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Erysipelas-like erythema of familial Mediterranean fever syndrome: a case report with emphasis on histopathologic diagnostic clues

We report histopathological findings in a case of familial Mediterranean fever (FMF) syndrome with an erysipelas-like erythema (ELE). ELE is the only pathognomic cutaneous manifestation of FMF. ELE is characterized by well-demarcated, tender, erythematous and infiltrated plaques recurring on the same site and resolving spontaneously within 48–72 h. FMF is a monogenic autoinflammatory syndrome highlighted by recurrent fever associated with polyserositis involving mainly the peritoneum, synovium and pleura. FMF results from a mutation of the MEFV gene, which encodes for pyrin, leading to Il-1β activation and promoting neutrophil migration into the dermis. Histopathological findings in our case showed a sparse superficial perivascular and interstitial lymphocytic infiltrate admixed with some neutrophils, no eosinophils and mild papillary dermal edema. Venules and lymphatics were dilated, though no vasculitis was identified. Neutrophils are the most common cutaneous marker of autoinflammation, and cutaneous manifestations of monogenic autoinflammatory syndromes are represented by the spectrum of aseptic neutrophilic dermatoses. Neutrophils in the presence of recurrent fever and in the correct clinical context of recurrent erysipelas in the same site are a diagnostic clue for FMF.

Keywords: autoinflammatory syndromes, erysipelas-like erythema, familial Mediterranean fever syndrome, neutrophilic dermatoses

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Familial Mediterranean fever (FMF) syndrome (OMIM 249100) represents a rare monogenic autoinflammatory disease.[1–4] Autoinflammatory syndromes are inherited disorders characterized by recurrent fever, increased cytokine expression and episodic inflammation with eventual end-organ damage. In contrast to autoimmune diseases, pathogenesis does not require autoreactive lymphocytes or immunoglobulins to self-antigens but results from aberrant regulation of innate immune cytokines signaling pathways, leading to persistent inflammation.[5–10]

Understanding FMF and the related monogenic autoinflammatory syndromes has been advanced with characterization of these diseases at a molecular level. As these diseases are rare, however, there

are a limited number of published cases described clinically and histologically, and a more precise clinicopathological and molecular correlation is needed. Thus, we present a case of FMF with erysipelas-like erythema (ELE), which is the only pathognomic cutaneous finding of the disorder. We provide a review of current understanding of ELE, especially as it relates to more common and possibly related entities, such as the spectrum of neutrophilic dermatitis.

Case Report

A 34-year-old woman of Portuguese origin experienced recurrence of an erysipelas-like rash on her right buttock (Fig. 1). The eruption had recurred in the exact same location once a month since the age of 30. The onset of lesions was rapid with spontaneous resolution within 48–72 h. There was concomitant fever, abdominal pain, non-migratory polyarthralgia and myalgia. Peripheral blood studies showed only increased acute phase reactants and neutrophilia, and a 24-h urine analysis showed an absence of proteinuria. An abdominal computed tomography scan was normal. The patient's mother had a history of recurrent febrile episodes without any other symptomatology. A biopsy was performed for conventional microscopy 48 h after the onset of the eruption.

Histopathology showed slight pallor of the papillary dermis (edema) and a mild superficial and deep perivascular lymphocytic infiltrate admixed with some neutrophils (Figs. 2–4). Eosinophils were absent. A few mast cells were identified and were highlighted best with toluidine blue and Giemsa stains (not shown). Dilated blood and lymphatic vessels were observed (Fig. 5). There was no deposition of fibrin or necrosis of vessel walls. There was no red cell extravasation. No nuclear debris (leukocytoclasia) was identified. An Alcian blue stain showed no increase in interstitial mucin.

On the basis of clinical presentation of a recurrent erysipelas-like eruption in the exact same location with spontaneous resolution within 2–3 days and on the presence of neutrophils within the infiltrate a diagnosis of ELE of FMF was considered. The patient was given 1 mg colchicine daily. There was a favorable response to the oral treatment with the absence of recurrence after a 7-month follow-up. A diagnosis of FMF was confirmed clinically, based on the Tel-Hashomer criteria (Table 1).[11,12] Our patient had two major criteria (recurrent febrile episodes with peritonitis manifested by abdominal pain and favorable response to continuous colchicine treatment) and two minor criteria (recurrent febrile episodes and ELE), thereby establishing a definitive diagnosis of FMF.

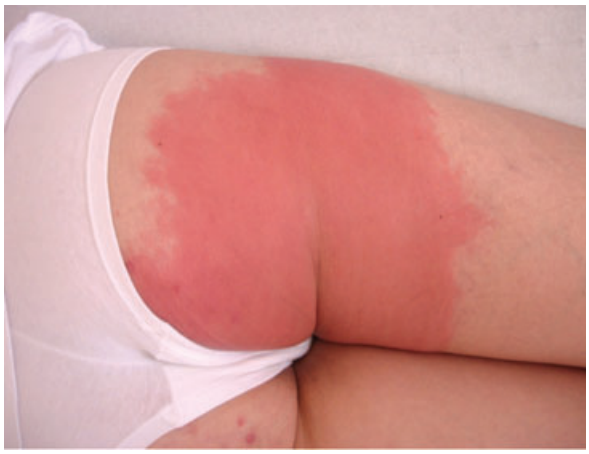

Fig. 1. A recurrent erysipelas-like eruption involved the right buttock.

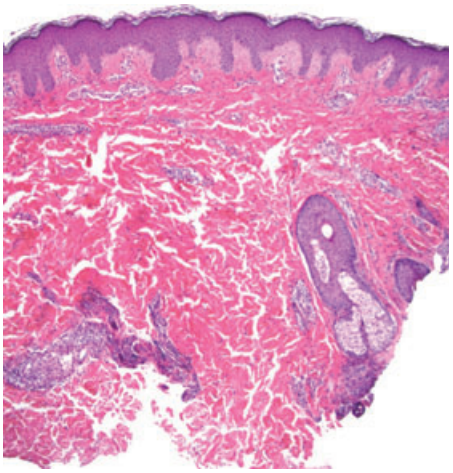

Fig. 2. No epidermal change is apparent above a superficial and deep inflammatory cell infiltrate.

Table 1. Tel-Hashomer criteria

- Major criteria
  - Recurrent febrile episodes with peritonitis, synovitis, pleuritis
  - AA Amyloidosis without predisposing disease
  - Favorable response to continuous colchicine treatment
- Minor criteria
  - Recurrent febrile episodes
  - Erysipelas-like erythema
  - Familial Mediterranean fever in a first-degree relative

Definitive diagnosis: two major or one major + two minor, probable diagnosis: one major + one minor.

Discussion

FMF results from recessively inherited mutations in the Mediterranean FeVer (MEFV) gene on chromosome 16p13.3. The disease occurs in Sephardic Jews, Armenians, Turks, Arabs, Italians and Greeks

Table 2. Histopathological differential diagnosis of Erysipelas-like erythema

Diagnosis	Infiltrate distribution	Infiltrate density	Infiltrate cell type	Leukocytoclasia	Vessels	Dermal edema
Erysipelas-like erythema	Pandermal, mainly perivascular	Mild	Mononuclear cells and neutrophils, absence of eosinophils	Variable	Absence of vasculitis, dilated blood and lymphatic vessels	Absent or mild within papillary dermis
Infectious erysipelas	Pandermal, perivascular and interstitial	Dense (but without abscess formation)	Neutrophils	Present	Absence of vasculitis, dilated blood and lymphatic vessels	Present, marked within papillary dermis
Neutrophilic urticarial dermatosis	Pandermal, perivascular and interstitial, also perieccrine in NOMID	Mild to moderate	Neutrophils, rare mononuclear cells and eosinophils	Present	Absence of vasculitis	Absent or mild
Neutrophilic urticaria	Mainly upper dermis, perivascular and interstitial	Mild to moderate	Neutrophils, mononuclear cells and eosinophils; number of mononuclear cells and eosinophils is usually related to neutrophilic density; increased mast cells	Variable	Absence of vasculitis, dilated blood and lymphatic vessels	Present
Urticartal vasculitis	Mainly upper dermis, more perivascular than interstitial	Variable	Mononuclear cells, neutrophils and eosinophils	Present	Presence of small-vessel vasculitis*, dilated blood and lymphatic vessels	Present
Sweet's syndrome	Pandermal, perivascular and interstitial	Dense	Neutrophils, few eosinophils. Mononuclear cells, the histiocytoid-rich variant	Present	Absence of vasculitis or discrete small vessel vasculitis*	Very marked within papillary dermis

NOMID, Neonatal onset multisystem inflammatory disease.
*Mural fibrin deposition with leukocytoclasia and red cell extravasation.

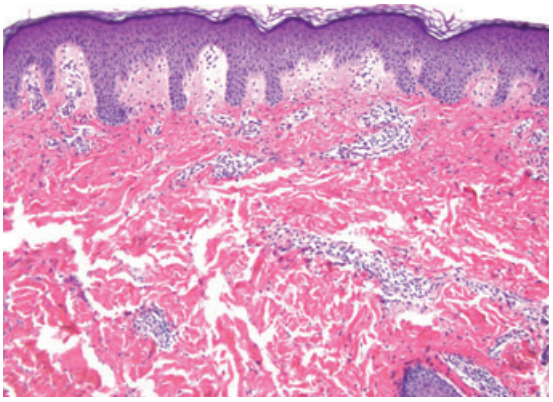

Fig. 3. No epidermal change, slight papillary dermal edema and a superficial and deep infiltrate are present.

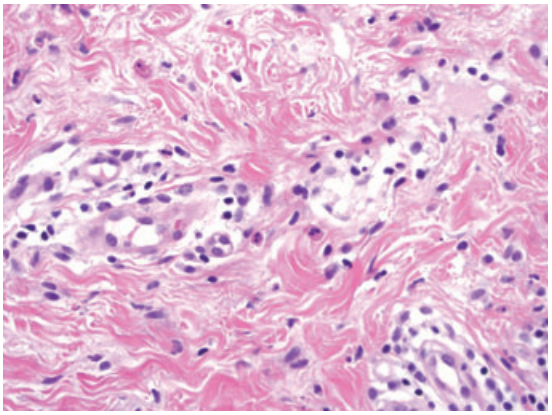

Fig. 4. The infiltrate is mostly lymphocytic with some neutrophils.

and is increasingly recognized across the world. MEFV encodes for pyrin, which, through caspase, leads to Il-1β activation. More than 70 putative mutations have been identified, most being missense substitutions. Most of the mutations are localized on exon 10, encoding B30.2 domain. MEFV mutations are identified in both alleles in only 38–72% of patients.[3,4,13–15] A diagnosis is therefore clinically

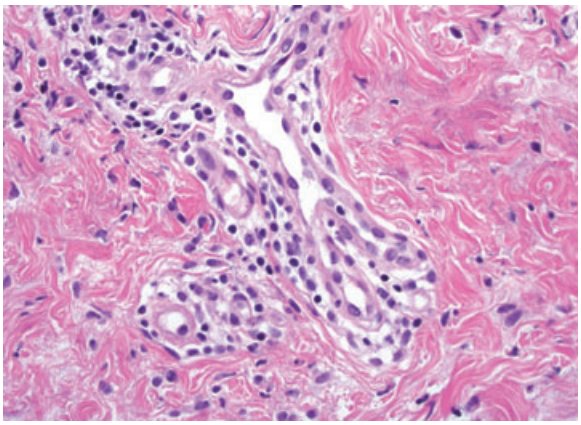

Fig. 5. Dilated blood vessels without fibrin were observed, which correlates with the erythematous clinical presentation of erysipelas-like erythema.

based, rather than on genetic analysis in both adults and children.[11,12,16,17]

The onset of symptoms in about 50% of the cases is in the first decade and in one third of pediatric patients before the age of 2.[18] Only 5% of patients develop disease onset after the third decade. FMF is characterized by recurrent and self-limited attacks of fever associated with polyserositis involving mainly the peritoneum, synovium and pleura. Attacks typically last 12–72 h. Frequency varies from once a week to once every 3–4 months or more. The intervals between attacks may vary in the same patient. Fever appears suddenly and may present spontaneously or be induced by exercise. Patients may present with abdominal pain, and the peritoneal inflammation may be so intense that the patient presents with a so-called 'acute abdomen'. There may also be unilateral pleuritis and chest pain, recurrent pericarditis, intense scrotal pain simulating testicular torsion in children and transient arthralgia involving large joints in the upper and lower limbs. Attacks are associated with increased acute phase reactants and peripheral blood neutrophilia. AA amyloidosis accompanied by renal involvement is a complication in colchicine-resistant or untreated patients.[4,13,19,20]

ELE is the only characteristic and pathognomic cutaneous finding in FMF. It is present in 15–20% of children with FMF, and the reported incidence in studies of patients of all ages, including adults, varies widely, from 3 to 48%. ELE is the result of an uncontrolled inflammatory process, characterized by complement activation and neutrophil migration into the dermis. The rash, which may be triggered by physical exercise, subsides spontaneously within 48–72 h of bed rest. Lesions typically develop on the extensor surface of the lower extremities, usually below the knee on the anterior legs and dorsal ankles and feet. The rash is usually unilateral but can be bilateral and symmetrical. Patches and plaques are well-demarcated, tender, warm and erythematous.[1,19,21,22] ELE is usually associated with a M694V homozygocity, a more severe FMF clinical phenotype, a higher fever and amyloidosis.[23–26] FMF patients with ELE as the first disease presentation and without any other systemic findings, experience a less severe disease phenotype. Their disease manifestations appear at an older age with a delayed diagnosis, and they have a lower frequency of M694V homozygocity.[25]

Vasculitis has also been associated with FMF. Henoch-Schonlein vasculitis has been reported in 2.6–5% and polyarteritis nodosa in 0.8–1% of patients.[27,28] A vasculopathic component within ELE has also been postulated: C3 deposits in the capillary walls of the papillary and upper reticular dermis have been detected. IgA and IgG are negative, and IgM and fibrinogen are variably detected in vessels walls. Although blurring of some capillary walls may be observed, no true small-vessel vasculitis is seen in biopsies of ELE. This may be due to the short duration of the attacks, which is insufficient to provoke vessel wall damage.[21] We are not convinced that the case presented in Aydin et al. represents leukocytoclastic vasculitis (LCV).[22] The published histopathologic picture displays a perivascular and intravascular infiltrate with an absence of mural fibrin deposition and leukocytoclasia. Thus, we do not believe that criteria are fulfilled for a diagnosis of LCV. Additionally, lesions of LCV do not completely resolve within 2–3 days, which is the case of the lesions in ELE. As previously mentioned, patients with FMF can develop true LCV, but vascular changes in the rapidly resolving lesions of ELE are only 'vasculopathic' in nature.

Other non-specific cutaneous manifestations associated with FMF include urticaria, angioedema, dermatographism, Raynaud's phenomenon, recurrent oral (aphthous) ulcers, diffuse erythema of the face, trunk, palms and soles, psoriasis and erythema nodosum.[2,26,29,30] Purpura, ecchymoses and petechiae have also been reported, but skin biopsies were not performed in these patients and it is not clear whether these manifestations were vasculitis.[26,29] Pathergy is absent in FMF.[31]

The importance of neutrophils in FMF is evident. Neutrophilic dermatoses associated with FMF include Sweet syndrome,[32,33] pyoderma gangrenosum[34] and neutrophilic panniculitis.[33] Neutrophils are also present within the bullous eruptions of FMF. Akman et al. reported a subepidermal split, a neutrophilic infiltrate and nuclear debris around mid-sized vessels in the reticular dermis.[35] Ronnen et al. observed mid epidermal bulla formation and a perivascular

infiltrate composed chiefly of neutrophils.[36] None of the authors observed vasculitis within bullous lesions. Neutrophils accompanied by nuclear debris in various amounts are also present in ELE.[21] It is reasonable to conclude that cutaneous lesions of FMF belong to the spectrum of neutrophilic dermatitis. A favorable response to treatment with colchicine, which inhibits neutrophil activity and mobility, is a major argument in favor of this conclusion.

A neutrophilic infiltrate can be seen in the other monogenic autoinflammatory syndromes, especially the cryopyrin-associated periodic syndromes (CAPS), encompassing the spectrum of familial cold autoinflammatory syndrome, Muckle–Wells syndrome and neonatal-onset multisystem inflammatory disease. The clinical presentations are different and characterized by an evanescent 'urticarial' eruption. This so-called 'urticarial eruption' is manifested by rose- or pale-red, flat or slightly raised, non-pruritic macules and plaques, mostly located on the trunk, upper and lower extremities.[37–40] The clinicopathological entity of 'neutrophilic urticarial dermatosis' (NUD) has been proposed in order to describe the cutaneous findings of CAPS.[41,42] Although not widely accepted as a distinctive pattern, the concept of NUD is useful as it delineates the eruption in autoinflammatory diseases from common neutrophilic urticaria. The microscopic findings of NUD appear to be similar to those seen in ELE. These similarities are understandable, as both CAPS and FMF share a common pyrin pathway. Schnitzler syndrome, adult-onset Still disease and lupus erythematosus (LE), may also have autoinflammation involved within their pathogenesis and may develop NUD. These processes have a more complex and polygenic etiology than monogenic autoinflammatory syndromes.[41–44]

The various neutrophilic dermatoses reported in association with connective tissue diseases, and particularly LE, reflect their complex pathogenesis, in which there may be both an autoimmune and autoinflammatory involvement.[44] A neutrophilic infiltrate is often encountered in cases of acute systemic LE and in bullous LE. Non-bullous neutrophilic LE is characterized by dermal neutrophils with leukocytoclasia, epidermal basal layer vacuolar change, absence of vasculitis and a positive direct immunofluorescence with C3 and immunoglobulin deposition in the basement membrane zone.[44–46] This variant of lupus is clinically similar with the so-called 'Sweet-like' eruptions associated with LE. Sweet-like eruptions lack vacuole change and show marked papillary edema, low-grade vasculitis and negative direct immunofluorescence studies.[45,47] A Sweet-like dermatitis has been reported with dermatomyositis and other autoimmune diseases.[48] Finally, amicrobial pustulosis of skin folds (APSS) is a relapsing aseptic pustular eruption affecting skin folds, the scalp and periorificial regions associated with connective tissue diseases and particularly with LE. Histopathological findings of APSS are characterized by an intraepidermal and subcorneal neutrophilic infiltrate with pustules and spongiosis, dermal neutrophils with a perivascular and perifollicular accentuation, absence of vasculitis and negative direct immunofluorescence studies.[44,49–52]

The histopathologic differential diagnosis of ELE, when correlated with the clinical presence of fever, includes erysipelas. Less likely is Sweet syndrome, neutrophilic urticaria, urticarial vasculitis and NUD.[21,32,39,41–44] Histopathologic differences among these entities are presented in Table 2. These microscopic differences may be subtle and therefore clinicopathologic correlation is necessary in order to establish a definitive diagnosis. In most of these cases, however, a diagnosis is often made clinically, based on biological and genetic testing, rather than on a strictly microscopic basis.

The presence of neutrophils is the hallmark of the cutaneous manifestations of autoinflammation and their presence in the context of recurrent fever should always lead to a suspicion of an autoinflammatory syndrome, once infection has been ruled out.[5–10] The presence of neutrophils in the clinical context of recurrent erysipelas within the same site is a diagnostic clue for FMF.

Conclusion

This case, including a histopathologic description of ELE in FMF, adds to the sparse literature of this rare genetic disease. Important in making a definitive diagnosis is recognizing the microscopic findings of a mixed infiltrate with neutrophils and no eosinophils in the clinical context of recurrent fever accompanied by recurrent erysipelas within the same site.

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