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Familial Mediterranean Fever and Inflammatory Bowel Disease Associated Arthritis in Palestinian Adult: Case Report with Review of Literature.

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Abstract

Familial Mediterranean fever is an inflammatory disorder that presents with episodes of fever and abdominal pain, caused by autosomal recessive mutations. Arthritis and skin involvement can also be seen in FMF. Inflammatory Bowel Disease is another, more common, inflammatory disorder affecting both small and large intestines. It has two types: Ulcerative Colitis (UC) and Crohn's Disease (CD). IBD can be associated with arthritis as well. We report a patient suffering from both FMF for 20 years and IBD for 12 years who then developed arthritis in the last year.

This case illustrates the importance of differentiating between arthritis associated with IBD and that seen with FMF. Also, it implies the significance of FMF on the incidence of IBD.

Introduction

Familial Mediterranean Fever (FMF) is a common hereditary auto-inflammatory periodic fever syndrome characterized by recurrent episodes of fever and severe abdominal pain, as well as monoarthritis and skin manifestations in some cases the disease is caused by autosomal recessive mutations in the MEFV gene located on chromosome 16 (16p13.3) **[1]**. FMF is most commonly found in the Middle East but can also occur in other populations. It affects both sexes equally, with symptoms usually appearing in childhood. The prevalence of FMF varies from 1 in 500 to 1 in 1,000 in endemic countries, with Turkey having the highest number of FMF patients due to its high prevalence and large population size **[2]**. Over 80 different mutations in the MEFV gene have been identified, with most disease-causing mutations occurring in exon 10 and potentially in exons 1, 2, 3, 5, 8, and 9 **[3]**.

Inflammatory Bowel Disease (IBD) refers to two major chronic relapsing inflammatory disorders of the bowel: Crohn's disease (CD) and ulcerative colitis (UC). The pathogenesis of IBD involves dysfunctions in innate and adaptive immune pathways, with mucosal immunity, particularly the T cell response, playing a major role. A Th1 response drives CD while UC is associated with a non-conventional Th2 response, with Th17 cells also being involved in the gut inflammatory response in IBD **[4]**.

FMF has been shown to facilitate the manifestation of associated inflammatory diseases, such as IBD. A large cohort study reported that the frequency of IBD in FMF patients was 1.6% **[5]**. In this case report, we present a 48-year-old Palestinian female patient who presented with recurrent attacks of arthritis initially confused as FMF, but later attributed to IBD. We conducted a literature review to find similar cases.

Case presentation

A 49-year-old female patient with a known history of Familial Mediterranean Fever (FMF) and Ulcerative Colitis (UC) presented at the rheumatology clinic with a complaint of joint pain that had been present for the past year. **[Figure 1]**

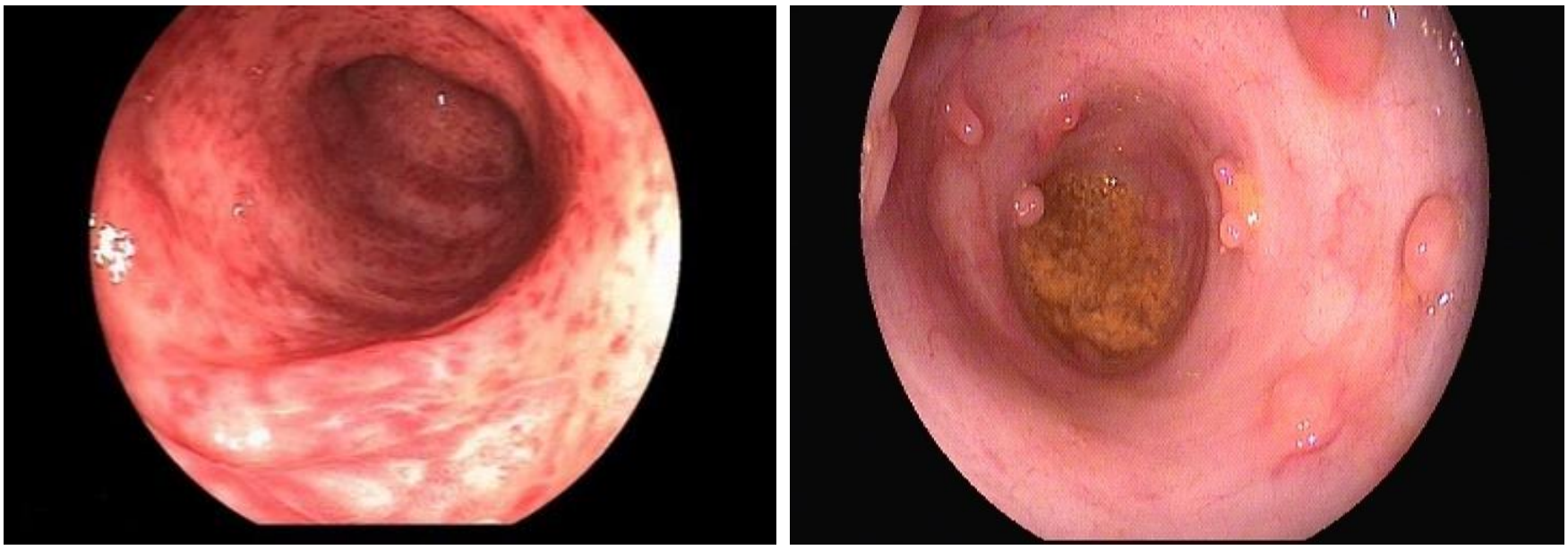

Figure 1: The upper endoscopic view is seen on the left. A colonoscopic view showing Ulcerative colitic lesions is seen on the right.

The patient had been in good health until one year prior when she began to experience symmetrical polyarticular joint pain in her small joints of both hands, wrists, and elbows. Over the last three months, the pain had worsened, becoming progressive and more severe in the mornings, with associated morning stiffness lasting for approximately two hours, swelling of the joints, paresthesia, fatigue, and limitations in movements. The patient reported no changes in skin color, fever, weight loss, skin rash, photosensitivity, oral ulcers, or nail changes.

Her medical history was significant for a 20-year history of FMF, a 12-year history of UC that had required multiple endoscopies, disc disease affecting four intervertebral discs, mild sensorineural hearing loss, a previous COVID-19 infection, and amenorrhea over the past two years. Her surgical history was unremarkable.

The patient was taking the following medications: Colchicine 0.5mg, Methylprednisolone 4mg, Celecoxib 200mg, Azathioprine, and Mesalazine (Pentasa). She occasionally used Esomeprazole.

Her family and social history revealed that she was a widow and the ex-husband was a first-degree cousin. She had five sons, two of whom had FMF, and her brother had UC. The patient had no known drug allergies.

On Examination

Symmetrical joint tenderness of both PIPs and MCPs

Few PIPs swelling

Right elbow swelling and tenderness

Left elbow tenderness

Laboratory Investigations

PPD SKIN TEST – NEGATIVE (recently-about 2 months ago).

Rheumatoid factor -ve (6 years ago)

FMF genetic test (16 years ago) this patient is heterozygous for one mutation M694V, which means that one copy of the gene is mutated(abnormal) and the other copy is normal.

The heterozygosity may not explain her clinical phenotype which might be attributed to an alteration in other factors in the MEFV (pyrin) pathway.

COLONOSCOPY (12 years ago) To 25 Cm Above Anus, The Mucosa is Severely Inflamed with Ulcers, Exudative Discharge and Oozing Blood Compatible with Severe Ulcerative Colitis. Severe Proctosigmoiditis.

Discussion

Familial Mediterranean Fever (FMF) is a hereditary periodic syndrome with a high prevalence in the Middle East and particularly in Arab countries **[6,7]**. According to available data, the estimated prevalence of FMF can range from 1:400 to 1:1000 in different countries, based on the ethnic group **[8-10]**. This disease is more commonly found in ethnic groups such as Sephardic Jews, Turks, Arabs, and Armenians. Despite the high prevalence of FMF, formal epidemiological studies have not been carried out in all populations, making it difficult to determine the exact frequency.

FMF is associated with a high degree of morbidity, and there is evidence linking it to several chronic inflammatory diseases such as rheumatoid arthritis, Henoch-Schonlein purpura, polyarteritis nodosa, chronic arthritis, systemic lupus erythematosus, and Crohn's disease (CD) **[11-13]**. The underlying mechanism linking these diseases is thought to be the presence of MEFV mutations.

A recent systemic review and meta-analysis, conducted in 2021, explored the relationship between MEFV mutations and inflammatory bowel disease (IBD) **[14]**. The study included 937 patients and 977 controls and found that the rate of MEFV mutations was 0.238 (95%CI: 0.209-0.270; I 2 =95%) in IBD patients. The frequency of MEFV mutations was found to be higher in IBD patients compared to controls, with p=0.03 for ulcerative colitis (UC) and p=0.01 for CD and indeterminate colitis (IC). Subgroup analysis showed that MEFV mutations were more common in patients with IC compared to UC and CD (I 2 =91%, p<0.001). Patients with extra-intestinal manifestations and pancolitis had a 2.57 (95%CI 1.07-6.14; p=0.03) and 2.02 (95%CI: 1.01-4.04, P=0.049) odds ratio, respectively, of carrying MEFV mutant genotypes.

There have been few studies and case reports describing patients with both FMF and IBD, particularly ulcerative colitis **[15]**. However, most of these cases have presented with abdominal pain and fever, unlike our patient who had a history of polyarticular joint pain. The patient was diagnosed with FMF in 2006 based on genetic testing that showed she was heterozygous for the M694V mutation. She was later diagnosed with UC in 2010 following a colonoscopy. Although it is rare to find a patient with FMF and polyarticular arthritis, this is a common symptom in patients with ulcerative colitis **[16]**. This case highlights the importance of considering the co-occurrence of both FMF and UC in patients presenting with polyarticular joint pain.

Conclusion

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It has been established that the MEFV gene mutation is more prevalent among individuals with Inflammatory Bowel Disease (IBD). This mutation is also known to cause Familial Mediterranean Fever (FMF). Despite this association, there is a need for additional studies to clarify the relationship between FMF and IBD, especially in instances where the predominant symptoms are polyarthritis instead of the typical symptoms of FMF, such as abdominal pain and fever. This is particularly relevant in the case of our patient, who primarily presents with symptoms of polyarthritis.

Ethical approval

The study is exempt from ethical approval in our institution.

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Registration of research studies

Not applicable.

Provenance and peer review

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Declaration of competing interest

The authors declare no conflicts of interest.

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