Atypical Autosomal-Dominant Inheritance of Familial Mediterranean Fever

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ABSTRACT

Familial Mediterranean fever (FMF) was previously believed to be an autosomal recessive disease. We present a patient with only one pathogenic variation of the MEFV gene due to the c.2177T>C mutation. The patient had clinical features of recurrent fevers and abdominal pain, serositis, and a history of multiple abdominal surgeries for pain. He was eventually diagnosed with FMF. This case report demonstrates an example of the rare autosomal-dominant phenotype of FMF.

INTRODUCTION

Siegal first described familial Mediterranean fever (FMF) in 1945 as “benign paroxysmal peritonitis.” FMF is characterized by paroxysmal abdominal pain, joint and chest pains, and fevers of unknown origin. It is typically categorized as an autosomal recessive disorder and occurs in patients of Turkish, Armenian, Iranian, Jewish, Spanish, and Mediterranean ethnic groups. The disease occurs by mutations in the MEFV gene on chromosome 16, which encodes pyrin. Pyrin seems to be responsible for the regulation of inflammation, apoptosis, and cytokines on mononuclear cells. Mutations cause multiprotein complexes are known as inflammation to malfunction, resulting in caspase-1 activation and interleukin (IL)-1β release, which ultimately contributes to the presenting symptoms. It seems to bind to interferon and normally suppresses excessive inflammasome activation and IL-1β activation. In FMF, this interaction seems to be blunted. Overall, FMF’s impaired pyrin inflammasomes cause excessive and extended inflammatory responses with blunting of normal autophagy and apoptosis. As a primarily autosomal recessive disorder, autosomal dominant inheritance of FMF is rare. There are 9 recognized mutations of autosomal-dominant mutations. The mutation presented in this patient, c.2177T>C, causes Val726Ala. This modification of the MEFV’s 10th exon has been associated with FMF. We present one copy of a the p.Val726Ala mutation was found. This case represents an atypical (autosomal dominant) inheritance of a common FMF mutation.

CASE REPORT

The patient is a 34-year-old man of Irish, German, and Spanish descent who presents to the clinic with recurrent attacks of generalized abdominal pain, nausea, vomiting, fever, arthralgia, and fatigue for the past 4 years. His symptoms were chronic and intermittent, with increasing frequency for the past 2 years. His abdominal pain is described as sharp, radiating to the back, and associated with multiple episodes of fasting diarrhea. Pertinent family history includes fibromyalgia and rheumatoid arthritis in his mother and ulcerative colitis in his maternal aunt.

He was hospitalized multiple times for severe dehydration secondary to the above symptoms. During his most recent hospitalization, he complained of right lower quadrant abdominal pain, fevers, and subacute worsening diarrhea. A computed tomography scan of his abdomen showed findings concerning for acute appendicitis and small bowel obstruction. He underwent a diagnostic laparoscopy with appendectomy and a 20-cm small bowel resection. Pathology revealed an inflamed jejunum with fibrous obliteration, serosal adhesions, and enteritis with cryptitis, but a normal appendix. His postoperative course was complicated by a high-grade
bowl obstruction requiring another diagnostic laparoscopy, resulting in further lysis of adhesions and an additional 50-cm small bowel resection.

Laboratory workup was remarkable for antinuclear antibody test 1:160 (homogeneous pattern), elevated C-reactive protein to 5.7 mg/dL, erythrocyte sedimentation rate of 23 mm/hr, and thyroid-stimulating hormone of 10 IU/mL. Inflammatory bowel disease was effectively ruled out with negative biopsies, endoscopy, video capsule endoscopy, and magnetic resonance enterography.

Because of the specific constellation of fevers, abdominal pain, and arthralgias, the patient was sent for autoimmune workup and was found to have positive MEFV gene analysis for FMF. A single gene pathogenic variation, c.2177T>C (p.Val726Ala), was found. He received a short trial of 3 months of colchicine and steroids, without significant improvement in his symptoms. The patient was referred to rheumatology and had symptomatic improvement in the severity of diarrhea and abdominal pain after a trial of amitriptyline and canakinumab. The canakinumab response, an IL-1 beta antibody, is observed because of continued attacks of abdominal pain and worsening diarrhea. The patient meets a diagnosis of FMF based on the Livneh et al criteria.23 Thus far, the patient has had no evidence of renal amyloid, no protein found in urine, and no elevation in creatinine. This case illustrates the importance of including clinical data in the interpretation of a genetic test, in this case, for an unusual genotype of FMF.

DISCUSSION

Symptomatic FMF from a single MEFV mutation suggests an autosomal dominant inheritance. Although FMF is viewed as an autosomal recessive disorder, recent evidence suggests additional complexity, supported by the work of Marek-Yagel et al. The study postulated that FMF may be represented as an autosomal dominant disorder with low penetrance rather than an autosomal recessive disorder.16 In a 2009 study by Booty et al., with phenotypical FMF secondary to a single identified MEFV mutation, the MEFV reverse transcription-polymerase chain reaction levels and pyrin expression levels were found to be similar in patients with one mutation vs those with 2 mutations. Ancestry of this population was more likely atypical, had a more mixed heritage, and was commonly of Spanish heritage, as in our patient.17 Evidence shows that asymptomatic carriers of one FMF mutation have subclinical inflammation.18 In nearly 30% of individuals with an FMF phenotype, no second allele is found.17,19,20 Variation in expression of the severity of the FMF phenotype and the susceptibility to amyloidosis is associated with specific MEFV mutations and its modifying alleles. Additional theories to explain the absence of a second mutation in an autosomal disease includes epigenetic mechanisms, genetic variations in the inflammatory cascade, and environmental factors.21,22

This case is notable for autosomal dominant diagnosis of FMF. He had “attacks” roughly monthly consisting of abdominal pain, joint pains, symptom-free intervals, transient inflammatory response, and repeated laparotomies. The patient did not tolerate a 3-month course of colchicine with prednisone because of attacks of abdominal pain and worsening diarrhea. The patient meets a diagnosis of FMF based on the Livneh et al criteria.23 Thus far, the patient has had no evidence of renal amyloid, no protein found in urine, and no elevation in creatinine. This case illustrates the importance of including clinical data in the interpretation of a genetic test, in this case, for an unusual genotype of FMF.

REFERENCES

1. Siegal S. Benign paroxysmal peritonitis. Gastroenterology 1949;12(2): 234–47.
2. Kogan A, Shinar Y, Lidor M, et al. Common MEFV mutations among Jewish ethnic groups in Israel: High frequency of carrier and phenotype III states and absence of a perceptible biological advantage for the carrier state. Am J Hum Genet 2001;102(3):272–6.
3. Gershoni-Baruch R, Shinawi M, Leah K, Badarnah K, Brik R. Familial Mediterranean fever: Prevalence, penetrance and genetic drift. Eur J Hum Genet 2001;9(8):634–7.
4. Aldea A, Calafell F, Aróstegui JJ, et al. The west side story: MEFV haplotype in Spanish FMF patients and controls, and evidence of high LD and a recombination “hot-spot” at the MEFV locus. Hum Mutat 2004;23(4):399.
5. Moradian MM, Babiyan D, Banoian D, et al. Comprehensive analysis of mutations in the MEFV gene reveal that the location and not the substitution type determines symptom severity in FMF. Mol Genet Genomic Med 2017;5(6):742–50.
6. Manukyan G, Aminov R. Update on pyrin functions and mechanisms of familial Mediterranean fever. Front Microbiol 2016;7:456.
7. Sari I, Birlik M, Kasifoglu T. Familial Mediterranean fever: An updated review. Eur J Rheumatol 2014;1(1):21–33.
8. Hoffman HM, Wanderer AA. Inflammamsose and IL-1 beta-mediated disorders. Curr Allergy Asthma Rep 2010;10(4):229–35.
9. Schnappauf O, Chae JJ, Kastner DL, et al. Genotype-phenotype correlation in FMF patients: A non classic recessive autosomal or “atypical” dominant autosomal inheritance? Gene 2018;641:279–86.
10. Touitou I. The spectrum of familial Mediterranean fever (FMF) mutations. Eur J Hum Genet 2001;9(7):473–83.
11. Neocleous V, Costi C, Kyriakou C, et al. Familial Mediterranean fever associated with MEFV mutations in a large cohort of Cypriot patients. Ann Hum Genet 2015;79(1):20–7.
12. Jarjour RA, Al-Berrawi S. Familial Mediterranean fever in Syrian children: Phenotype-genotype correlation. Rheumatol Int 2015;35(4):629–34.
13. Marek-Yagel D, Berkun Y, Padeh S, et al. Clinical disease among patients heterozygous for familial Mediterranean fever. Arthritis Rheum 2009;60(6):1862–6.
14. Neocleous V, Costi C, Kyriakou C, et al. Familial Mediterranean fever with a single MEFV mutation: Where is the second hit? Arthritis Rheum 2009;60(6):1851–61.
18. Tunca M, Kirkali G, Soytürk M, Akar S, Pepys MB, Hawkins PN. Acute phase response and evolution of familial Mediterranean fever. *Lancet* 1999; 353(9162):1415.

19. Medlej-Hashim M, Rawashdeh M, Chouery E, et al. Genetic screening of fourteen mutations in Jordanian familial Mediterranean fever patients. *Hum Mutat* 2000;15(4):384.

20. Cazeneuve C, Sarkisian T, Pécheux C, et al. MEFV-gene analysis in Armenian patients with familial Mediterranean fever: Diagnostic value and unfavorable renal prognosis of the M694V homozygous genotype-genetic and therapeutic implications. *Am J Hum Genet* 1999;65(1):88–97.

21. Manna R, Rigante D. Familial Mediterranean fever: Assessing the overall clinical impact and formulating treatment plans. *Mediterr J Hematol Infect Dis* 2019;11(1):e2019027.

22. Rigante D, La Torraca I, Avallone I, Pugliese AL, Gaspari S, Stabile A. The pharmacologic basis of treatment with colchicine in children with familial Mediterranean fever. *Eur Rev Med Pharmacol Sci* 2006;10(4):173–8.

23. Livneh A, Langevitz P, Zemer D, et al. Criteria for the diagnosis of familial Mediterranean fever. *Arthritis Rheum* 1997;40(10):1879–85.

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