at diagnosis of FMF, years | 6.85 ± 3.97 | 6.81 ± 4.05 | .965\* |
| Fever | 32 (91.4) | 450 (93.8) | .483* |
| Abdominal pain | 30 (85.7) | 429 (89.4) | .570\* |
| Chest pain | 12 (34.3) | 119 (24.8) | .214\* |
| Acute arthritis | 25 (71.4) | 101 (21.0) | .001\* |
| Protracted febrile myalgia | 2 (5.7) | 4 (0.8) | .057\* |
| Subclinical inflammation | 23 (65.7) | 83 (17.3) | <.001\* |
| Associated diseases of FMF | 4 (11.4) | 51 (10.6) | .780\* |
| Family history of FMF | 26 (74.3) | 327 (68.1) | .459\* |
| Homozygous M694V mutation | 22 (62.9) | 144 (30.0) | <.001\* |
| Biallelic exon 10 mutations | 29 (82.9) | 272 (56.7) | .002\* |
| Colchicine dosage at latest visit, mg/m²/day | 1.07 ± 0.30 | 0.89 ± 0.30 | .001* |
| Treatment with IL-1 inhibitor | 2 (5.7) | 27 (5.6) | 1.000* |

\( n (%) \) or mean ± standard deviation; \*the chi-square test, \*the independent samples t-test, or \*the Fisher’s exact test were used; statistical significance level is \( P < .05.\)

ELE, erysipelas-like erythema; FMF, familial Mediterranean fever.
exon 10 mutations (n = 301), patients with subclinical inflammation more frequently presented with ELE compared to others without subclinical inflammation (22.6% vs. 6.9%, P < .001). Phi correlation coefficient between the presence of ELE and subclinical inflammation was found at 0.301 (P < .001). The risk of ELE was 9.17 (95% CI: 4.39-19.16) in the presence of subclinical inflammation.

DISCUSSION

This study demonstrated that ELE was an uncommon manifestation in pediatric patients with FMF. When compared to other patients in the cohort, patients presented with ELE had significantly higher frequencies of acute arthritis and biallelic exon 10 mutations that were signs of severe disease phenotype of FMF leading to the usage of significantly higher colchicine doses in these patients. Further, there was a positive correlation between ELE and subclinical inflammation.

Erysipelas-like erythema is the pathognomonic skin manifestation of FMF (Figure 1). It results from neutrophilic infiltration of the dermis without findings of vasculitis that differentiates it by the presence of vasculitic rashes, possibly associated with FMF. As ELE is a relatively more frequent symptom in later ages, it is rarely seen in the pediatric population and is related to exon 10 mutations of the MEFV gene and severe disease phenotype of FMF. It generally presents in lower legs, and acute arthritis involving adjacent joints is a frequently coexisting manifestation (Figure 2). Erysipelas-like erythema can be the only or the first clinical finding of FMF. The frequency of ELE was found to be 7% in the current cohort which was similar or relatively low when compared to the pediatric studies from Turkey. Further, our study showed that ELE could exhibit as early as 3 years of age. All ELE lesions were seen on lower extremities and bilaterality was very rare. Arthritis was present in more than half of the patients. Histopathological examination was needed only in 1 patient with a suspect of vasculitis and it demonstrated classical findings of ELE.

Exon 10 mutations of the MEFV gene cause earlier onset of disease, more severe disease course, higher risk for renal amyloidosis and associated inflammatory diseases, and increasing need for higher colchicine doses and anti-IL-1 therapies in FMF. Arthritis, chest pain, ELE, and protracted febrile myalgia are clinical manifestations that are more frequently encountered in patients carrying biallelic exon 10 mutations. Accordingly, this study demonstrated higher frequencies of biallelic exon 10 and homozygous M694V mutations in patients presented with ELE. Moreover, these patients had acute arthritis and subclinical inflammation more commonly, and higher doses of colchicine were used at the latest visits when compared to other patients in the cohort. Therefore, ELE may be an alerting symptom for pediatric rheumatologists dealing with FMF patients as a sign of severe disease phenotype.

Subclinical inflammation is an important finding which may result in anemia, growth impairment, and secondary amyloidosis in children with FMF. It is defined as ongoing inflammation between attacks despite colchicine treatment.
that can be detected by increased APRs in asymptomatic patients. Although there are no exact measures for subclinical inflammation, it was accepted as positive in the current study if it persisted for 3 consecutive visits with at least 2 months apart. Subclinical inflammation was identified in 20.6% of the cohort. This rate was found to be 12%-65% in various pediatric studies of FMF. The adoption of different criteria for subclinical inflammation may cause this wide range of results. Several clinical and genetic features related to subclinical inflammation have been reported. Erysipelas-like erythema was one of these findings that are more common in patients with FMF who had persistent inflammation. Similar to previous reports, this study showed significantly higher frequencies of subclinical inflammation in patients who presented with ELE despite a weak correlation between them. Moreover, the presence of subclinical inflammation showed 9 times increased risk for the occurrence of ELE. Reversely, patients displaying subclinical inflammation more frequently had ELE with an odds ratio of 5.5 among patients carrying biallelic exon 10 mutations. Thus, ELE is an important sign of ongoing inflammation in patients with FMF.

This study was limited by its retrospective design. Disease severity assessment tools were not evaluated for the study. Despite these, it was one of the largest assessed ELE in a pediatric cohort of FMF patients. Besides, the discordance between the patient numbers of groups with and without ELE might have limited the comparison analysis.

In conclusion, ELE is an uncommon but important finding that can be a sign of severe disease course and subclinical inflammation in the pediatric population with FMF. Its manifestation in very early ages of childhood is possible. Questioning ELE during visits may help clinicians to suspect severe disease phenotype and to manage the disease more thoroughly in pediatric FMF patients.

**Ethics Committee Approval:** This study was approved by Ethics committee of Ankara University, (Approval No: i8-540-20).

**Informed Consent:** Written informed consent was obtained from the patients who agreed to take part in the study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – P.Ö.A.A., Z.B.Ö.; Design – P.Ö.A.A., Z.B.Ö.; Supervision – Z.B.Ö., F.A., N.Ç., F.Y.; Funding – None; Data Collection and/or Processing – P.Ö.A.A., D.K.; Analysis and/or Interpretation – P.Ö.A.A., Z.B.Ö.; Literature review – P.Ö.A.A., Z.B.Ö., F.A., N.Ç., F.Y.; Writing – P.Ö.A.A.; Critical Review – Z.B.Ö., F.A., N.Ç., F.Y.

**Declaration of Interests:** The authors have no conflict of interest to declare.

**Funding:** The authors declared that this study has received no financial support.

**REFERENCES**

1. Ben-Chetrit E, Levy M. Familial mediterranean fever. *Lancet*. 1998;351(9103):659–664. [CrossRef]
2. Tunca M, Kirkali G, Soytürk M, Akar S, Pepsy MB, Hawkins PN. Acute phase response and evolution of familial mediterranean fever. *Lancet*. 1999;353(9162):1415. [CrossRef]
3. Goldfinger SE. Colchicine for familial mediterranean fever. *N Engl J Med*. 1972;287(25):1302. [CrossRef]
4. Hentgen V, Vinit C, Fayand A, Georgin-Lavialle S. The use of interleukin-1 inhibitors in familial mediterranean fever patients: a narrative review. *Front Immunol*. 2020;11:1–11.
5. Barzilai A, Langevitz P, Goldberg I, et al. Erysipelas-like erythema of familial mediterranean fever: clinicopathologic correlation. *J Am Acad Dermatol*. 2000;42(5 Pt 1):791–795. [CrossRef]
6. Tunca M, Ozdogan H, Kasapcopur O, et al. Familial mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. *Med (Baltim)*. 2005;84(1):1–11. [CrossRef]
7. Öztürk K, Coşkunten T, Bağlan E, et al. Real-life data from the largest pediatric familial mediterranean fever cohort. *Front Pediatr*. 2021;9:805919. [CrossRef]
8. Yalcinlakaya F, Özen S, Özcakar ZB, et al. A new set of criteria for the diagnosis of familial mediterranean fever in childhood. *Rheumatology (Oxford)*. 2009;48(4):395–398. [CrossRef]
9. Azizi E, Fisher BK. Cutaneous manifestations of familial mediterranean fever. *Arch Dermatol*. 1976;112(3):364–366.
10. 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(7):912–915. [CrossRef]
11. Radakovic S, Holzer G, Tanew A. Erysipelas-like erythema as a cutaneous sign of familial mediterranean fever: a case report and review of the histopathologic findings. *J Am Acad Dermatol*. 2013;68(2):e61–e63. [CrossRef]
12. Gezgin Yildirim D, Seven MB, Gonen S, Söylemezöğlu O. Erysipelas-like erythema in children with familial mediterranean fever. *Clin Exp Rheumatol*. 2020;38(5):101–104.
13. Tanatar A, Karadağ ŞG, Çakan M, Sänmez HE, Ayaz NA. Age of onset as an influencing factor for disease severity in children with familial mediterranean fever. *Med Rheumatol*. 2021;31(1):219–222. [CrossRef]
14. Ayaz NA, Tanatar A, Karadağ ŞG, Çakan M, Keskindemirci G, Sänmez HE. Comorbidities and phenotype-genotype correlation in children with familial mediterranean fever. *Rheumatol Int*. 2021;41(1):113–120. [CrossRef]
15. Avar-Aydin PO, Ozccakar ZB, Çakan N, Fitoz S, Karakas HD, Yalcinlakaya F. Nutcracker syndrome: a potentially underdiagnosed cause of proteinuria in children with familial mediterranean fever. *Pediatr Nephrol*. 2021. [CrossRef]
16. Avar-Aydin PO, Ozccakar ZB, Aydin F, Karakas HD, Çakan N, Yalcinlakaya F. The expanded spectrum of arthritis in children with familial mediterranean fever. *Clin Rheumatol*. 2022;41(5):1535–1541. [CrossRef]
17. Bayram MT, Çankaya T, Bora E, et al. Risk factors for subclinical inflammation in children with familial mediterranean fever. *Rheumatol Int*. 2015;35(8):1393–1398. [CrossRef]
18. Gezgin Yildirim D, Esmeray Senol P, Söylemezöğlu O. Predictors of persistent inflammation in children with familial Mediterranean fever. *Modern Rheumatology* 2021;00:1–5. [CrossRef]
19. Korkmaz C, Özdogan H, Kasapçopur O, Yazıcı H. Acute phase response in familial mediterranean fever. *Ann Rheum Dis*. 2002;61(1):79–81. [CrossRef]
20. Yoldas TC, Çakan N, Bayaran Ö, Acar B, Uncu N, Çayci FŞ. The effect of colchicine and disease severity on physical growth in children with familial mediterranean fever. *Clin Rheumatol*. 2016;35(6):1603–1607. [CrossRef]
21. Celikan T, Çelik M, Kasapçopur O, et al. The anemia of familial mediterranean fever disease. *Pediatr Hematol Oncol*. 2005;22(8):657–666. [CrossRef]
22. Zung A, Barash G, Zadik Z, Barash J. Familial mediterranean fever and growth: effect of disease severity and colchicine treatment. *J Pediatr Endocrinol Metab*. 2006;19(2):155–160. [CrossRef]
23. Babaoglu H, Armagan B, Bodakti E, et al. Predictors of persistent inflammation in familial mediterranean fever and association with damage. *Rheumatol (United Kingdom)*. 2021;60(1):333–339. [CrossRef]