Deep Dive Into Familial Mediterranean Fever in a Child Without Fever

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Abstract

This case report entails the details of a 12-year-old Egyptian boy who had recurrent episodes of shortness of breath, ascites, and pericardial effusions starting at the age of 10, returning with worsening symptoms in April of 2020. The lab findings indicated a critically elevated C-reactive protein (CRP) of 107.2 mg/L; a clinically notable inflammation process was festering. This case was all the more interesting as this boy did not present with a fever, making the diagnosis a difficult one. Nonetheless, genetic Mediterranean fever (MEFv) and polymerase chain reaction (PCR) testing confirmed the diagnosis of familial MEFv. Steroids and colchicine-salicylate decreased the frequency of the attacks and are now on half a dose of colchicine to keep his symptoms at bay. What we see here is the risk-to-benefit ratio of the therapeutic use of colchicine in children outweighs potential side effects such as nausea, vomiting, abdominal pain, diarrhea, kidney or liver failure. However, further research is needed to access better long-term treatment plans. Another key takeaway point that can be highlighted in this case is that the patient does not need to be febrile to diagnose FMF.

Categories: Genetics, Internal Medicine
Keywords: familial Mediterranean fever, infection, colchicine, rare genetic diseases, autoinflammatory disease

Introduction

Familial Mediterranean fever (FMF) is an inherited autoinflammatory disorder characterized by recurrent episodes of fever, peritonitis, arthritis, pleuritis, and rash [1]. Some long-term complications of FMF include systemic amyloidosis and renal impairment [2]. FMF typically occurs in individuals of Mediterranean origin, but it may affect people of any ethnicity [3]. Patients usually present with inflammatory attacks before the age of 20, and symptoms persist for three days or less before they are spontaneously resolved [1,4]. The Mediterranean fever (MEFv) gene encodes for the Pyrin protein, which regulates inflammation and innate immunity [4]. The diagnosis of FMF is predominantly clinical and may be confirmed by MEFv gene mutation analysis [5]. Colchicine is the gold standard treatment of FMF that prevents recurrent seizures and is protective against the development of renal amyloidosis due to MEFv gene mutations [6]. In recent years, clinical management options of FMF have expanded, but data of Egyptian descent remain limited. In this report, an emphasis is placed on the clinical presentation and management of a 12-year-old male patient who had an atypical presentation with MEFv gene mutation.

Case Presentation

A 12-year-old Egyptian male patient presented to the outpatient department with complaints of shortness of breath. On general physical examination, distant heart sounds and abdominal ascites were noted. A hemoglobin level of 10.6 g/dL indicating anemia was noted on laboratory testing, and he was admitted as an inpatient.

The echocardiogram revealed significant circumferential pericardial effusion, with no echocardiographic signs of cardiac tamponade. Thickening of the bilateral visceral and parietal pericardium was seen along with a shaggy appearing pericardial space and fibrinous threads all over, represented by maximal posterior dimensions measuring 1 cm and anterior dimensions measuring 0.5 cm in width. Other abnormalities on the echocardiogram were consistent with bilateral atrial enlargement, accompanied by a mild grade 1 diastolic dysfunction.

After these findings were noted, a pericardiocentesis was performed. The hematology report showed low hematocrit (HCT=35.2%), mean corpuscular hemoglobin (MCH=23.7 pg/cell), and elevated levels of red cell distribution width (RDW=15.7%). These levels were borderline normal.

A pleural fluid test was conducted to identify the cause of the pleural effusion. The pleural culture revealed a yellowish, turbid specimen with moderate amounts of pus on gram stain and lymphocytes on Leishman stain. The pericardial culture revealed a few pus cells on gram staining, however, the results were otherwise unremarkable. This patient’s sodium level was low (Na=136 mmol/L) and the C-reactive protein (CRP=107.2 mg/L) was critically elevated consistent with severe inflammation.

The patient was put on a steroid treatment of prednisolone 20 mg, three times a day, on which improvement was noted and the patient was discharged. After he was tapered off of the steroid treatment he returned to the hospital six months post-initial presentation with similar symptoms, namely pericardial effusion and ascites.

The MEFv genetic mutation was positive, which is the gold standard test for FMF. A polymerase chain reaction (PCR) test was done to confirm the diagnosis of FMF, which returned positive as well. Colchicine 1 mg, an anti-inflammatory drug, was commenced daily to which the patient responded with dramatic improvement. The patient was discharged after two weeks of colchicine therapy. On 6 months follow up, the patient was reviewed and the use of colchicine continued.
improvement.

There was no presence of family FMF history; however, the response to colchicine, radiological and laboratory results aided in the workup at the onset. Because FMF mainly affects the people of Mediterranean and Middle Eastern origin, it is essential to note that the afebrile presentation was primarily supported by response to therapy and was corroborated by MEFv gene confirmation.

One year post initial presentation to the outpatient department, the patient was being administered with colchicine 0.5 mg daily, which kept his symptoms subsided. Echocardiogram and ultrasound tests were conducted once a month to monitor the patient’s condition. On the last follow-up, the patient was progressing well, with no abnormal signs.

Discussion

In addition to the 12-year-old boy’s case, we conducted a literature review of 23 FMF cases (Table 1). Of the 23 reported cases, 11 originated from Turkey, three from Italy, and one each from Armenia, Colombia, Germany, Iran, Israel, Japan, Morocco, and Pakistan. When noting the FMF criteria, gene mutations were noted in all the listed cases, with nine heterozygous MEFv gene mutations, six homozygous mutations, and seven otherwise unspecified MEFv gene mutations. The most commonly reported clinical manifestations of disease included fever, abdominal pain, bloody or mucous diarrhea, diffuse myalgia, and rashes. On documenting the family history, eight of the 23 studies confirmed a positive family history with a sibling, parent, or the first-degree relative diagnosed with FMF or being heterozygous/homozygous for the same mutation. The laboratory values suggested a rise in serum amyloid A (SAA) of the included cases, in addition to elevated CRP, ESR, ALT, and AST levels. The most common treatment option was colchicine, given its importance as the gold standard treatment. However, the inclusion of recent reports (2016-2021) led to the elimination of biologics and chemotherapeutic drugs being prescribed with documented recovery among patients.

### Table 1

| No | Author          | Title                                                                 | Country | Age       | Gender | FMF criteria                      | Clinical Manifestations                                      | Family History | Lab Values                  | Intervention          |
|----|-----------------|------------------------------------------------------------------------|---------|-----------|--------|-----------------------------------|-------------------------------------------------------------|----------------|-----------------------------|-----------------------|
| 1  | Maggio et al.   | Familial Mediterranean fever: an unusual cause of liver disease       | Italy   | 10.6 years| Male   | Homozygous MEFv gene mutation     | Recurrent fever, aphthous stomatitis, rash, arthralgia,     | N/A            | SAA=33 mg/L, CRP=24.8 mg/dL, ESR=86, AST and ALT were elevated | Colchicine           |
|    |                 |                                                                        |         |           |        | associated with abdominal pain,  | vomiting, lymphadenopathy                                   |                |                             |                       |
| 2  | Atmış et al.    | Concomitance of familial Mediterranean fever and Gitelman syndrome in  | Turkey  | 9 years   | Male   | Homozygous MEFv gene mutation     | Recurrent abdominal pain, fever, joint pain, and swelling   | The patient has one sibling and was diagnosed with FMF      | Hypokalemia, hyponatremia, hypomagnesemia               | Colchicine           |
|    |                 | an adolescent                                                        |         |           |        |                                   | for 3 years                                                | homozygous M694V                                        |                             |                       |
| 3  | Javascript et al. | Tofacitinib for familial Mediterranean fever: a new alternative  | Colombia| 16 years  | Male   | Heterozygous MEFv gene mutation   | Recurrent fevers, cutaneous rash, and recurrent abdominal   | N/A            | N/A                         | Tofacitinib            |
|    |                 | therapy?                                                              |         |           |        |                                   | pain with diarrhea                                         |                |                             |                       |
| 4  | Yasuda et al.   | Canakinumab Eliminates Resistant Familial Mediterranean Fever in a    | Japan   | 7 years   | Female | Heterozygous MEFv gene mutation   | Recurrent febrile attacks including abdominal pain lasting  | N/A            | Elevated CRP                | Canakinumab          |
|    |                 | Japanese Girl                                                         |         |           |        |                                   | 2-3 days                                                  |                |                             |                       |
| 5  | Yıldırım et al. | Protracted febrile myalgia as a challenging manifestation of familial | Turkey  | Median=6 years | 3 Male | MEFv gene mutation                | Severe myalgia, fever, abdominal pain, diarrhea, and       | N/A            | N/A                         | Corticosteroids, NSAIDs, anakinra, anti-interleukin-1   |
|    |                 | Mediterranean fever: case-based review                                 |         |           | 2 Female |                                   | arthralgia/arthritis                                       |                |                             |                       |
| 6  | Gökçe et al.    | Polyarthritis nodosa in case of familial                               | Turkey  | 14 years  | Male   | Homozygous MEFv gene              | Fever, diffuse myalgia, abdominal pain,                     | N/A            | Leukocytosis, normal platelets, hemoglobin 13.3 normal area and creatinine ESR 93 | Prednisolone, azathioprine,         |
|    |                 |                                                                      |         |           |        |                                   |                                                             |                |                             |                       |
| Study | Title | Geographic Location | Age | Gender | Mutation | Symptoms | Treatment | Outcome |
|-------|-------|---------------------|-----|--------|----------|----------|-----------|---------|
| 7 Frenkel et al. | A novel treatment of temporomandibular joint arthritis as a complication in familial Mediterranean fever: literature review and a case report | Israel | 14 years | Female | Homozygous MEFV gene mutation | Painful swelling and redness over the involved TMJ area and severe trismus | Two siblings were diagnosed with FMF | High level of CRP (71) was noted | Colchicine |
| 8 Boytlor et al. | A case of familial Mediterranean fever having intermittent leukopenia | Turkey | 13 years | Female | Heterozygous MEFV gene mutation | Recurrent pain, swelling, and hyperemia attacks on her ankle | Mother and uncle were diagnosed with FMF in past | Elevated ESR, CRP, SAA, leukopenia, and neutropenia | Colchicine |
| 9 Yildirim et al. | Chronic non-bacterial osteomyelitis coexistent with familial Mediterranean fever | Turkey | 11 and 13 years | Male | Heterozygous MEFV gene mutation | Case 1: Persistent swelling at medial region of right clavicle, relapsing fever and concomitant osteomyelitis. Case 2: Fever, swelling, warmth of left shoulder | N/A | NSAIDs, colchicine, methotrexate |
| 10 Maggio et al. | Kawasaki disease triggered by EBV virus in a child with familial Mediterranean fever | Italy | 3 years | Male | Heterozygous MEFV gene mutation | Fever, non-saccular conjunctivitis, lymphadenitis of the neck, generalized, fixed rash | A 6-year-old and the father had the same gene mutation | Leukocytosis, hyponatremia (128 mEq/L), hypoaalbuminemia, elevated CRP, ESR, D-dimer, AST, ALT, SAA | Intravenous immune globulin, acetylsalicylate acid, h |
| 11 Farjadian et al. | A new MEFV gene mutation in an Iranian patient with familial Mediterranean fever | Iran | 12 years | Male | MEFV gene mutation | Recurrent episodes of fever abdominal pain, nausea, vomiting, and general myalgia | N/A | Elevated CRP, ESR | Colchicine |
| 12 Baysal et al. | Transient pancytopenia and granulocytic abnormalities after suicide attempt with colchicine in a patient with familial Mediterranean fever | Turkey | 16 years | Female | MEFV gene mutation | Vomiting, Diarrhea | N/A | Pancytopenia | Colchicine |
| 13 Cazzolla et al. | Orthopedic and orthodontic management in a patient with DiGeorge Syndrome and familial Mediterranean fever: a case report | Italy | 8 years | Male | MEFV gene mutation | Recurrent fever episodes, arthritias, polyserositis, hepatic-splenomegaly | Mother and maternal cousin of first degree were affected | N/A | Immunosuppressive agents, colchicine, antihypertensive therapy, calcitriol, erythropoietin |
| 14 Gökçe et al. | Polyarteritis nodosa in case of familial Mediterranean fever | Turkey | 14 years | Male | Homozygous MEFV gene mutation | Fever, diffuse myalgia, abdominal pain and purpura | No family history | Leukocytosis, elevated ESR, CRP, and proteinuria | Colchicine |
| 15 Demir et al. | Systemic amyloidosis in a patient with familial Mediterranean fever and Hodgkin | Turkey | 12 years | Female | Heterozygous MEFV gene mutation | Abdominal pain and episodes of fever | Consanguinity marriage; three sons of her uncle had been | Elevated SAA, CRP, and ESR | Colchicine (2 mg/day); anakinra (2 mg/kg/day); dexamethasone, bleomycin, |
| Case Report | Description | Country | Age | Gender | MEFV Gene Mutation | Symptoms | Treatment | Outcome |
|-------------|-------------|---------|-----|--------|-------------------|----------|-----------|---------|
| Aydoğdu et al. | An extraordinary complication in a child with combined familial Mediterranean fever and inflammatory bowel disease: multiple ileal perforations | Turkey | 5 years | Female | Heterozygous MEFV gene mutation | Fever, abdominal pain, vomiting | Elevated CRP and ESR | Recovery |
| Sag et al. | Neonatal ulcerative colitis associated with familial Mediterranean fever: a case report | Germany | 3 months | Female | Homozygous MEFV gene mutation | Bloody and mucous diarrhea, two episodes of high fever | Elevated CRP | Colchicine |
| Ceylan et al. | Intermittent right bundle branch block in a child with familial Mediterranean fever | Turkey | 8 years | Male | Heterozygous MEFV gene mutation | N/A | N/A | Recovery |
| Zerkaoui et al. | A novel single variant in the MEFV gene causing Mediterranean fever and Behçet’s disease: a case report | Morocco | 10 years | Female | MEFv gene mutation | Periodic fever, abdominal pain, mucocutaneous symptoms, and joint pain | The mother was normal, and her father was heterozygous for the same mutation | Elevated CRP | Colchicine, methylprednisolone, opioids, intravenous anticoagulation for sinus thrombosis |
| Yoldas et al. | Massive pericardial effusion and tamponade can be a first sign of familial Mediterranean fever | Turkey | 10 and 13 years | Male, Female | Heterozygous MEFV gene mutation | Chest pain, dyspnea, and fever | Elevated ESR, CRP | Colchicine |
| Shahsuvaryan et al. | Is plasmapheresis a potential treatment for familial Mediterranean fever patients resistant or intolerant to colchicine? | Armenia | 17 years | Female | MEFv gene mutation | Recurrent attacks of fever and abdominal pain | Elevated ESR and CRP | Colchicine |
| Maggio et al. | PAPA and FMF in two siblings: possible amplification of clinical presentation? A case report | Italy | 8.4 and 16 years | Male | Homozygous MEFV gene mutation | Fever, oral aphthous stomatitis, abdominal pain, arthritis, undefined dermatitis, vomiting, diarrhea | Both parents were heterozygous for the same mutation p.M680I | Elevated AST, ALT, CRP, ESR, SAA, leukocytosis with neutrophilia | Colchicine |
| Hong et al. | Autoinflammation due to homozygous S208 MEVF mutation | Pakistan | 9 and 12 years | Male | MEFV gene mutation | Recurrent fever, oral ulceration, purpuric rashes, arthropalgia, eosinophilia, and osteitis | No family history of genetic testing | Elevated SAA, CRP, and leukocytosis | Lipopolysaccharide, IL-1 blockade |

**TABLE 1: Characteristics of study findings of cases reported from 2016-2021.**

ALT=alanine transaminase; AST=aspartate aminotransferase; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; N/A=not available; RBBB=right bundle branch block; SAA=Serum amyloid A.

The striking feature of our case presentation is the fact that the young male patient did not present with fever, similar to findings observed by Hotta and Mattiassich et al. [7,8]. Cekin and Aslan et al. [9,10] had identical complaints to our patient comprising abdominal ascites. Aslan et al. [10], however, did not note...
abdominal pain, which was identified by Tatar and Lee et al. [11,12], but without distention secondary to ascites. Incidentally, it was discovered soon after the initial workup that our patient also had added heart sounds, who was later diagnosed to have pericardial effusion. Abukhalaf and Ceylan et al. [13,14] also reported cardiac complications among their patients, namely cardiac amyloidosis and right bundle branch block, respectively.

Despite the differences in age groups, clinical presentations, family history, or laboratory results, colchicine remains the first-line treatment modality for a majority of the tabulated patients, with documented recovery. However, Ceylan et al. point out an unprecedented view of FMF, where colchicine may exacerbate pre-existing cardiac conditions [14]. Even though the presentation was an isolated incident, it is pivotal to monitor colchicine during and post-administration on a regular basis. When identifying clinical practice points highlighted with our case and subsequent tabulation of recent trends in treatment, it is pertinent to note the European League Against Rheumatism (EULAR) recommendations for FMF management supported by the best evidence available [15]. As with EULAR recommendations, the best management strategy for FMF is to control acute attacks, minimize any chronic subclinical inflammation, improve the acceptable quality of life, and prevent recurring complications.

While FMF is mostly a clinical diagnosis, laboratory analysis may reveal elevated white blood cell count with peaked neutrophil. An elevation of acute-phase reactants, such as erythrocyte sedimentation rate (ESR), SAA, and CRP, is not uncommon. Radiological testing may be utilized to reveal other causes of abdominal pain, such as the acute abdomen. Gene mutation testing may be utilized to confirm the diagnosis with atypical presentations, particularly in non-endemic areas.

Overall, a central challenge for interprofessional healthcare teams managing FMF is to reach a diagnostic conclusion. Education about the etiology, family history, and testing options, in addition to associating typical or atypical clinical presentations to FMF, is necessary. Once the diagnosis is established, the clinician, nurse, and other providers ought to work closely. The use of colchicine, in addition to biologics and chemotherapeutic drugs along with noting the normal or abnormal clinical presentation, is essential in any clinical setting.

Conclusions

FMF is the most common autoinflammatory disease. The usual presentation of FMF in patients is fever; but in this case, the patient was afebrile whereas the diagnosis was confirmed on PCR testing. Colchicine, which has been the prescribed treatment for FMF since 1972, has shown a promising impact on patient conditions and is currently the first-line treatment for management. Further research is needed to access better long-term treatment plans such as the use of biologics namely anti-interleukin 1, anti-interleukin 6, Janus kinase inhibitors, and anti-TNF drugs. It is recommended that colchicine-resistant and intolerant cases be monitored for certain cytokines, along with genetic studies to improve clinical outcomes and compliance to treatment in endemic countries.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Fatima Jinnah Medical University issued approval Not applicable. The patient signed an informed consent form as per the ethical guidelines of the hospital board. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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