Case Report

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Familial Mediterranean fever: a differential diagnosis for the surgical abdomen

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Abstract

FMF is characterised by dysregulation of the inflammatory process in the body, presenting as recurrent episodes of serositis. Patients with FMF commonly present with episodes of fever, peritonitis, synovitis, pleuritis, arthritis, and occasionally pericarditis. We present a case of a young 19-year old female, who presented to hospital four times over several months with intermittent fevers, abdominal pain and pleuritic chest pain. After being initially admitted under the surgical team, she was reviewed by the medical team who referred her for genetic testing, which subsequently confirmed the diagnosis. She was started on colchicine, and her symptoms remain well controlled one-year post diagnosis.

Keywords

Abdominal pains, fever, recurrent, familial Mediterranean fever

Introduction

We present a case of a young female presenting frequently to hospital over several months with abdominal pains, fevers, and multiple other symptoms. She was eventually referred to the medical team for a second opinion. Her symptoms, along with her ethnicity, led to a presumed diagnosis of Familial Mediterranean fever. She was started on Colchicine, and genetic testing later confirmed the diagnosis.

Case report

A 19-year-old British female with no significant past medical history presented to the emergency department with a 2-week history of abdominal pain associated with fever, dysuria, and nausea. She had seen her GP two weeks earlier, who had started omeprazole with no improvement in her symptoms.

On arrival the patient was tachycardic (Heart rate of 130 beats per minute), blood pressure 117/89 mmHg and a low-grade fever of 37.7C. Clinical examination revealed

Bloods	Laboratory results	Normal limits
Hemoglobin	129	120–150 g/L
White blood count	12.7 ↑	3.7–11.1*10^9/L
Platelet count	419 ↑	150–400*10^9/L
Mean cell volume	78↓	82–98 fL
Neutrophil count	9.1↑	1.5–7.4 *10^9/L
Lymphocyte count	2.5	1.1–4.0*10^9/L
Monocyte count	*1.1	0–0.95*10^9/L
Eosinophil count	0.1	0.0–0.7*10^9/L
Basophil count	0.1	0–0.2 *10^9/L
C –reactive protein	232↑	0–5 mg/L
Albumin	47↑	32–45 g/L
Total protein	87↑	64–83 g/L
Total bilirubin level, blood	15	0–21umol/L
Alanine aminotransferase	14	0–33 iu/L
Alkaline phosphatase	68	45–87 iu/L
Sodium level	138	136–145 mmol/L
Potassium level	4.0	3.5–5.1 mmol/L
Urea	3.1	2.1–7.1 mmol/L
Creatinine	62	44–80 µmol/L
Urine MCS	Results	
White blood cells	<50 * 10 ^ 6/L	
Red blood cells	<50* 10 ^ 6/L	
Urine culture	No evidence of infection by automated digital microscopy	
Faeces MCS	Negative	

generalized guarding in the epigastrium and suprapubic region. Her admission bloods are summarized below:

The patient was admitted under the surgeons and underwent CT scan of the thorax, abdomen and pelvis, which identified non-specific mild fat stranding in the right distal paracolic gutter, but no obvious cause for her symptoms. Abdominal ultrasound was performed the following day due to ongoing pain, which was unremarkable. She was subsequently discharged with a short course of oral amoxicillin with clavulanic acid. C-reactive protein (CRP) on discharge was 126 and no specific diagnosis was made.

One month later, the patient presented again with abdominal pain: worse in the epigastrium, and radiating into the right lower abdomen, with associated dysuria and dark orange colored urine. Observations revealed a sinus tachycardia of 119 bpm and a temperature 37.4°C. Her blood tests revealed an elevated CRP of 109 mg/l, with all other blood tests within normal parameters.

Urine dipstick examination was positive for blood and protein. Urine microscopy and cytology revealed no growth. Coronavirus PCR testing was negative. She underwent a MRI small bowel study, which identified degenerative changes involving the L4-L5 intervertebral discs. She also mentioned a history of intermittent abnormal vaginal discharge, and was therefore seen by the gynecological team, who did not have any concerns. Higher vaginal swabs were taken. Her abdominal pain settled with simple analgesics and her CRP dropped to 32mg/l and she was discharged.

Four weeks later, she returned to emergency department with similar symptoms and was admitted under the surgical team again. Her blood tests were unremarkable apart from an isolated CRP rise of 55mg/l. A repeat ultrasound scan of the abdomen and pelvis was normal. She was given fluids and simple analgesics, and was subsequently discharged with an urgent outpatient gastroenterology review requested.

Three weeks later, she presented with recurrent abdominal pain, accompanied with right sided pleuritic chest pain, and associated with a fever of 38.4°C. She was admitted under the medical team on this admission. On taking a detailed history, the patient reported a three-year history of intermittent symptoms of varying severity, having worsened over the past year. Episodes would last between two to five days, occasionally occurring with her menstrual periods. Episodes would typically start with abdominal pain and would occasionally be associated with right-sided pleuritic chest pain and fevers. She denied arthralgia, ulcers or skin changes. A family history revealed that both her parents were born in Turkey. All investigations, including a urine sample, blood cultures, vaginal swabs and stool samples were normal.

With the history of recurrent admissions with abdominal pain; with raised inflammatory markers, fevers, and a history of parents from Turkey: a provisional diagnosis of familial Mediterranean fever (FMF) was considered. An autoimmune serology panel was requested, as well as viral hepatitis serology, and HIV. Ferritin levels were also requested. In the context of dark orange-coloured urine, urinary and faecal porphyrins levels were sent. An outpatient echocardiogram was performed, to look for any evidence of pericarditis. She was commenced on Colchicine 500 micrograms twice daily and was discharged. A referral was made to the National Amyloidosis Centre.

A phone-call follow-up was arranged for 5 weeks later. The patient reported that her symptoms had significantly improved since starting colchicine and she had not needed any further hospital admissions. The autoimmune panel sent previously was within normal parameters. Her viral serology for Hepatis B, C, D, and HIV were all negative. Urinary Porphyrinogens were sent incorrectly and could not be processed, but stool Porphyrinogen's were negative. The echocardiogram identified increased echogenic appearance of pericardium near the inferolateral region of Left ventricle, possibly suggestive of mild pericarditis.

A few weeks later she was seen at the National Amyloidosis Centre where genetic testing identified a MEFV M680I homozygous positive mutation, confirming the diagnosis of Familial Mediterranean Fever. She continues to be followed up by the National Amyloidosis Centre. She has remained asymptomatic at the time of writing (one year post diagnosis).

Discussion

Familial Mediterranean Fever (FMF) is typically an autosomal recessive condition, caused by a mutation in the MEFV gene. The MEFV gene codes for a protein called Pyrin, which is involved in the regulation of the inflammatory process. Currently, over 80 MEFV gene mutations have been linked to FMF, leading to reduced or malformed pyrin protein. While it can affect any population, it is more common in those of Arabic, North African Jewish, Armenian, and Turkish descent, with an estimated prevalence as high as 1 in 7 in in specific populations.[1]

FMF is characterised by dysregulation of the inflammatory process in the body, presenting as recurrent episodes of serositis. Patients with FMF commonly present with episodes of fever, peritonitis, synovitis, pleuritis, arthritis, and occasionally pericarditis. Approximately 50% of patients with FMF will experience a prodromal phase, described as 'physical or psychological discomfort' prior to an acute attack.[1]

Figure 1. Simplified Tel-Hashomer Criteria for the diagnosis of FMF.[2]

Major criteria	Minor criteria
1. Recurrent febrile attacks accompanied by peritonitis, synovitis or pleuritis. 2. Amyloidosis of the AA-type without predisposing disease. 3. Favourable response to continuous colchicine treatment.	1. Recurrent febrile attacks. 2. Erysipelas-like erythema 3. FMF in a first degree relative

Figure 1 highlights the characteristic symptoms of FMF, however DNA testing for known MEFV mutations is the only definitive diagnostic test. Raised inflammatory markers alongside any appropriate samples obtained (e.g. synovial fluid) during an acute presentation of FMF would be expected to support the diagnosis.[1]

In this case, the patient presented with the classical "periodic peritonitis", which occurs in up to 90% of affected individuals.[1] Understandably, these clinical features often lead to unnecessary diagnostic laparoscopy or laparotomy as common surgical conditions such as appendicitis, bowel obstruction, and cholecystitis may be perceived as causes of the aboveKasifoglu et al. report a significantly higher rate of appendicectomy in FMF patients prior to their diagnosis compared to a healthy control population (26.7% vs. 4.9%; $p = 0.0001$).[3] This study alone highlights the importance of FMF as a differential in any patient presenting with an 'acute abdomen,' to avoid unnecessary major surgery and the associated risks.

This case highlights the importance of recognising this rare condition in patients of Mediterranean origin presenting with acute abdomen, particularly in children and adolescents. Our patient presented at the age of 18 years but had been experiencing symptoms for three years. This condition is, however, not unique to people of Mediterranean origin and has also been reported in the Japanese population.[1] This case highlights the possibility that a lack of accurate prevalence data in countries such as Japan or the perceived rarity of FMF in many 'non-typical' countries could potentially contribute to delay in diagnosis and poorer patient outcomes. NHS England estimates 40 people in England who are receiving treatment for FMF.[4] There is little data published on the distribution, ethnic background and accurate prevalence of FMF patients in the United Kingdom, perhaps highlighting an area for further research.

A 2020 report identifies a unique MEFV variant causing dominant FMF complicated by AA Amyloidosis in four generations of a British family.[5] AA Amyloidosis is one of the most significant and well-reported long-term complications of FMF. Amyloidosis is a multi-system disease, caused by the aggregation of amyloid protein. In patients with FMF, these deposits commonly accumulate within the kidneys, progressing to nephrotic syndrome and resulting in end stage renal failure.[1] A retrospective cohort study of over 1000 participants with FMF revealed renal amyloidosis as the cause of 35% and 60% of deaths, in men and women with FMF respectively.[6]

Colchicine has been the mainstay of treatment since the 1970's with some evidence that it reduces progression to amyloidosis.[7] In patients with ineffective response or intolerable side effects of Colchicine, biologics inhibiting interleukin 1 have been used; Canakinumab is licensed for treatment in the UK.[4] A 2019 study suggested there was an association between constantly high CRP levels during 'attack-free' periods and the development of amyloidosis in patients with FMF, further highlighting the importance of research into alternative treatment options for patients with an ineffective response to Colchicine.[8] In addition to Canakinumab, Anakinra, another interleukin 1 inhibitor, has also been shown to reduce symptom frequency, normalisation of inflammatory markers, as well as limiting the progression of renal amyloidosis.[9,10]

Clinical assessment alone carries the risk of missing another pathology such as appendicitis and imaging can help exclude an alternative diagnosis. Although imaging is not included in the diagnostic criteria for FMF (Figure 1), it is still advised to exclude other conditions that may co-exist. In one study, 21% of patients had features of acute surgical pathology, 2 patients had signs of acute appendicitis, and 1 patient had features of small bowel obstruction.[11] In this case, CT scan revealed non-

specific inflammatory changes with mild fat stranding. A retrospective cohort analysis performed by Zissin et al. on 17 patients with FMF revealed that 70% had features of non-specific inflammation such as mesenteric vessel engorgement and mesenteric lymphadenopathy.[11] Radiologists should be familiar with the differential of FMF and may suggest this in the context of the above findings in a young patient of a certain ethnicity presenting with an acute abdomen. Conversely, one should err on the side of caution when diagnosing a known FMF patient with an acute FMF flare, as acute pathology cannot always be ruled out clinically.

This case presented with a history of passing 'dark urine' in association with the pain in chest and abdomen. Although urinalysis was normal in this case, acute intermittent porphyria remains a differential diagnosis. Both conditions have been reported to co-exist in one case, but this is rare.[12]

In this case, the diagnosis was confirmed by genetic testing and the excellent response to Colchicine. The patient subsequently remained free from further attacks on long-term colchicine.

Colchicine has shown to be very efficacious in preventing FMF attacks and long-term amyloidosis. Currently, Colchicine is only licenced in the UK for management of gout and FMF.[13] Colchicine should be avoided in patients with an eGFR less than 10mL/minute/1.73m^2 due to a significantly increased risk of drug toxicity.[13] It is advised that Colchicine is prescribed with caution and dose adjustments considered in all patients with reduced renal function. Colchicine cannot be significantly eliminated from the body via dialysis; hence it is paramount to focus on preventing toxicity. Common side-effects of Colchicine include diarrhoea, vomiting and abdominal pain. These side effects can potentially be managed by reducing the dose, or by prescribing smaller doses, twice daily. However, it is important to note gastrointestinal symptoms can also represent the initial symptoms of Colchicine toxicity. Additional side effects including bone marrow disorders, myopathy, neuropathies, and liver and kidney injury have also been reported. A 2018 meta-analysis revealed no significant adverse effects associated with the use of colchicine in pregnancy.[14]

This case highlights the importance of a careful history and the consideration of FMF as a differential in children of Mediterranean origin presenting with acute surgical abdomen. One should consider FMF particularly with a history of recurrent admissions with similar clinical features. Timely diagnosis not only reduces the risk of unnecessary surgical intervention, but also offers the opportunity to start timely treatment with Colchicine which has been reported to be effective in not only preventing acute attacks but also reducing the risk of life-threatening end-organ failure secondary to amyloidosis.

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