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Case Report

Familial Mediterranean Fever Triggered by Menstruation – A Case Report from Zambia

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Abstract:

Familial Mediterranean Fever (FMF) is an autoinflammatory autosomal-recessive disorder that is characterized by recurrent attacks of abdominal pains, fevers and serositis. It is highly prevalent among people from the Mediterranean basin including Arabs and Turks. However, due to the increase in migration worldwide, we start to recognize cases of FMF outside the Mediterranean region. We present the case of a 27-year-old Lebanese female residing in Zambia whose recurrent attacks constantly coincided with her menstruation. Due to the rarity of occurrence of FMF in regions such as Zambia, the coming up with the diagnosis was delayed and unnecessary interventions such as exploratory laparotomy were done. This case aims to highlight the importance of considering FMF and its potential triggers especially menstruation by the healthcare providers in non-Mediterranean areas to ensure timely recognition and management to avoid serious future complications such as amyloidosis.

Keywords: Familial Mediterranean Fever (FMF), Menstruation, Trigger, MEFV gene, Abdominal pain.

Introduction

Familial Mediterranean Fever (FMF) is a hereditary, autosomal recessive disorder that is characterized by recurrent, self-limited episodes of fevers, sterile peritonitis and other serositis [1]. This disease is quite common among people originating from Mediterranean ancestry such as Arabs (including Lebanese, Libyans etc.), Turks, Armenians, and Jews [2]. Some of the known provoking factors of the attacks of FMF include; emotional stress, trauma, cold weather and menstruation. Several studies were conducted on women suffering from FMF to identify the potential triggers for the attacks and menstruation was a significant factor among them [3, 4]. Since the symptoms highly resemble gynecological disorders and other causes of acute abdomen, there is an increased likelihood of misdiagnosis and unnecessary surgeries. Laboratory tests such as Complete blood Counts (CBC) usually show nonspecific changes in these patients. However, during the attacks, Acute phase reactants (including ESR and CRP) were noticed to be elevated in most patients [5, 6]. We herein present a case report of a Lebanese female living in Ndola, Zambia who came to our clinic with abdominal pains and fevers repeatedly associated with her menstruation for 5 years. Lack of encountering FMF in our region prolonged diagnosing our patient, but she was eventually correctly diagnosed and treated.

Case Presentation

A 27-year-old Lebanese female who has been residing in Zambia for over 20 years presents to our clinic in December 2023, with complaints of a sudden attack of generalized abdominal pain that was accompanied with acute onset of fever and 2 episodes of vomiting. These symptoms had started on her day of admission early in the morning and she came to our clinic 3 hours after the onset. Her symptoms were also accompanied with right knee joint pain that started later that day.

Past Medical History

According to our patient, these symptoms were recurrent monthly for the past 5 years and were usually associated with her menstruation. The attacks lasted 3-4 days with varying severity and resolved spontaneously with her menstruation that also lasted approximately 5 days. She started menstruating at the age of 15 years and had a regular menstrual cycle occurring every 28 days. Before the start of these episodes, the patient described that her menstruation did not occur with painful cramps and stated that the abdominal pains only started 5 years ago. She led a completely normal life in between the attacks and did not suffer from anything else.
Due to the severity of her attacks, she was admitted to about two different hospitals in the past few years several times. At first it was thought to be primary dysmenorrhea, but due to the severity and the specific pattern, more investigations were carried out. Various laboratory tests and imaging were done but all were negative, and the cause of her attacks remained unknown. She was also treated with systemic antibiotics previously, but no improvement was shown. 5 months earlier to her admission in our clinic, she had also undergone Exploratory Laparotomy to exclude possible surgical causes of peritonitis that were suspected but no pathological findings were found, and the course of her attacks continued.

Personal History

The patient has no history of smoking or alcohol drinking. She has no history of allergies, any infectious diseases, or chronic diseases. No history of blood transfusions.

No family history of FMF or other hereditary diseases was recorded.

Differential Diagnosis Listings

1. Familial Mediterranean Fever
2. Pelvic Inflammatory Disease (PID)
3. Other Gynecological causes such as ovarian cyst torsion, ruptured ovarian cyst

Physical Examination on Admission

General examination revealed a distressed patient with normal level of consciousness. Vital signs were as follows; Temperature 38.2°C, Respiratory Rate (RR) 23/min, Heart Rate (HR) 110/min, Oxygen Saturation 97%, Blood Pressure 126/82mmHg.
Abdominal palpation revealed generalized abdominal tenderness accompanied with guarding and rebound tenderness. Joint examination revealed right knee joint pain out of proportion to the swelling with no limitation of movement. No joint deformity was found, and there was no organomegaly or lymphadenopathy. Thyroid examination was normal.
A gynaecological examination was also conducted and revealed no abnormalities.
All other systemic examinations were unremarkable.

Initial Diagnostic Workups

Complete Blood Count (CBC) results; Hb 11.2g/L, WBC 17 x 10^9/L, Platelet 230 x10^9/L, Neutrophils 14.69 x10^9/L – Conclusion; Leucocytosis with predominant neutrophils.
Erythrocyte Sedimentation Rate (ESR) in 1st hour was elevated – 24 mm/hr.
C-reactive protein elevated - 9 mg/L
Kidney Function Tests, Liver Function Tests and Urinalysis were all normal. Random Blood Sugar (RBS) was 5.3mmol/L.
Both malaria test and typhoid Fever test were negative.
Patient was menstruating – no pregnancy.
Abdominal Ultrasound was conducted, and no pathological lesion was found. Electrocardiography (ECG) showed no abnormalities.

Diagnosis and Initial Therapy

After the physical examination and diagnostic workups, the gynaecological causes of the symptoms of our patient were ruled out as it was less likely and diagnosis of FMF was made clinically. The patient was started on colchicine – 500 mcg (1 tablet) twice a day.
Fortunately, there was positive response and the following month the patient did not show any symptoms of the attacks, making a definitive diagnosis of FMF by the Tel-Hashomer Diagnostic criteria after meeting 2 major criteria (recurrent febrile attacks with peritonitis and favourable response to colchicine).

Follow Up and Outcomes

The patient continued with the colchicine therapy from December 2023, up to date (June 2024), with positive response, good tolerance, and no side effects. The dose of colchicine was lowered to 500mcg once daily. Patient did not develop any complications from the disease itself or the treatment till this day. Colchicine therapy will be continued with the same dose.

Discussion

FMF symptoms include episodes of abdominal pain, fever, arthritis, pleuritis and even sometimes pericarditis. These episodes can vary from one person to another in severity and triggers.One known trigger factor is menstruation. The concept of menstruation-induced FMF has been recorded in several case studies and a few case reports that have been published before. One of the early studies by Ben-Chetrit E, 2001 had shown that 10 out of 141 females that is 7%, had their attacks triggered by menstruation [3]. Another study was conducted some years later, by Karadag O et al, 2013 that comprised 275 FMF patients of which 98 were females and 33.7% of this number revealed to have menstruation-associated FMF [4]. Using a standardized questionnaire among 72 female patients, it was also shown that 53% of them had correlation with their menstruation [7]. One of the recent retrospective studies was done on Japanese patients with FMF, of which menstruation was the most common trigger among the females by 39.7% [8]. Few other case reports with patients having menstruation as their provoking factor have also been published. One of the first recorded cases was presented by Schwartz J in 1960 [9]. Other trigger factors also identified and include psychological and physical stress, cold weather and infections [4].

Diagnosis of FMF using the Tel Hashomer Diagnostic criteria has been a common practice for many years. This criterion helps us suspect the disease clinically. Meeting 2 major or 1 major and 2 minor criteria provides a definitive diagnosis [10]. In our case, our patient had recurrent peritonitis and fever and showed a positive response on Colchicine therapy making us draw a conclusion of FMF diagnosis based on these diagnostic criteria.
Acute Phase reactants especially CRP and ESR show elevations during the attacks and usually return to normal levels shortly after the attack. Serum Amyloid a (SAA) has also shown to be increased once the attack begins [5, 11]. As was seen in our patient, during the attack, her ESR and CRP levels were elevated and there was also an increase in the WBCs.
An additional way of confirming the diagnosis is genetic testing of pathogenic variants of the MEFV gene, however it is not currently available in Zambia and other countries.
Colchicine therapy has been widely used for the prophylaxis of FMF attacks. In the 1970s a double-blind controlled trial was carried out and showed the efficacy of colchicine when used as prophylaxis with the evident reduction in the number of attacks the patients experienced [12]. The preferred dose of colchicine is 1.0-1.5mg per day for adults, to reduce the duration and severity of attacks and prevent the long-term complication of Amyloidosis in these patients [13].
There has also been recorded evidence of the efficacy of Colchicine in patients that have menstruation-induced FMF [3, 14].
Some patients have no favorable response to Colchicine or poor tolerance and thus the use of biologic drugs such as Interleukin

1 receptor antagonists such as Canakinumab and Anakinra has been recommended [15,16].

Conclusion

This case underscores the diagnostic challenges that could be faced in non-Mediterranean regions such as Zambia, as FMF can sometimes be overlooked by healthcare practitioners due to its rarity in these regions. It also highlights the importance of considering it as a potential diagnosis with patients presenting with unusual attacks during their menstruations. FMF could be misleading and can direct us to unnecessary invasive procedures and thus we should always keep it in our minds.

Patient Consent

Informed consent was obtained from the patient

Conflict of interest: None

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Author contributions

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