# A young woman with fever and polyserositis caused by familial Mediterranean fever

Kayla Richard BMSc MBS, Sara Glazer MD BHSc, Erkan Demirkaya MD MSc, Natalya Karp MD MSc

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In 2015, a 28-year-old woman of Ashkenazi Jewish descent presented to the medical genetics clinic with concerns about flexible joints, easy bruising, stretchable skin, chronic back pain and mild scoliosis since childhood. Differential diagnoses included connective tissue disorders such as Ehlers–Danlos (EDS), Marfan and Loeys–Dietz syndromes. She had an elevated Beighton score (6/9), reflecting joint hypermobility, and none of the features consistent with Marfan syndrome or Loeys–Dietz syndrome. Her echocardiogram was normal and her family history was unremarkable. A 13-gene panel was negative for EDS, and she was given a clinical diagnosis of hypermobile EDS.

Over the next 5 years, the patient developed recurrent episodes of fever, elevated C-reactive protein (CRP), abdominal pain and other symptoms (Table 1). Although most episodes lasted 1–3 days, the patient often noted recurrence or worsening of symptoms after interventions, such as fever or abdominal pain after various surgeries.

In 2016, the patient had an ovarian cystectomy for suspected ovarian torsion (no torsion found), an appendectomy for suspected appendicitis (no appendicitis found) and an endoscopic retrograde cholangiopancreatography with stent placement for presumed chronic pancreatitis. In 2017, she received diagnoses of cholecystitis, chronic pancreatitis and malnutrition, which led to a cholecystectomy and central line placement for total parenteral nutrition. She also had chest pain and shortness of breath with pleural effusions; presumed volvulus, which led to emergency laparotomy, with no evidence of volvulus intraoperatively; and thrombophlebitis of the internal jugular vein. Intermittent abdominal pain, distension and nausea were attributed to colonic dysmotility related to hypermobile EDS. She had serious malnutrition, and her body mass index dropped from 20.3 to 15.8, which led to placement of a gastrojejunostomy tube to support enteral feeds and avoid complications associated with prolonged total parenteral nutrition.

The patient's clinical status deteriorated through 2018, with flares of abdominal pain, constipation and feeding intolerance, which continued to be attributed to colonic dysmotility secondary to hypermobile EDS. Gram-negative enteric bacteria were identified on blood cultures twice, and were attributed to the impact of her EDS on the integrity of the bowel wall leading to bacterial translocation. Total colectomy and ileostomy were performed, followed by prolonged recovery, with recurrent fevers, elevated CRP and abdominal pain. After a period of stability, reversal of her ileostomy with J-pouch formation was complicated by postoperative abdominal pain, fever and elevated CRP. In 2019, she had episodes of left lower quadrant pain and tenesmus, diagnosed as pouchitis and managed with antibiotics. In 2020, the patient had episodes of pelvic pain and fever lasting 2–3 days, elevated inflammatory markers, pericardial effusion, hepatosplenomegaly and blood cultures positive for *Escherichia coli*. She was given a diagnosis of urosepsis and prescribed antibiotics.

In 2020 the patient sought a genetics reassessment. No clinical diagnosis was made; however, it was thought that her history could not be explained by hypermobile EDS. A geneticist ordered whole exome sequencing, which found compound heterozygous pathogenic DNA variants in the *MEFV* gene, namely c.2084A>G (p.Lys695Arg) and c.2177T>C (p.Val726Ala), consistent with familial Mediterranean fever (FMF).

The patient was referred to a rheumatologist and started on colchicine 0.6 mg once a day. During the 2 years since she started taking colchicine, she has had 2 mild, self-resolving flares of FMF that did not require hospital admission or intervention. She has returned to her baseline strength and nutritional status, and has stopped all other medications. She has no evidence of renal amyloidosis; her serum creatinine (71 mmol/L) and urea (4.4 mmol/L) are within normal ranges, and she has no protein in her urine.

## Key points

- Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disorder; it is characterized by self-limited episodes of fever, polyserositis and elevated inflammatory markers.
- While symptoms are nonspecific, FMF should be suspected in patients with recurrent febrile episodes accompanied by peritonitis, pleuritis, pericarditis and elevated C-reactive protein, especially among people of Ashkenazi Jewish descent and other at-risk ethnic groups.
- Treatment with colchicine prevents clinical flares and the amyloidosis and renal failure that can be associated with the disease.
- Delayed diagnosis can have grave consequences for patients, including unnecessary surgeries and associated complications.

**Table 1 (part 1 of 3): Chronology of events for a 28-year-old woman with familial Mediterranean fever**

| Date | Admission duration, d | Symptoms | | | Laboratory abnormalities* | | Diagnosis | Investigations, procedures, interventions, intraoperative findings, pathology, complications and treatments |
|---|---|---|---|---|---|---|---|---|
| | | Fever | Abdominal pain | Other | Max. CRP | Other | | |
| February 2015 | Outpatient genetics | No | No | Back pain, hypermobility | NA | EDS gene panel negative | • Hypermobile EDS | |
| March 2015 | Outpatient medicine | No | Yes | Back pain, shortness of breath | NA | Hemoglobin 74 g/L | • NSAID-induced gastric ulceration | • Endoscopy |
| July 2016 | 6 | Yes | Yes, LLQ | No | 163 | Lipase 100–155 U/L | • Preoperative: ovarian torsion<br>• Postoperative: endometritis and urinary retention | • Ultrasonography of abdomen and pelvis: left ovarian cyst, could not rule out torsion<br>• Laparoscopic ovarian cystectomy: left ovarian hemorrhagic cyst, no torsion<br>• Complications: postoperative fever, urinary retention and pain treated as endometritis |
| July–August 2016 | 19 | No | Yes, RLQ | Nausea, vomiting | 82 | NA | • Admission: appendicitis<br>• Discharge: abdominal pain NYD, postoperative ileus | • Ultrasonography of abdomen: hyperemia to appendix, free fluid in RLQ<br>• Laparoscopic appendectomy: no evidence of appendicitis<br>• Pathology: mild inflammatory changes, lymphoid hyperplasia<br>• Complications: postoperative abdominal pain with ileus |
| October 2016 | 35 | Yes (after procedure) | Yes, RUQ | Nausea, vomiting | 201 | Lipase 75–81 U/L, amylase 143 IU/L | • Admission: pancreatitis<br>• Discharge: sphincter of Oddi dysfunction | • Ultrasonography of abdomen: gall bladder wall thickening, biliary sludge<br>• ECRP and stent placement with papillotomy<br>• Complications: postprocedure spike in CRP, RLQ pain and fever |
| February–March 2017 | 51 | Yes | Yes, RUQ | Nausea, vomiting | 111 | Lipase 102–189 U/L | • Admission: cholecystitis, pancreatitis<br>• Discharge: malnutrition, culture-negative sepsis | • Ultrasonography of abdomen: gall bladder wall thickening, biliary sludge<br>• Cholecystectomy<br>• Pathology: lymphocytic inflammatory infiltrate<br>• PICC line insertion<br>• Complications: postprocedure fever diagnosed as culture-negative sepsis<br>• Sepsis treated with antibiotics |
| May 2017 | 6 | No | No | Chest pain, shortness of breath | NA | NA | • Bilateral pleural effusions, cause unclear | • Chest radiography: pleural effusions, lung fields clear<br>• Supportive, low-flow oxygen for 48 h |
| August 2017 | 14 | Yes | Yes | Obstipation, abdominal distention | NA | Lipase 77–220 U/L | • Admission: volvulus<br>• Discharge: transverse colon dilatation secondary to EDS and constipation | • CT of abdomen: concerning for sigmoid volvulus<br>• Sigmoidoscopy, colonoscopy, exploratory laparotomy: no volvulus evident, redundant colon, thinning of bowel wall<br>• Complications: postoperative pain and fever |

**Table 1 (part 2 of 3): Chronology of events for a 28-year-old woman with familial Mediterranean fever**

| Date | Admission duration, d | Symptoms | | | Laboratory abnormalities* | | Diagnosis | Investigations, procedures, interventions, intraoperative findings, pathology, complications and treatments |
|---|---|---|---|---|---|---|---|---|
| | | Fever | Abdominal pain | Other | Max. CRP | Other | | |
| October 2017 | 7 | Yes | Yes, epigastric | Left hand pain, redness, swelling | 55 | Leukocyte 16 × $10^9$/L | • Cellulitis | • Intravenous antibiotics, analgesia |
| November 2017 | 10 | Yes | No | Neck pain, headache | NA | Leukocyte 18 × $10^9$/L | • Septic thrombophlebitis (Lemierre syndrome) | • Ultrasonography of neck: evidence of clot extending to right jugular vein and tributaries<br>• Intravenous antibiotics |
| December 2017 | 6 | Yes | Yes | Headache | NA | Blood culture positive for CONS | • Admission: central line infection<br>• Discharge: bacteremia | • CT of head: normal<br>• Lumbar puncture, PICC line removal, port-a-cath insertion<br>• Intravenous antibiotics |
| December 2017 | 34 | Yes | Yes, RUQ | Headache, blurred vision, constipation, weight loss | NA | Lipase 103 U/L, AST and ALT > 1000 U/L | • Admission: small bowel obstruction, possible stroke<br>• Discharge: small bowel obstruction, migraine | • MRI brain with MRA and MRV: normal<br>• Ultrasonography of abdomen: hepatomegaly, splenomegaly<br>• Abdominal radiography: air fluid levels, concerning for small bowel obstruction.<br>• Laparoscopy with lysis of adhesions<br>• Gastrostomy tube insertion |
| December 2017 | 4 | No | Yes | Headache, nausea, feeding intolerance | NA | NA | • Colonic and gastric dysmotility, feeding intolerance | • Gastrostomy tube replaced with gastrojejunal tube |
| April 2018 | 87 | Yes | Yes | Abdominal distension, nausea | 88 | Blood culture positive for *Escherichia coli*, *Enterococcus* species | • Admission: sepsis<br>• Discharge: colonic distension with bacterial translocation, bacteremia | • CT of abdomen: redundant sigmoid colon, colonic distension, free fluid<br>• Total colectomy and ileostomy<br>• Complications: postoperative fevers, pain and feeding intolerance |
| November 2018 | 21 | Yes | Yes, RLQ | NA | 76 | NA | • Admission: ileostomy reversal<br>• Discharge: postoperative pain, surgical site infection | • Planned Ileostomy reversal<br>• Intravenous antibiotics<br>• Complications: postoperative RLQ pain, fever managed as infection |
| November–December 2019 | Recurrent outpatient emergency visits | Yes | Yes | Pelvic pain, tenesmus, bloody diarrhea | 94 | NA | • Pouchitis | • CT of abdomen and pelvis: bowel wall thickening consistent with pouchitis<br>• Pouchoscopy: colonic mucosal inflammation, lymphoid aggregation<br>• Intravenous and oral antibiotics, intravenous steroids |
| March 2020 | Emergency department visit | Yes | Yes, RLQ | Pelvic pain, urinary retention | 83 | NA | • Pouchitis | • CT of abdomen and pelvis: RLQ fluid collection concerning for infection, abscess<br>• Analgesia, discharge with oral antibiotics, intermittent self-catheterization |

**Table 1 (part 3 of 3): Chronology of events for a 28-year-old woman with familial Mediterranean fever**

| Date | Admission duration, d | Symptoms | | | Laboratory abnormalities* | | Diagnosis | Investigations, procedures, interventions, intraoperative findings, pathology, complications and treatments |
|---|---|---|---|---|---|---|---|---|
| | | Fever | Abdominal pain | Other | Max. CRP | Other | | |
| March–May 2020 | 47 | Yes | Yes | Chest pain, vomiting, rectal bleeding | 151 | ALT 134–368 U/L<br>Blood culture positive for *E. coli* | • Urosepsis | • Ultrasonography of abdomen: hepatomegaly (19.6 cm), splenomegaly (15.5 cm)<br>• CT of chest: pericardial effusion, pulmonary nodules |
| June–December 2020 | Outpatient genetics | No | No | NA | NA | NA | • FMF | • Whole exome sequencing (GeneDx Laboratory, United States): positive for mutations causing FMF<br>• Urgent referral to rheumatology, colchicine started |

Note: ALT = alanine aminotransferase, AST = aspartate aminotransferase, CONS = coagulase-negative *Staphylococcus aureus,* CRP = C-reactive protein, CT = computed tomography, EDS = Ehlers–Danlos syndrome, ERCP = endoscopic retrograde cholangiopancreatography, FMF = familial Mediterranean fever, LLQ = left lower quadrant, Max. = maximum, MRA = magnetic resonance angiography, MRI = magnetic resonance imaging, MRV = magnetic resonance venography, NA = not measured or not relevant, NSAID = nonsteroidal anti-inflammatory drug, NYD = not yet diagnosed, PICC = peripherally inserted central catheter, RLQ = right lower quadrant, RUQ = right upper quadrant.
*Normal reference ranges are as follows: ALT = 7–55 U/L, amylase = 28–100 U/L, AST = ≤ 32 U/L, CRP = 3–5 mg/L, hemoglobin = 115–160 g/L, lipase = 13–60 U/L, leukocyte = 4–10 × $10^9$/L.

## Discussion

Familial Mediterranean fever is the most common monogenic autoinflammatory disorder; it is characterized by self-limited episodes of fever, polyserositis and elevated inflammatory markers.[1–4] The condition is associated with gain-of-function sequence variations in the *MEFV* gene that encodes for the pyrin protein, and results in uncontrolled production of interleukin-1β and an exaggerated inflammatory response.[1,2,4] The disease manifests as recurrent bouts of fever, abdominal pain and chest pain that start abruptly and peak soon after onset, last for 1–4 days and then resolve spontaneously. Patients typically have no symptoms between attacks.[2] Familial Mediterranean fever should be considered for patients who have undergone laparotomy or laparoscopy with no pathology identified. Stress, cold exposure, fat-rich meals, infections, vigorous exercise, surgery and the menstrual cycle may all provoke an attack. Familial Mediterranean fever may present uncommonly as erysipelas-like erythema, aseptic meningitis, recurrent urticaria or vasculitis.[3]

Laboratory abnormalities during attacks are nonspecific and include elevated systemic markers of inflammation, leukocytosis with neutrophilia, and elevated erythrocyte sedimentation rate, CRP and fibrinogen. Serum amyloid A protein is also elevated during attacks, but is not routinely measured unless a diagnosis of FMF is suspected.[3] One of the long-term complications of untreated disease is amyloidosis of the kidneys, which has been reported to be present in about 12% of patients with FMF; it can have severe complications, including renal failure.[1,2] Amyloidosis may also develop in the spleen, liver, gastrointestinal tract, thyroid and testes. Small bowel obstruction may develop because of recurrent peritonitis and adhesion formation. Before colchicine was used in the treatment of FMF, infertility was common and was thought to be caused by obstruction of fallopian tubes in females and testicular amyloidosis in males.[2,3]

Familial Mediterranean fever is common in people of Ashkenazi Jewish descent, with a substantial gene carrier rate (about 1:7.8).[5] The prevalence is about 1 in 500 to 1 in 1000 among people of other at-risk ethnic descents, including those of Turkish, Armenian, Arabic, non-Ashkenazi Jewish, North African, Italian, Greek, Chinese and Japanese ancestry. Known risk factors include family history of FMF, present in 30%–50% of people with the condition, and belonging to an at-risk ethnic group.[6] More than 95% of genetic carriers are asymptomatic; however, some individuals with a single mutation may manifest symptoms and may benefit from treatment with colchicine.[1]

Our patient's many episodes of fever and abdominal pain led to different diagnoses, invasive procedures and complications. Intraoperative findings and postoperative pathology reports were often inconsistent with the initial diagnosis of hypermobile EDS, and hospital admissions were prolonged owing to postoperative flares of pain, fever and elevated CRP. Over the course of her illness, treating clinicians appeared not to have considered FMF.

Hypermobile EDS is the mildest subtype of EDS, with no life-threatening complications, although patients with hypermobile EDS can have various types of gastroesophageal dysmotility such as esophageal dysmotility, gastroparesis, small bowel or colon altered transit time or global dysmotility.[7] However, unlike the vascular EDS subtype, hypermobile EDS does not cause bowel wall fragility or rupture. Genes for hypermobile EDS have not yet been identified. Vascular EDS and other EDS subtypes were highly unlikely in this patient, given her negative results from genetic testing. Hypermobile EDS would not explain this patient's symptoms, except perhaps colonic dysmotility.[7]

**Table 2: Differential diagnosis for patients with periodic fevers and elevated inflammatory markers**

| Condition | Unique features |
|---|---|
| Familial Mediterranean fever | • Polyserositis, recurrent fevers, brief flares lasting 1–4 d, variable interval between flares |
| Periodic fever, aphthous stomatitis, pharyngitis, adenitis | • Onset in childhood (age < 5 yr)<br>• Recurrent fevers lasting 3–7 d<br>• Aphthous stomatitis, tonsillitis (occasionally with white exudates), pharyngitis with diffuse hyperemia of the entire palate, cervical and mesenteric lymphadenopathy, abdominal pain, chills, headache, vomiting, diarrhea, hepatosplenomegaly and joint pain<br>• Flares every 3–5 wk. Patients are well between episodes |
| Cryopyrin-associated periodic syndromes | • **Chronic infantile neurologic cutaneous and articular syndrome:** neonatal onset of urticarial skin rash and arthropathy, chronic aseptic meningitis, brain atrophy and sensorineural hearing loss<br>• **Familial cold autoinflammatory syndrome:** recurrent episodes of urticaria-like skin rash that is triggered by exposure to cold associated with low-grade fever, general malaise, conjunctivitis, and arthralgia or myalgia<br>• **Muckle–Wells syndrome:** recurrent fever, recurrent urticaria-like skin rash, sensorineural deafness, generalized symptoms of inflammation (conjunctivitis, headaches, arthralgia or myalgia) and secondary amyloidosis |
| Tumour necrosis factor receptor–associated periodic syndrome | • Onset is usually in infancy or childhood but occasionally in adolescence or adulthood<br>• Episodes start with myalgia, joined by fever for 1–3 wk, accompanied by skin, joint, abdominal and ocular symptoms. Skin lesions may include centrifugal, migratory or erysipelas-like erythema, edematous plaques and urticarial lesions. Ocular symptoms can manifest as conjunctivitis, periorbital edema (pathognomonic) or uveitis. Serositis and secondary amyloidosis are common |
| Cyclic neutropenia | • Recurrent decrease in blood neutrophil counts (ranging from subnormal levels to severe neutropenia), usually with a cycle length of about 21 d<br>• Symptoms during the neutropenic phase include fever, mouth ulcers, pneumonia and peritonitis |
| Recurrent viral infections | • Common in preschool- and school-aged children, sick contacts<br>• Associated symptoms of coryza, cough |
| Infective endocarditis | • Janeway lesions, Osler nodes, splinter hemorrhages<br>• History of congenital heart disease with surgical repair |
| Immunodeficiency | • Recurrent deep-seated infections, poor response to antibiotics, failure to thrive<br>• Family history of immunodeficiency |
| Parasitic infection, such as malaria | • Associated travel history |
| Systemic lupus erythematosus | • Skin findings, positive immunologic criteria (antinuclear antibody or anti–double-stranded-DNA, anti-Smith, antiphospholipid, low complement, direct Coombs test) |
| Inflammatory bowel disease | • Can present with low-grade fever and abdominal pain. Predominantly gastrointestinal symptoms |
| Malignancy (leukemia, lymphoma) | • Weight loss, night sweats, bone pain, bruises, lymphadenopathy, hepatosplenomegaly |

After the patient developed new symptoms in 2015, genetics specialists were not consulted again until the patient requested a follow-up in 2020. She qualified for whole genome sequencing based on the Ministry of Health of Ontario's testing criteria of severe functional impairment, multisystem involvement and progressive clinical course. When FMF or another periodic fever syndrome is suspected, a gene panel for periodic fever syndromes can identify pathogenic DNA variants. When variants of unknown clinical importance or single pathogenic DNA variants are found, a diagnosis can still be made based on clinical findings, with the help of diagnostic criteria such as the Eurofever-PRINTO classification criteria.[1,8] Whole genome sequencing can be useful in patients with severe multisystem involvement, even in the absence of a clear diagnosis. A patient may also have more than 1 genetic disorder, as in our patient with FMF and hypermobile EDS.

Most patients with FMF are symptomatic by age 20 years.[4] In hindsight, the patient had fevers with severe abdominal pain a few times a year, starting in early childhood. Familial Mediterranean fever should be considered in a differential for recurrent fevers, peritonitis and elevated CRP (Table 2).

Treatment with colchicine is effective, preventing FMF flares in more than 60% of patients and reducing the number of attacks in a further 20%–30% of patients. Colchicine can also prevent deposition of amyloid fibrils and subsequent renal failure.[2–4,7,9] Anti–interleukin-1 biological therapy can be used in patients unresponsive to colchicine.[2–4]

The symptoms of FMF can mimic other conditions and, unfortunately, patients with FMF often experience years of misdiagnosis, unnecessary surgeries and prolonged hospital admissions.[4,6,10] Delays in diagnosis likely occur because of the lack of specificity in symptoms, and the relapsing and remitting pattern of disease. Furthermore, clinicians may not consider the disease in at-risk ethnic populations.[4]

## References


1. Sönmez HE, Batu ED, Özen S. Familial Mediterranean fever: current perspectives. *J Inflamm Res* 2016;9:13-20.
2. Kucuk A, Gezer IA, Ucar R, et al. Familial Mediterranean fever. *Acta Medica (Hradec Kralove)* 2014;57:97-104.
3. Ozen S, Demirkaya E, Erer B, et al. EULAR recommendations for the management of familial Mediterranean fever. *Ann Rheum Dis* 2016;75:644-51.
4. Borges T, Barbosa A, Silva S. Adult-onset systemic autoinflammatory disorders: a clinical approach. *Reumatismo* 2020;71:177-88.
5. Daniels M, Shohat T, Brenner-Ullman A, et al. Familial Mediterranean fever: high gene frequency among the non-Ashkenazic and Ashkenazic Jewish populations in Israel. *Am J Med Genet* 1995;55:311-4.
6. Lidar M, Tokov I, Chetrit N, et al. Diagnosis delay in familial Mediterranean fever: social and gender gaps disclosed. *Clin Exp Rheumatol* 2005;23:357-63.
7. Alomari M, Hitawala A, Chadalavada P, et al. Prevalence and predictors of gastrointestinal dysmotility in patients with hypermobile Ehlers-Danlos Syndrome: a tertiary care center experience. *Cureus* 2020;12:e7881.
8. Gattorno M, Hofer M, Federici S, et al. Classification criteria for autoinflammatory recurrent fevers. *Ann Rheum Dis* 2019;78:1025-32.
9. Demirkaya E, Erer B, Ozen S, et al. Efficacy and safety of treatments in familial Mediterranean fever: a systemic review. *Rheumatol Int* 2016;36:325-31.
10. Erdogan M, Ugurlu S, Ozdogan H, et al. Familial Mediterranean fever: misdiagnosis and diagnostic delay in Turkey. *Clin Exp Rheumatol* 2019;37:119-24.


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**Affiliations:** Schulich School of Medicine and Dentistry (Richard, Glazer, Demirkaya, Karp), Western University; Department of Pediatrics, Division of Rheumatology (Demirkaya) and of Medical Genetics (Karp), London Health Sciences Centre, London, Ont.

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**Correspondence to:** Natalya Karp, natalya.karp@lhsc.on.ca

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