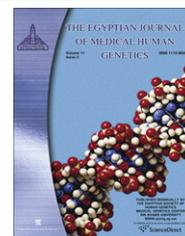




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CASE REPORT

Colchicine resistant FMF is not always true resistance

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Abstract Crohn's disease and familial Mediterranean fever are both inflammatory diseases characterized by similar clinical manifestations. The concurrence of the two diseases may pose a challenge to diagnosis and treatment. In this report, we present a child with familial Mediterranean fever and undiagnosed Crohn's disease which made him apparently resistant to colchicine therapy. Symptoms of Crohn's disease were masked by the resistant fever of FMF. Amelioration of symptoms of both diseases was achieved when treatment of both diseases were gradually introduced. Searching of IBD in children with colchicines resistant FMF is mandatory, as both diseases have similar symptoms and responsible genes may modify one another.

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1. Introduction

Familial Mediterranean fever (FMF) is an inherited disorder characterized by recurrent self-limiting attacks of joint, chest and abdominal pain associated with fever. It occurs predominantly in those of Mediterranean origin [1]. On the other hand,

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Crohn's disease (CD) is an inflammatory disease of the intestines that may affect any part of the gastrointestinal tract from mouth to anus, causing a wide variety of symptoms. It primarily causes abdominal pain, diarrhea, vomiting, fever or weight loss, but may also cause complications outside of the gastrointestinal tract such as skin rashes, arthritis, inflammation of the eye, tiredness, and lack of concentration [2]. Both diseases share common clinical and biologic features; they are both inflammatory disorders characterized by the same chronic relapsing behavior, infiltration by neutrophils at the site of injury, and abnormal regulation of apoptosis [3,4]. The concurrence of the two diseases may pose a challenge to diagnosis and treatment.

In this report, we present a child with both FMF and CD which made him apparently resistant to colchicine therapy. Amelioration of symptoms of both diseases was achieved when treatment of both diseases were gradually introduced.

2. Case presentation

Our patient is an 8-year-old boy, the first in order of birth of first cousin marriage presented to our clinic with resistant

FMF. The patient history actually started at the age of one year when he had recurrent attacks of fever and abdominal colic every 45 days that progressively became more frequent. According to the parents' history, abdominal colic was partially relieved by defecation while the fever may subside spontaneously or with analgesics. The child was diagnosed at the age of 3 years as FMF patient and received 1.5 g colchicines daily for the last 5 years with no improvement. On examination (at the age of 8 years), the patient looked pale, in agony; his weight and height were at the 50th percentile. He had no organomegaly and his chest and heart were clinically free. CBC showed only moderate microcytic hypochromic anaemia (haemoglobin was 9.6 g/dl); white blood cells and platelets were within normal ranges. Stool examination revealed no abnormalities. Liver and kidney function tests showed no abnormalities, ESR was 56, CRP was 4.4 mg/dl (normal: 6) and IgD level was 69 U/ml (normal up to 100).

Abdominal ultrasound showed diffuse and extensive hyperperistalsis of the small intestinal loops all over the abdomen and pelvis. They were seen collapsed with diffusely thickened and prominent internal rugosities of the inner wall. Barium follow-through revealed rapid transient time. Colonoscopy revealed bossy mucosa of the ileum (follicular nodular hyperplasia). Duodenal and jejunal mucosal biopsies revealed normal villous pattern with oedema and congestion of the mucosal lumina with diffuse infiltration by plasma cells and small number of lymphocytes and eosinophils. The lymphoid aggregations in the mucosa were slightly hyperplastic causing mild elevation of the mucosa simulating sessile polypi. Ileal mucosal biopsy revealed picture of mild non-specific ileal enteritis with preserved villous pattern and colonic biopsy showed mild superficial erosions. The lamina propria showed moderate chronic inflammatory cellular infiltrate which was mainly lymphoplasmocytic at the luminal side with occasional neutrophils and few eosinophils with focal cryptitis. Crypts were regular with preserved mucin production. There was focal oedema of the lamina as well as crypt enlargement, Fig. 1.

Molecular analysis for FMF was done by sequencing of exon 10 and exon 2 of MEFV gene on chromosome 16p13 revealed compound heterozygous for M694V and M694I mutations in exon 10 confirming the diagnosis of FMF [5].

Considering that FMF and IBD symptoms are similar and that GIT inflammation and erosions are not signs of FMF, an

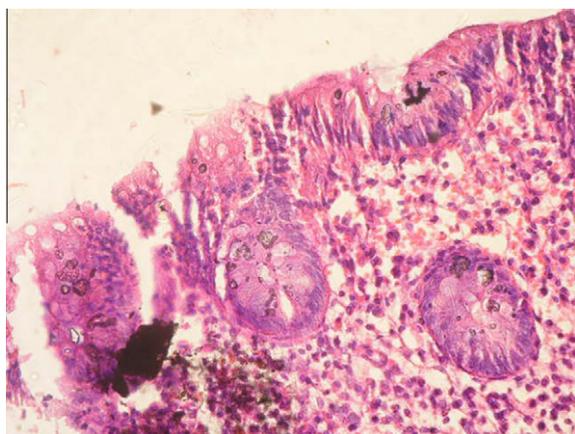


Figure 1 Biopsy of the ileal mucosa of the patient.

association of CD was suggested. Treatment was started with 5-aminosalicylates at a dose of 50 mg/kg/day. After 3 months, a decrease in the frequency of attacks of fever and colic was noticed but was not satisfactory. Oral corticosteroids were added at the dose of 1 mg/kg/day and a satisfactory improvement was noticed in the form of absence of these attacks, an improvement of appetite, weight gain and normalization of ESR.

Gradual decrease of steroids was started till the minimal dose that aborts that attacks (0.6 mg/kg/day) was reached. This was given together with a maintenance dose of azathioprine at a dose of 2 mg/kg/day. Colchicines were gradually introduced with starting dose of 0.25 mg/day and a maximum dose of 1.5 mg/day and since then, all attacks subsided.

3. Discussion

Colchicine is the sole treatment of FMF. It reduces the frequency of attacks and prevents amyloidosis [6]. Complete remission is seen in about 65% of patients and partial remission is experienced in another 20–30%. Still there are 5–10% non-responders [7]. Reasons for non-responsiveness remain a puzzle; an abnormality in colchicines consumption by mononuclear cells suggests that these patients sustain an additional genetic defect [8].

On the other hand, some multifactorial inflammatory diseases are more frequent in FMF patients than in the ethnically matched general population as inflammatory bowel disease [9,10]. Investigators stated that CD appears to be more prevalent in FMF patients and presents later than in patients without FMF. FMF in patients with CD shows a higher attack frequency and is more often complicated by amyloidosis [10]. Recently, Sari et al. reported the concurrent manifestation of IBD and FMF in three infants (less than 6 months of age) in whom infantile ulcerative colitis (UC) was associated with the MEFV mutation and suggested that the onset of UC in infants should prompt a search for MEFV mutations as this association may influence the management of the disease [11].

This is similar to what occurred in our patient in whom the attacks started very early and very severe. The findings of the GIT biopsies and the response to 5-aminosalicylate therapy aided to support the diagnosis of CD in our patient. It is unlikely that these findings could be explained by FMF.

Cattan et al. suggested that the genes responsible for one disorder could have a modifying effect on the other inflammatory disease which was quiet evident in our patient in whom the FMF attacks were ameliorated when CD was effectively managed and even the fake resistant to colchicines disappeared [9].

4. Conclusion

Searching of IBD in children with colchicines resistant FMF is mandatory, as both diseases have similar symptoms and responsible genes may modify one another.

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References

- [1] Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever. A survey of 470 cases and review of the literature. *Am J Med* 1967;43:227–53.
- [2] Baumgart DC, Sandborn WJ. Inflammatory bowel disease: clinical aspects and established and evolving therapies. *Lancet*. 2007;369:1641–57.
- [3] Lichtenberger GS, Flavell RA, Alexopoulou L. Innate immunity and apoptosis in IBD. *Inflamm Bowel Dis* 2004;10:S58–62.
- [4] McDermott MF. A common pathway in periodic fever syndromes. *Trends Immunol* 2004;25:457–60.
- [5] Akar N, Misiroglu M, Yalcinkaya F, et al. MEFV mutations in Turkish patients suffering from Familial Mediterranean Fever. *Hum Mutat* 2000;15:118–9.
- [6] Dinarello CA, Wolf SM, Goldfinger SE, et al. Colchicine therapy for familial Mediterranean fever. A double blind trial. *N Engl J Med* 1974;291:934–7.
- [7] Ben-Chetrit E, Levy M. Familial Mediterranean fever. *Lancet* 1998;351:659–64.
- [8] Lidar M, Scherrmann JM, Shinar Y, et al. Colchicine non-responsiveness in familial Mediterranean fever: clinical, genetic, pharmacokinetic, and socioeconomic characterization. *Semin Arthritis Rheum* 2004;33:273–82.
- [9] Cattan D, Notarnicola C, Molinari N, et al. Inflammatory bowel disease in non-Ashkenazi Jews with familial Mediterranean fever. *Lancet* 2000;355:378–9.
- [10] Fidler H, Chowers Y, Ackerman Z, et al. The familial Mediterranean fever (MEVF) gene as a modifier of Crohn's disease. *Am J Gastroenterol* 2005;100:338–43.
- [11] Sari S, Egritas O, Dalgic B. The familial Mediterranean fever (MEFV) gene may be a modifier factor of inflammatory bowel disease in infancy. *Eur J Pediatr* 2008;167:391–3.