J Ped Surg Case Reports 3 (2015) 4–6

Contents lists available at ScienceDirect

Journal of Pediatric Surgery CASE REPORTS

journal homepage: www.jpscasereports.com

Acute appendicitis in a 14-year-old boy with familial Mediterranean fever☆

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ARTICLE INFO

Article history:
Received 1 September 2014
Received in revised form
19 November 2014
Accepted 19 November 2014

Key words:
Familial Mediterranean fever
Acute abdomen
Appendicitis

ABSTRACT

Familial Mediterranean fever (FMF) is one manifestation of a heritable periodic fever syndrome that is characterized by recurrent attacks of febrile polyserositis, most frequently peritonitis. An FMF abdominal attack is often misdiagnosed as acute appendicitis, a more common cause of an acute abdomen. We report a 14-year-old boy with FMF who developed acute appendicitis during his follow-up. The patient had a several-year history of abdominal pain episodes, and was initially admitted for an acute abdominal attack. The attack resolved over three days, following administration of intravenous fluids, alone. Upon admission, serology revealed elevated serum levels of amyloid A. An analysis of the *MEFV* gene revealed compound heterozygous Glu148Gln/Ser503Cys, resulting in an FMF diagnosis. Seven months after discharge, the patient was re-admitted with an acute abdomen. Following ultrasonographically diagnosed appendicitis, an appendectomy was performed, and acute phlegmonous appendicitis was confirmed, based on the pathologic examination of the resected specimen. The present case suggests that upon examining an FMF patient with abdominal pain, appendicitis should not be arbitrarily discounted from the differential diagnosis.

Familial Mediterranean fever (FMF) is a heritable periodic fever syndrome, most prevalent among multiple populations in the eastern Mediterranean basin. The disease is caused by mutations in the *MEFV* gene that encodes pyrin [1,2], a protein involved in innate immunity [3,4]. FMF is characterized by recurrent attacks of febrile and painful polyserositis affecting the synovium, pleura, and most commonly, the peritoneum. Peritonitis in FMF patients is often misdiagnosed as acute appendicitis [5] or a surgical acute abdomen [6,7], which may consign the patients to extensive evaluations and even unnecessary surgery [8]. Nevertheless, acute appendicitis may develop in some FMF patients, as evidenced by this case report.

1. Case report

A 14-year-old boy was admitted to our hospital complaining of high fever and severe abdominal pain that had persisted since the previous day. The boy's family history was positive for acute appendicitis involving the mother and her siblings who underwent appendectomies during their teenage years. The mother had a pathologically mild (phlegmonous) appendix, but one sibling had a gangrenous appendix. The patient had suffered from occasional high fevers with or without abdominal pain, a few years previously, and he had also been examined by a dermatologist for erythematous plaques that had developed on his anterior neck, axilla, back, groin, and knees.

A physical examination showed a high temperature (38.9 °C) with diffuse abdominal tenderness, especially around the periumbilical region; neither arthralgia nor cutaneous symptoms were observed. Upon admission, a blood analysis revealed generalized inflammation with elevated levels of white blood cells (15,700/μL; neutrophils, 87.6%), C-reactive protein (CRP; 16.15 mg/dL), and procalcitonin (PCT; 1.32 ng/mL). To rule out an acute abdomen due to appendicitis, abdominal ultrasonography and computed tomography were performed, revealing mild edema in the ileocecal region, pooled intestinal fluid, and mild lymphadenopathy in the periumbilical region and right lower quadrant; the findings did not suggest appendicitis. On the basis of these findings, he was diagnosed with acute colitis and followed in-hospital, only receiving intravenous fluids for dehydration. His temperature and abdominal pain were reduced on hospitalization day 2 and gradually resolved,

Abbreviations: CRP, C-reactive protein; FMF, familial Mediterranean fever; PCT, procalcitonin; SAA, serum amyloid A.

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http://dx.doi.org/10.1016/j.epsc.2014.11.008

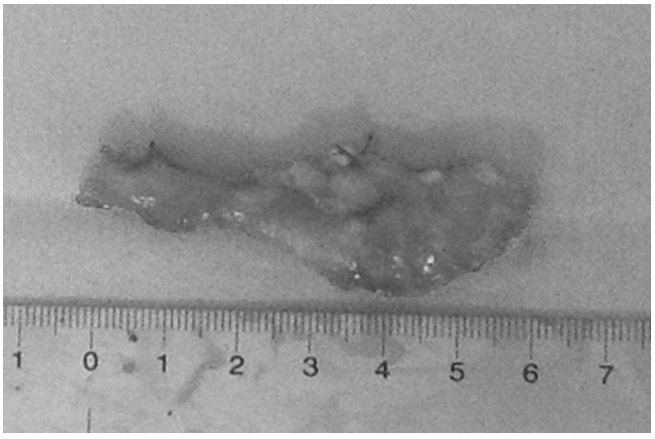

Fig. 1. The resected appendix appears significantly thickened and turgid, the distal portion is distended and has a 20-mm diameter; the mucosa is ulcerated.

spontaneously; he was discharged on hospitalization day 4. After discharge, the results of his serum amyloid A (SAA) test, conducted upon admission, revealed elevated levels (2,689.5 μg/mL). Together, these findings strongly suggested FMF.

Clinically, the patient fulfilled the Tel-Hashomer diagnostic criteria (Sohar criteria) [9] with one major criterion (recurrent febrile episode associated with peritonitis) and two minor criteria (recurrent febrile episodes and a history of erysipelas-like erythema). A genetic study revealed compound heterozygosis, with a Glu148Gln mutation and a second mutant Ser503Cys allele in the *MEFV* gene, confirming an FMF diagnosis. The patient was followed, without prophylactic colchicine therapy (at the request of the patient and his family), after the risks of no treatment were explained; the family approved the use of colchicine when symptoms developed. Two months after discharge, the patient developed abdominal pain once, but the pain was mild and subsided quickly without colchicine administration.

Seven months after discharge, the patient again developed severe abdominal pain, with a high fever (38.2 °C). He was admitted to our hospital because his symptoms did not improve, despite a single administration of oral colchicine. A physical examination revealed lower abdominal tenderness and a positive McBurney's sign. A blood analysis revealed elevated levels of white blood cells (18,000/μL; neutrophils, 87.5%), CRP (5.64 mg/dL), and PCT (0.82 ng/mL). Furthermore, abdominal ultrasonography showed an enlarged appendix in the ileocecal region, different from the findings during his previous admission. On the basis of the ultrasonographic findings, an appendectomy was conducted. A pathological examination of the resected appendix (diameter, 20 mm) (Fig. 1) confirmed a diagnosis of acute phlegmonous appendicitis. The patient's SAA level, prior to his appendectomy was elevated (493.1 μg/mL), but had decreased to 5.4 μg/mL within one month after discharge. During the six months since his appendectomy, the patient has not shown significant symptoms and has not required any treatment. The patient's parents approved the various diagnostic procedures and treatments described in this report. To date, the patient's parents have not consented to a genetic analysis.

2. Discussion

The diagnosis of FMF is occasionally challenging. Although the pathogenic mechanism of FMF has been elucidated, the diagnosis still relies mainly on clinical criteria. Several diagnostic criteria have been presented in the literature (Table 1). The most widely used criteria is so-called Tel Hashomer criteria, but it actually refers to either Livneh [10] or Sohar criteria [9]. Aside from these criteria, Pras

Table 1
Representative diagnostic criteria for familial Mediterranean fever.

Livneh criteria[a]
Major criteria
Peritonitis (generalized)
Pleuritis (unilateral) or pericarditis
Monoarthritis (hip, knee, or ankle)
Fever alone
Minor criteria
Incomplete attacks affecting one or more sites
Abdomen
Chest
Joint
Exertional leg pain
Response to colchicine
Sohar criteria[b]
Major criteria
Recurrent febrile episodes with serositis
Amyloidosis of amyloid A type without predisposing disease
Response to colchicine
Minor criteria
Recurrent febrile episodes
Erysipelas-like erythema
Family history in a first-degree relative
Yalcinkaya criteria for pediatric patients[c]
Fever: axillary temperature >38 °C, duration 6–72 h and ≥3 attacks
Abdominal pain: duration 6–72 h and ≥3 attacks
Chest pain: duration 6–72 h and ≥3 attacks
Arthritis: duration 6–72 h, ≥3 attacks, and oligoarthritis
Family history of FMF

This table reflects an abbreviated version of the criteria; details, such as the supportive criteria, are omitted.
When diagnosing patients, the original criteria should be referenced.
[a] Definitive diagnosis: ≥1 major criterion or ≥2 minor criteria.
[b] Definitive diagnosis: ≥2 major criteria, or 1 major plus 2 minor criteria.
[c] Definitive diagnosis: ≥2 criteria.

presented simplified criteria composed of short-term episodes of fever, serositis, and a favorable response to colchicine treatment [11]. Recently, Yalcinkaya et al. proposed another set of criteria for pediatric FMF [12], but is limited by its applicability only to children from a single ethnic group with *MEFV* mutations in both alleles [13]. Our patient was diagnosed with FMF, according to the Sohar criteria; retrospectively, he also met the Livneh and Yalcinkaya criteria.

Although genetic analysis has a low sensitivity [14], it plays a certain role in the diagnosis of the disorder. FMF exhibits an autosomal recessive pattern of inheritance, and patients are either homozygous or compound heterozygous for *MEFV* mutations (NM_000243.2). However, the registered mutations do not necessarily cause true disease, and nearly 300 sequence variants have been registered, to date, in the Infevers registry of *MEFV* sequence variants [15]. The various combinations of mutations may cause a range of phenotypic manifestations, from asymptomatic to severe symptoms. The major disease-causing mutations are located in the last exon (exon 10) and account for the majority of the mutations in typical cases [1,2,16,17]. There is controversy regarding whether the Glu148Gln mutation, identified in our case, causes disease [18–20] or is simply a gene polymorphism [17,21–23]. In a recent review, Glu148Gln was associated with a generally mild form of FMF [24]. Whether the second mutation in our case, Ser503Cys, causes disease is also unclear. Most recently, in a review of 311 Japanese FMF patients, 5 patients were heterozygous for Ser503Cys and two were compound heterozygous for this variant and Glu148Gln; both were included as FMF-causing genotypes [25]. The latter combination is same as the one detected in our present case. Considering our patient's past history, family history, clinical symptoms, physical findings, laboratory findings, and the *MEFV* mutations, a final diagnosis of FMF was made, albeit a potentially mild form.

Severe abdominal pain occurring in patients with FMF is often misdiagnosed as acute appendicitis, especially in an undiagnosed

FMF case. Greater awareness of this disease has resulted in physicians paying more attention to the symptoms and avoiding unnecessary abdominal surgeries in FMF patients. Furthermore, a familial aggregation of appendicitis cases has come to be considered a noteworthy sign associated with FMF. However, FMF patients may develop appendicitis dependently or independently of their FMF. Some FMF patients who are homozygous for the Met694Val mutation are predisposed to developing appendicitis [8]. A change of abdominal pain from diffuse to localized to right lower quadrant well predict the inflammation of appendix in FMF patients [8]. On the other hand, previous studies have indicated that appendicitis, especially when it develops during childhood, can be inherited [26,27]. These observations suggest that the familial clustering of acute appendicitis might not be of value in a differential diagnosis for distinguishing FMF from appendicitis.

Acute episodes of FMF are associated with acute inflammation markers, such as CRP, SAA, and fibrinogen. In our case, a marked increase in SAA suggested FMF. However, elevated levels of SAA, CRP, and fibrinogen are nonspecific and do not critically contribute to the diagnosis [28]. In our patient, the SAA level was also elevated during his case of appendicitis, which may also elicit non-specific elevations of SAA levels. PCT is also known as an inflammation marker, and has been advocated as a useful test for differentiating abdominal FMF attacks from acute appendicitis. This suggestion is based on the observations that PCT levels tend to remain <0.5 ng/mL during FMF abdominal attacks, but are elevated during acute appendicitis [29]. In our case, although the preoperative PCT level (0.65 ng/mL) was consistent with previous findings, the PCT level was much higher (1.32 ng/mL) at the time of the patient's first admission for an FMF abdominal attack. Thus, differentiating between an acute appendicitis attack and an FMF abdominal attack, using laboratory tests, is likely to remain difficult.

Whether familial clustering of acute appendicitis in the family described in this report indicates FMF, familial appendicitis, or a predisposition to appendicitis in FMF remains to be elucidated. In addition, whether patients with a mild type of FMF are more likely to develop acute appendicitis than those with typical FMF also remains unclear. A further accumulation of appendicitis cases developing in FMF patients is warranted to address these issues.

3. Conclusions

FMF abdominal attacks have been frequently misdiagnosed as acute appendicitis and unnecessary surgeries have been performed. Physicians need to remain aware of the possibility of FMF when diagnosing an acute abdomen. However, acute abdominal episodes in patients with FMF are believed to be due to the nature of the disease and acute appendicitis is not seriously considered in the differential diagnosis. Nevertheless, our case indicates the possible development of acute appendicitis in FMF patients. When encountering a patient with suspected or diagnosed FMF, who presents with severe acute abdominal pain, the possibility of acute appendicitis should not be arbitrarily dismissed.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgments

We would like thank to Drs. Yuki Takaoka and Ryuta Nishikomori (Department of Pediatrics, Kyoto University Graduate School of Medicine, Kyoto, Japan) for their cooperation in identification of the *MEFV* mutation.

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