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PROTRACTED FEBRILE MYALGIA SYNDROME AS INITIAL PRESENTATION OF FAMILIAL MEDITERRANEAN FEVER IN A PATIENT OF NORTHERN EUROPEAN EXTRACTION THOUGHT TO HAVE ULCERATIVE COLITIS

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ABSTRACT

Introduction: Protracted febrile myalgia syndrome is a rare vasculitic manifestation of familial Mediterranean fever that presents as the initial familial Mediterranean fever manifestation in one-third of cases. While familial Mediterranean fever is classically autosomal recessive and associated with Mediterranean ancestry, the p.Met694del variant demonstrates autosomal dominant inheritance with a Northern European founder effect. MEFV-related enterocolitis can produce histologic features indistinguishable from inflammatory bowel disease.

Case description: A 24-year-old European American man with no Mediterranean, Middle Eastern or Armenian ancestry, with biopsy-confirmed ulcerative colitis on upadacitinib, presented with six weeks of high-grade fevers, incapacitating myalgias, a 30-pound weight loss and pericardial effusion. Faecal calprotectin was markedly elevated (>8,000 µg/g) without gastrointestinal symptoms. Inflammatory markers were noticeably elevated with normal creatine kinase; extensive infectious and malignancy workup was negative. Bone marrow biopsy demonstrated focal haemophagocytosis without malignancy. Dramatic improvement occurred within 24–48 hours of corticosteroid initiation. Genetic testing revealed heterozygous p.Met694del, confirming autosomal dominant familial Mediterranean fever. At six-month follow-up on colchicine monotherapy without inflammatory bowel disease-directed therapy, inflammatory markers, faecal calprotectin and pericardial effusion had completely normalised, fulfilling Tel Hashomer criteria.

Conclusion: This case highlights protracted febrile myalgia syndrome as an under-recognised initial presentation of autosomal dominant familial Mediterranean fever in non-Mediterranean populations. Colchicine-responsive normalisation of faecal calprotectin raises the possibility that MEFV-mediated enterocolitis contributed to intestinal inflammation initially attributed to ulcerative colitis. Early recognition enables amyloidosis prevention and essential genetic counselling for first-degree relatives.

KEYWORDS

Familial Mediterranean fever, protracted febrile myalgia syndrome, MEFV gene, ulcerative colitis, inflammasome

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LEARNING POINTS

- Protracted febrile myalgia syndrome – prolonged fever, incapacitating myalgia and normal creatine kinase, should prompt consideration of familial Mediterranean fever regardless of ancestry, as the p.Met694del variant follows autosomal dominant inheritance with a Northern European founder effect.
- Colchicine-responsive normalisation of faecal calprotectin (>8,000 to normal) without inflammatory bowel disease-directed therapy in a patient with biopsy-confirmed ulcerative colitis and a pathogenic MEFV variant, raises the possibility that MEFV-mediated enterocolitis contributed to intestinal inflammation initially attributed to inflammatory bowel disease, a distinction with direct therapeutic implications.
- Autosomal dominant MEFV variants carry critical implications for family counselling: first-degree relatives have a 50% risk of inheriting the variant and developing familial Mediterranean fever, including phenotype II amyloidosis (renal amyloidosis without preceding typical attacks).

INTRODUCTION

Protracted febrile myalgia syndrome (PFMS) is a rare but severe manifestation of familial Mediterranean fever (FMF), characterised by 4–6 weeks of disabling myalgia, fever, markedly elevated inflammatory markers and normal creatine kinase[1,2]. The syndrome represents a vasculitis condition primarily affecting the fasciae rather than muscle tissue, with histopathology demonstrating T-cell rich inflammatory infiltrates (predominantly CD8+ > CD4+) and non-necrotising vasculitis of small vessels in the fasciae[1]. PFMS presents as the initial manifestation of FMF in approximately 33% of cases[3].

FMF is an autoinflammatory disease caused by mutations in the MEFV gene, which encodes pyrin, a key regulator of the inflammasome and interleukin-1β production[1]. While classically autosomal recessive, autosomal dominant inheritance occurs with specific severe exon 10 variants, including p.Met694del, p.Ile692del and p.Tyr688Ter[4]. Up to 25% of individuals with FMF have only one MEFV pathogenic variant identified, while an additional 10–20% show a classical FMF phenotype and respond to colchicine despite no detectable mutations; clinical criteria with an emphasis on colchicine response remain the main diagnostic tool[1]. The p.Met694del variant is an in-frame deletion with a Northern European founder, also found in Iranian and Azari Turkish populations[4]. Heterozygotes typically present later (median onset 18 years) than classic recessive FMF, and the incidence of AA amyloidosis is approximately 14%, possibly reflecting diagnostic delay in non-Mediterranean populations[4]. FMF amyloidosis carries a poor prognosis, with 82% progressing to end-stage renal disease or death within 11 years, underscoring the need for early colchicine therapy[1].

The association between FMF and inflammatory bowel disease reflects shared inflammasome dysregulation. A nationwide Israeli study found FMF prevalence of 0.5% in IBD patients vs 0.2% in controls (OR 2.68; 95% CI 2.2–3.3), with FMF diagnosis preceding IBD in 83% of cases; MEFV variation frequency has been reported at 25.5% in IBD patients vs 9.9% in controls in populations with high carrier rates[5,6]. Importantly, MEFV-related enterocolitis can produce histologic features indistinguishable from IBD, including chronic colitis with crypt architectural distortion, and a substantial proportion of patients diagnosed with IBD unclassified carry MEFV mutations and respond to colchicine[7,8].

We present PFMS as the initial manifestation of autosomal dominant FMF in a European American man with biopsy-confirmed ulcerative colitis, in whom the clinical course raised the possibility that MEFV-mediated enterocolitis contributed to the intestinal inflammatory burden.

CASE DESCRIPTION

A 24-year-old European American man with no Mediterranean, Middle Eastern or Armenian ancestry had a three-year biopsy-confirmed ulcerative colitis managed with upadacitinib.

He presented with six weeks of high-grade fevers, night sweats, profound fatigue, severe deep bone and muscle pain involving extremities and bilateral feet, a 13.6 kg unintentional weight loss and progressive exertional dyspnoea with tachycardia. He denied gastrointestinal symptoms despite markedly elevated faecal calprotectin (>8,000 µg/g).

He described the pain as 'deep, aching and incapacitating', limiting ambulation. Examination revealed fever (38.6°C), tachycardia (105–130 bpm), severe foot tenderness without oedema or erythema, distant heart sounds and hepatomegaly (3 cm below the costal margin). A salmon-pink rash, pharyngeal erythema, lymphadenopathy, splenomegaly, skin lesions and synovitis were absent.

Laboratory evaluation demonstrated leucocytosis (12.3 $\times 10^3$/µl, 67% polymorphonuclear cells), thrombocytosis (551 $\times 10^3$/µl), normocytic anaemia (haemoglobin 8.5 g/dl), severe hypoalbuminaemia (2.0 g/dl), markedly elevated inflammatory markers (C-reactive protein 81 mg/l, erythrocyte sedimentation rate 79 mm/hr), and modestly elevated ferritin (366–378 ng/ml). Creatine kinase remained normal (31 IU/l), aldolase 5.1 U/l (1–7.5 U/l). Autoimmune serologies and comprehensive infectious workup were negative.

Imaging revealed moderate-to-large pericardial effusion

on an echocardiogram *(Fig. 1A)* and hepatomegaly on computed tomography without lymphadenopathy or splenomegaly *(Fig. 1B)*. Bone marrow biopsy showed normocellular trilineage haematopoiesis with focal haemophagocytosis and reactive megakaryocytic atypia without dysplasia, increased blasts or amyloid deposition *(Fig. 2)*. Primary hemophagocytic lymphohistiocytosis was excluded (met only 3/8 HLH-2004 criteria; it lacked marked hyperferritinaemia, splenomegaly, hypertriglyceridemia, hypofibrinogenemia and elevated soluble interleukin-2 receptor); focal haemophagocytosis was attributed to autoinflammation. Upadacitinib was held on admission given the concern for opportunistic infection.

Upadacitinib-related adverse effects were excluded; Janus kinase inhibitors characteristically elevate creatine kinase and have demonstrated therapeutic benefit in refractory FMF, making drug-induced autoinflammation unlikely[1]. Ulcerative colitis extraintestinal manifestations were excluded based on absent gastrointestinal symptoms, pain pattern inconsistent with inflammatory bowel disease arthropathy, absence of characteristic skin lesions, normal creatine kinase (typical of PFMS fasciitis rather than myositis). In addition, there was a prolonged 4–6-week course characteristic of PFMS and serositis, recognised in familial Mediterranean fever/PFMS but not a typical ulcerative colitis extraintestinal feature[1,2]. Adult-onset Still's disease was excluded: the patient met only fever (major) and negative rheumatoid factor/antinuclear antibody (minor) Yamaguchi criteria, lacking leucocytosis ≥10,000/µl with ≥80% granulocytes (67% in this patient), arthralgia/arthritis ≥2 weeks, salmon-pink evanescent rash and markedly elevated ferritin (typically >1,000 ng/ml in adult-onset Still's disease)[9]. The modest ferritin (366–378 ng/ml), deep incapacitating myalgia with normal creatine kinase and prolonged 4–6-week course strongly favoured PFMS. Poststreptococcal myalgia was excluded by normal creatine kinase and lack of response to NSAIDs[1]. Polyarteritis nodosa was considered given the known familial Mediterranean fever–polyarteritis nodosa association and overlapping features including fever, myalgia and normal creatine kinase[1]. However, the patient lacked peripheral neuropathy, cutaneous findings, hypertension, renal involvement and visceral aneurysms on a computed tomography scan. The self-limited course with complete resolution on corticosteroids and colchicine alone favours PFMS over systemic polyarteritis nodosa[1,2].

Following exclusion of infectious aetiologies and malignancy, intravenous methylprednisolone 40 mg daily produced a dramatic improvement within 24–48 hours, with normalising vital signs and significant myalgia

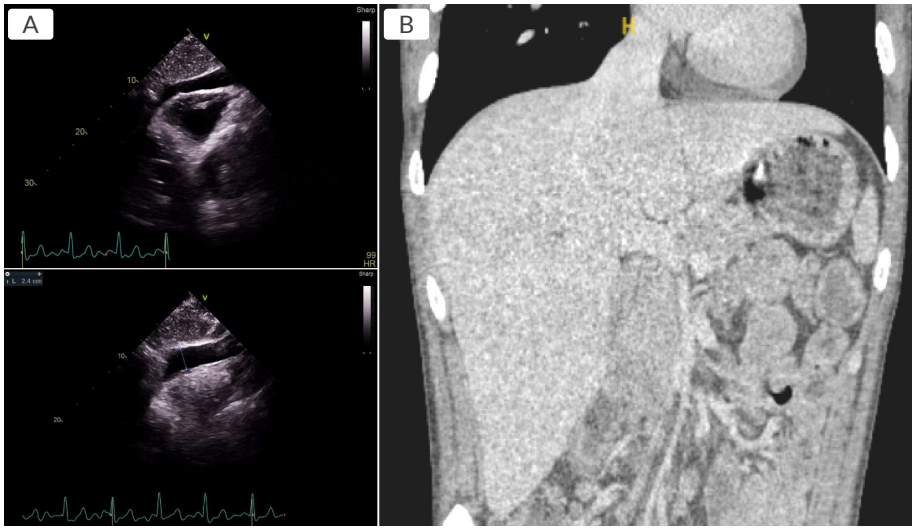


Figure 1. *Imaging findings. A) Echocardiogram demonstrating moderate-to-large pericardial effusion; B) Computed tomography of the chest and abdomen demonstrating pericardial effusion and hepatomegaly without lymphadenopathy or splenomegaly.*

Parameter	Admission	Hospital discharge	6-month follow-up	Reference range
C-reactive protein (mg/l)	81	18	3	<10
Erythrocyte sedimentation rate (mm/hr)	79	41	12	<20
Haemoglobin (g/dl)	8.5	9.8	13.4	-
Faecal calprotectin (µg/g)	>8,000	Not tested	Normal	<50
Pericardial effusion	Moderate to large	Mild	Resolved	-
Therapy	IV methylprednisolone + colchicine	Prednisone taper + colchicine	Colchicine monotherapy	-

Table 1. *Clinical and laboratory timeline demonstrating disease course from presentation through six-month follow-up on colchicine monotherapy.*

Criterion type	Tel Hashomer criterion	Patient finding
Major	Recurrent febrile episodes	6 weeks of high-grade fever ✓
Major	Serositis (pericarditis/peritonitis/pleuritis)	Moderate-to-large pericardial effusion ✓
Major	Favourable colchicine response (complete remission)	Sustained remission on colchicine monotherapy at 6 months ✓
Minor	Elevated erythrocyte sedimentation rate / C-reactive protein	Erythrocyte sedimentation rate 79 mm/hr; C-reactive protein 81 mg/l ✓
Minor	Leukocytosis	12.3 ×103/µl ✓

Table 2. Tel Hashomer clinical criteria for familial Mediterranean fever with patient-specific findings.

reduction. Pulse corticosteroid therapy alleviates PFMS pain within hours in over 90% of cases, with oral corticosteroids (1–2 mg/kg) tapered gradually over six weeks[1,2]. The patient transitioned to oral prednisone taper and colchicine 0.6 mg twice daily for pericarditis, long-term FMF prophylaxis and AA amyloidosis prevention. MEFV gene sequencing revealed heterozygous p.Met694del (c.2082_2084delAAG), an in-frame deletion in exon 10. No second pathogenic variant was identified.

At six-month follow-up, the patient remained asymptomatic on colchicine monotherapy, without resumption of upadacitinib or any IBD-directed therapy. Laboratory evaluation demonstrated normalised inflammatory markers and faecal calprotectin. Repeat echocardiography confirmed complete pericardial effusion resolution *(Table 1)*. This sustained colchicine response fulfils Tel Hashomer clinical criteria for FMF *(Table 2)*[1].

DISCUSSION

This case illustrates three clinically significant findings:

1) PFMS as the initial presentation of autosomal dominant FMF in a European American patient;
2) the diagnostic challenge posed by MEFV-related intestinal inflammation overlapping with biopsy-confirmed ulcerative colitis;
3) the critical importance of identifying autosomal dominant MEFV variants for family counselling.

The presentation fulfilled PFMS diagnostic criteria: severe disabling myalgia ≥5 days, fever, elevated inflammatory markers and normal creatine kinase[3]. The six-week duration, severe foot-predominant pain, pericardial effusion and dramatic corticosteroid response are characteristic features[1–3]. The patient fulfilled Tel Hashomer clinical criteria for FMF: fever (major), pericarditis (major), elevated erythrocyte sedimentation rate (minor), leucocytosis (minor) and a favourable response to continuous colchicine (major)[1].

Heterozygous p.Met694del confirms autosomal dominant FMF. This in-frame deletion produces a shortened pyrin protein distinct from the more common p.Met694Val Mediterranean variant[1,4]. Haplotype analysis traces a single Northern European founder effect approximately 550 years ago, consistent with our patient's ancestry and underscoring that FMF should not be excluded based on ethnicity[4]. In the largest reported cohort, all 15 heterozygotes treated with colchicine demonstrated excellent responses, mirroring our patient's sustained remission[4].

The autosomal dominant inheritance pattern carries immediate implications for family counselling: first-degree relatives have a 50% chance of inheriting the variant and developing FMF[4]. Asymptomatic carriers remain at risk for phenotype II FMF (amyloidosis without typical attacks), making systematic genetic screening of first-degree relatives essential[4,10].

The intestinal inflammatory findings merit particular attention. Faecal calprotectin was markedly elevated (>8,000 µg/g) without gastrointestinal symptoms, a dissociation unusual for typical ulcerative colitis flares, where calprotectin elevation generally correlates with symptomatic disease activity. More importantly, faecal calprotectin normalised completely on colchicine monotherapy without resuming upadacitinib or any IBD-directed therapy. While ulcerative colitis was biopsy-confirmed, MEFV-related enterocolitis can produce

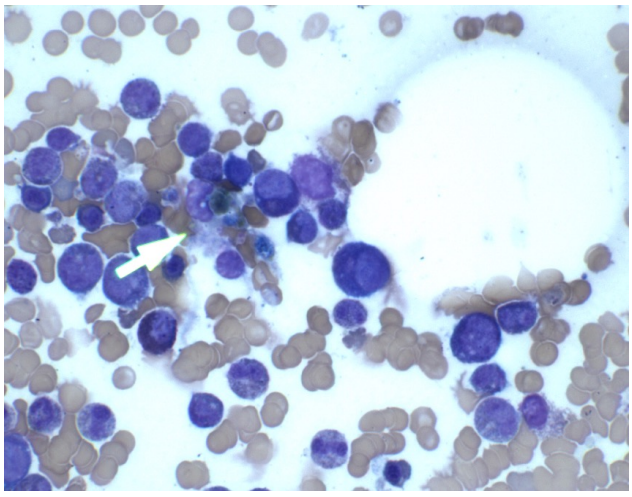


Figure 2. Bone marrow biopsy showing normocellular marrow for age with trilineage haematopoiesis, focal haemophagocytosis and reactive megakaryocytic atypia. No dysplasia, increased blasts or AA amyloid deposition were identified.

histologic features indistinguishable from IBD, including chronic colitis with crypt architectural distortion[7,8]. Nakase et al. demonstrated that 60.1% of patients diagnosed with IBD unclassified carried MEFV mutations, with colchicine efficacy of 84.6%[8]. The clinical trajectory raises the possibility that MEFV-mediated intestinal inflammation contributed significantly to the mucosal inflammatory burden initially attributed to ulcerative colitis. Long-term follow-up will clarify whether the intestinal disease is best characterised as true ulcerative colitis coexisting with FMF, an MEFV-modified ulcerative colitis phenotype or MEFV-related enterocolitis with histologic features mimicking ulcerative colitis[7,8].

FMF patients show elevated faecal calprotectin even in attack-free periods, and levels normalise with colchicine, serving as a biomarker of subclinical intestinal inflammation[7]. The co-occurrence of FMF and IBD reflects shared pathogenic mechanisms: pyrin regulates both inflammasome activation and intestinal barrier integrity, and IBD patients have 2.68-fold higher odds of having concomitant FMF (OR 2.68; 95% CI 2.2–3.3)[5,6].

In partial corticosteroid responders, anti-interleukin-1 agents (anakinra, canakinumab) may be beneficial but should always be given with concomitant colchicine, as no controlled trials demonstrate that interleukin-1 blockade alone prevents amyloidosis[1]. Colchicine remains the cornerstone of FMF treatment and prevents both secondary amyloidosis and PFMS recurrences[1].

CONCLUSION

In conclusion, PFMS should be considered in patients presenting with prolonged fever, incapacitating myalgia and normal creatine kinase, regardless of ancestry. Early recognition is critical to initiate colchicine therapy and prevent secondary AA amyloidosis. The identification of autosomal dominant p.Met694del carries immediate implications for genetic counselling and systematic screening of first-degree relatives.

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