

H. pylori status was assessed by histology (n = 47) or by 13C urea breath test (n = 3). Of this cohort, 40 patients were affected by lymphocytic colitis and 10 by collagenous colitis. *H. pylori* resulted positive in 18 patients (36%), of whom 13 affected by lymphocytic colitis and 5 affected by collagenous colitis; the difference was not statistically significant (Chi-squared test, $P = 0.51$). These data were compared with a control population of 404 subjects suffering from constipation, who underwent urea breath test for study purposes. This cohort included 224 women (55.4%) and 180 men (44.6%) (statistically significant difference with cases, $P = 0.038$), with median age of 55 years (not statistically significant difference, Mann-Whitney test, $P = 0.4$).

H. pylori infection was reported in 166 controls (41.1%), without difference with cases (Chi-squared test, $P = 0.59$).

Of the 18 patients with *H. pylori* positive status in the MC populations, in 8 (44%), the *H. pylori* infection was eradicated before the diagnosis of MC. Thus, at the diagnosis of MC, only 10 patients (20%) were *H. pylori* positive. Considering patients with history of *H. pylori* positivity but with eradication before the diagnosis of MC as patients with negative *H. pylori* status, there was a statistically significant difference between cases and controls (Chi-squared test, $P = 0.006$).

In conclusion, to be *H. pylori* negative, ab initio or after antibiotic treatment seem to be a risk factor for the onset of MC.

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Triple Disease Combination: Familial Mediterranean Fever, Crohn's Disease, and Chronic Idiopathic Urticaria with Angioedema

To the Editor:

Familial Mediterranean fever (FMF) is an autoinflammatory disorder associated with the abnormal activation of the innate immunity.¹ Crohn's disease (CD) and chronic idiopathic urticaria with angioedema (CIUA) are considered as immune disorders. The coexistence of both FMF and CD, or CD and CIUA has been rarely reported.² Here, we report a unique case of triple disorder combination.

A 23-year-old Ashkenazi Jewish male medical student presented with episodes of severe, colicky epigastric pain for 3 weeks. He felt stuffy in his chest and difficulty breathing during these episodes with significant fatigue. The abdominal pain was accompanied by fever up to 38.3°C, nonpruritic erythema across the neck, bilateral knee pain, and drenching night sweats. These episodes typically lasted 2 to 3 days with peaking severity on the second day, followed by symptomatic dissipation in a week. He was a nonsmoker with no family history of FMF, CD, or urticaria. The

patient had episodic marked swelling in his face, limbs, and torso (Fig. 1) for the previous 3 years, and CIUA was diagnosed. After inadequate response to high-dose antihistamine therapy (cetirizine 30 mg twice a day and doxepin 50 mg at bedtime), anti-IgE IgG monoclonal antibody, omalizumab, was initiated with complete resolution of the hives and swelling.

Laboratory findings, including complete blood count, complete metabolic panel, and urinalysis, were all within normal range. Serum C-reactive protein level was 2.8 mg/dL (normal, 0–1.0 dL), and erythrocyte sedimentation rate and ferritin level were normal. Serum amylase, lipase, C1 esterase inhibitor function, complement 4, and trypsin levels were all normal. An infectious workup for human immunodeficiency virus, Epstein-Barr virus, *Bartonella*, *Borrelia*, and toxoplasmosis was negative. Serum antinuclear antibodies, rheumatoid factor, and transglutaminase antibodies were all negative as were urine tests for 5-hydroxyindoleacetic acid and porphobilinogen. A computed tomography of the neck and abdomen demonstrated mildly prominent mesenteric lymph nodes and multiple prominent retroperitoneal lymph nodes. Owing to a concern for FMF, genetic testing was positive for heterozygous *MEFV* mutations P369S and R408Q, and no *NOD2* mutations were detected. FMF was diagnosed and treated with colchicine 0.6 mg twice daily with complete resolution of fever and significant relief in the abdominal pain for up to 3 weeks. The patient then developed recurrent nonbloody diarrhea, oral ulcers, and weight loss. Examination with esophagogastroduodenoscopy and colonoscopy showed duodenal ulcers with histological evidence of granulomatous inflammation, as was also found throughout the colon, ileocecal valve, and terminal ileum. Additionally, a capsule endoscopy showed multiple small ulcers in the jejunum and ileum. The gastrointestinal symptoms abated with a short course of prednisone 80 mg daily, but these symptoms recurred after steroid taper off, and sulfasalazine was administered in addition to oral topical steroid for oral ulcers. Regardless, the patient still had some breakthrough fever and abdominal cramping, and colchicine and subcutaneous methotrexate were used.

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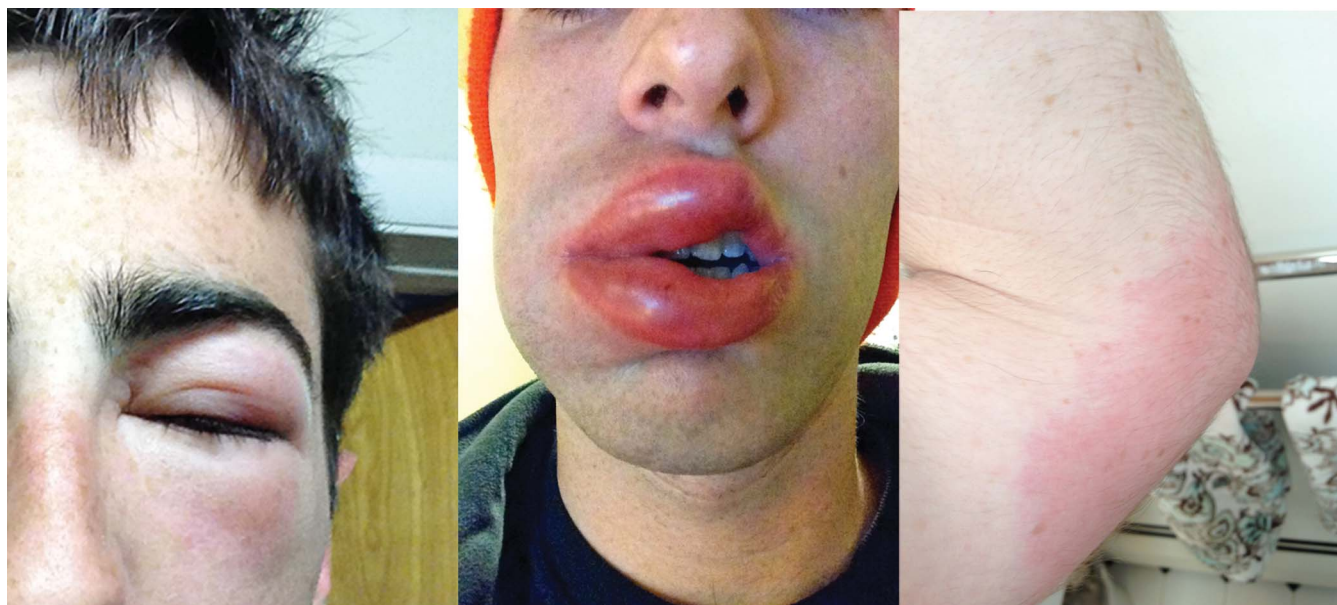


FIGURE 1. Lip and periorbital swelling and leg erythema.

The disease course of this case is characterized by recurrent short bouts of fevers, abdominal pain, chest pain, oral ulcers, knee pain, rash/angioedema, and the presence of the *MEFV* mutations. The granulomatous inflammation occurring in both small and large bowels supports the diagnosis of CD. The typical short bouts of symptoms are consistent with FMF as per the Tel Hashomer criteria³ as were his partial response to colchicine and the presence of the *MEFV* mutations. The P369S/R408Q substitutions in the *MEFV* as in our case are reportedly associated with a highly variable phenotype and are infrequently associated with typical FMF symptoms.⁴

There have been scarce reports of coexisting FMF and CD, and no association between the *MEFV* mutations and CD susceptibility is found.⁵ To our knowledge, there have been no reports of granulomatous inflammation seen in patients with concurrent FMF and CD. Clinically, the dual disease combination may pose diagnostic and therapeutic challenge. The management strategy may be to cover both conditions, and the therapeutic agents include 5-aminosalicylic acids, glucocorticoids, thiopurines, and anti-tumor necrosis factor agents and also colchicine.⁶ There is a recent report of success of using leukopheresis in the treatment of the dual disease.²

Angioedema refers to nonpruritic, nonpitting areas of swelling, affecting deep dermal, subcutaneous, mucosa, and submucosal layers.⁷ Both CD and CIUA are believed to be immune disorders, yet their coexistence has been rarely reported.⁸ In a case report, an adult female patient with CD and CIUA received intravenous immunoglobulin immunotherapy, danazol, prednisone, and hydroxyzine.⁸ As a result of inadequate symptomatic control, infusions of infliximab were started, and her angioedema, urticarial, and gut symptoms completely resolved. These data suggest that both CD and CIUA may share the similar pathogenesis to some extent.

In conclusion, we present a unique case of the triple immune/autoinflammatory disorders for the first time. The triple disorders occurring in an individual may also raise a speculation that autoinflammatory and immune disorders may share the similar pathogenic pathways, as evidenced by the altered expression of interleukin-17 and tumor necrosis factor α .⁸ Our case report also supports the current view that autoimmune and autoinflammatory disorders may not be mutually exclusive.

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