Cytomegalovirus-associated hemophagocytic syndrome in a patient with Crohn's disease receiving azathioprine

To the Editor,

A 35-year-old man, non–smoker, had ileocolonic Crohn´s disease diagnosed 15 years before that required right hemicolectomy and sigmoidectomy for recurrent sigmoid stenosis and ileo-rectal fistula, respectively. He was placed on maintenance therapy with azathioprine (AZA) without complications after surgery and has been in clinical remission for years. He was admitted to the hospital for fever over four weeks and malaise. Hepatosplenomegaly was the only relevant finding on physical examination. Laboratory tests revealed pancytopenia (hemoglobin 9.7 g/dl, white blood count 1,500/mcl, platelets 84,000/mcl), triglycerides 243mg/dl, alkaline phosphatase 217 IU/L, GGT 777 UI/L, ferritin 1197 ng/ml and C reactive protein 113 mg/L. Bowel inflammation was excluded by abdomen CT and labeled leukocyte scintigraphy. Despite intensive antibiotic therapy, the patient status worsened. Microbiologic studies were all negative except for a positive CMV (cytomegalovirus) IgM serology. Erythrophagocytosis and activated macrophages were shown on bone marrow aspirate (Fig. 1). Intravenous corticosteroids together with ganciclovir treatment was initiated. Fever disappeared after 48 hours and progressive improvement of hematologic parameters and inflammation markers was observed. After 10 days of treatment the patient was discharged with tapering of steroids and discontinuing AZA therapy. After 4 months the patient was totally recovered with normal hemogram, without steroids and starting methotrexate as immunomodulatory treatment.

Hemophagocytic syndrome (HS) is a potentially fatal hyperinflammatory condition caused by a highly stimulated but ineffective immune response [1]. Hemophagocytic syndrome can be primary (genetic) or secondary to another condition, especially severe infections, rheumatologic disorders or malignancies. Mortality rate associated with secondary HS ranges between 8% and 24% [1]. Epstein Barr virus (EBV) infection is the most common cause of infection associated with secondary HS. The pathogenesis remains unclear but may be related to

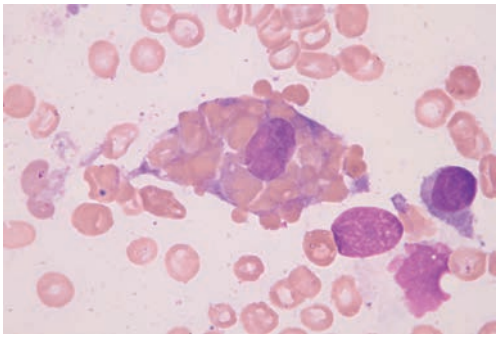

Fig.1. Bone marrow aspirate showing erythrophagocytosis and activated macrophages.

CD8+ T lymphocytes and macrophages hyperactivation and infiltration into various organs with hypercytokinemia resulting in progressive multiorgan dysfunction. Hemophagocytic syndrome presentation is characterized by high-grade and prolonged fever, hepatosplenomegaly and pancytopenia. Elevated triglyceride levels and hyperferritinemia are some of the typical laboratory findings. Diagnosis is made when specific criteria are met including the clinical findings defined before. Hemophagocytosis is a hallmark of macrophage activation, and it is neither essential nor specific for HS. Hemophagocytic syndrome therapy should be instituted promptly to prevent irreversible tissue damage. Immunosuppressive therapy is the basis of the therapy in combination with the specific treatment for the suspected cause. Hemophagocytic syndrome associated-CMV infection is an infrequent but severe condition related to AZA treatment in patients with inflammatory bowel disease (IBD). Azathioprine discontinuation is recommended to avoid future CMV reactivation or reinfection. Few similar cases have been reported with different outcomes [2-5]; all of them were patients in clinical remission. Our patient had evidence of active CMV infection that was not associated with an exacerbation of Crohn´s disease and only corticosteroid and antiviral treatment were sufficient to control HS.

Hemophagocytic syndrome is a rare and potentially fatal disorder that may occur in IBD patients submitted to immunomodulatory therapy (especially thiopurines). Early diagnosis of this condition is crucial because prompt and effective therapy reduces mortality.

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Long-lasting unspecific intestinal inflammation in ankylosing spondylitis evolving into Crohn's disease

To the Editor,

Ankylosing spondylitis (AS) is a chronic systemic inflammatory rheumatic disease that affects primarily the axial skeleton along with the sacroiliac joint [1]. Crohn's disease (CD) is a chronic inflammatory gastrointestinal disease, which involves joints in about 28% of the patients [2]. It often presents endoscopic and histological signs of gut inflammation, but a real IBD rarely occurs in rheumatic patients [3].

In September 2003, a 43-year-old male was referred to our attention due to recurrent bleeding diarrhea. He had been suffering from AS since he was 19, was HLA-B27+ and was under cyclic treatment with salazopyrin and steroids. Colonoscopy showed multiple ulcerations in the left colon within a normal colonic mucosa, but histology showed only unspecific active inflammation. After induction of remission with steroids, mesalazine 2.4 g/day was prescribed. In December 2012, he experienced again severe diarrhea and abdominal pain. A new colonoscopy gave similar results to that of 2003, but histology showed severe transmural inflammation (Fig. 1). Diagnosis of colonic CD in AS was confirmed, and the patient was successfully treated with adalimumab (ADA).

In April 2008, a further 52-year-old male was referred to our attention due to recurrent diarrhea. He had been suffering from AS since he was 38, and was HLA-B27+. He was under continuous treatment with prednisone 4 mg/day and salazopyrin 3 g/day. Colonoscopy showed multiple ulcerations on the ileo-cecal valve, but histology showed only unspecific active inflammation. In January 2009 he started therapy with infliximab (IFX) 5 mg/Kg i.v. and metothrexate 7.5 mg i.m. every week due to worsening of AS. In May 2013 he was referred to our ward due to abdominal pain, weight loss and diarrhea. Colonoscopy showed multiple erosions of the cecum; histology showed severe inflammation suspected of CD (Fig. 2). EnteroCT found a 15-cm long thickening of the terminal ileum, associated with mesenteric fat involvement and diffuse mesenteric lymphadenopathy. Diagnosis of ileo-colonic CD in AS was established, and the patient was successfully treated with ADA instead of IFX.

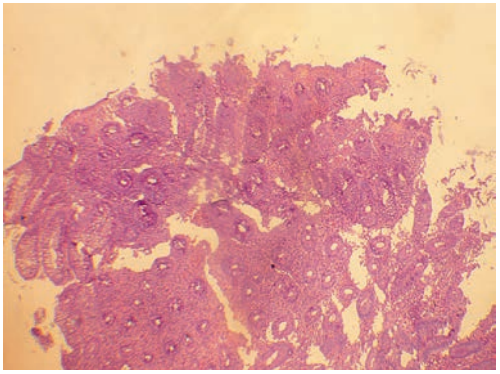

Fig. 1. Histology in the first patient in 2012: active inflammation with glandular distortion (H&E, x2.5)

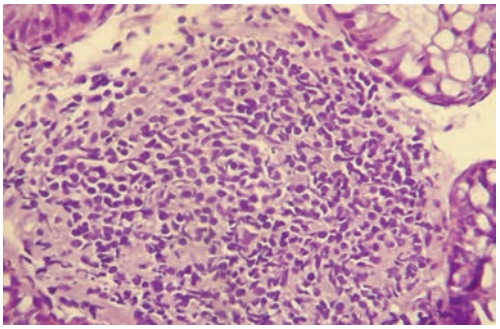

Fig. 2. Histology in the second patient in 2013: intramucosal granuloma in the cecal mucosa (H&E, x40).

Crohn's disease is rarely associated with AS. This is probably because AS is strongly related to HLA-B27 which in turn is generally not linked to IBD [4]. However, the cases reported above confirm that evolution of AS towards IBD, and CD in particular, may indeed occur.

Interestingly, one case of CD in AS occurred despite continuous treatment with IFX. The reason is yet unknown. A pathophysiological hypothesis is that, in predisposed patients with genetic susceptibility, i.e. harbouring *CARD15* gene variants, the introduction of anti-TNF alpha may modify the cytokine balance and lead to development of IBD. Another hypothesis is that profound inhibition of the inflammation by IFX could trigger a marked immune deficiency with development of severe inflammation.

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Celiac disease and common variable immunodeficiency: a familial inheritance?

To the Editor,

Celiac disease (CD) is associated with autoimmune disorders and immune deficits, such as common variable immunodeficiency (CVID) [1]. CVID is a heterogeneous group of deficient antibody production diagnosed by well-stated criteria [2]. It may display infectious diarrhea [3] and its association with CD has been controversial, since villous atrophy may not always be improved by a gluten-free diet (GFD). This aspect has been clarified by Biagi et al who pointed out the possibility that the only suitable tool is the response to GFD [4]. Both CD and CVID show a family inheritance and inducible co-stimulator (ICOS, a genetic polymorphisms invoked for CD) has a crucial role in altered lymphocyte maturation characterizing CVID [5]. Nevertheless, the presence of CD in first-degree relatives of patients affected by CVID has never been detected. Therefore, we believe it is of interest to report the case of a 30-year young male patient with CD whose sister suffered from CVID.

Admitted to our Unit for acute diarrhea and fever, his family history revealed a sister affected by CVID, treated with periodic immunoglobulin replacement. Empiric rehydration and antibiotic therapy (ciprofloxacin 250mg x 2/day) induced rapid disappearance of symptoms. Laboratory tests excluded humoral immune deficiency, but showed folate, B12 vitamin, iron and transferrin saturation deficiency. So, we performed the anti-tissue transglutaminase and anti-endomysium assay (positive) and upper endoscopy with distal duodenum histology (Marsh grade 3A CD). A GFD was initiated and six months later laboratory and duodenal histology became normal.

Accordingly, we believe that this case could stimulate a better knowledge of the topic. The principal point is the possibility that CD and CVID association may be observed not only in the same subject, but even in two different first-degree relatives. Moreover, it emphasizes some other points. Firstly, patients with CVID could be screened for infectious, immunological causes of gastrointestinal symptoms and CD. In the presence of malabsorption and absence of intestinal infections, a distal duodenal biopsy should be performed. On the other hand, in first-degree relatives of patients with CVID, in the presence of either atypical clinical signs of CD and features of malabsorption, the search for anti-transglutaminase antibodies could be useful. This approach may be interesting to detect inheritance patterns between CD and CVID in a large series of patients.

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Renal amyloidosis after a short period since diagnosis of ileocolonic Crohn's disease

To the Editor,

We read the study of Pukitis et al with great interest. Pukitis and colleagues described a patient with Crohn's disease (CD) complicated by AA amyloidosis, which was treated with infliximab [1]. On this occasion, we would like to share our experience with a case of AA amyloidosis due to ileocolonic CD.

A 44 year-old man presented with peripheral edema of both lower extremities. The patient had a history of ileocolonic CD for six months and had been on corticosteroid (60 mg/day) and azathioprine (200 mg/day) treatment for three months owing to activation of CD. After the active disease was controlled, remission was continued with azathioprine treatment. He had 1-2 stools per day with normal form. On physical examination,

he was afebrile, had marked peripheral edema in both lower extremities and Muehrcke's lines on nails. Blood tests showed a white-cell count of 12,100 per mmc, erythrocyte sedimentation rate 71 mm, C reactive protein 40 mg/l, total protein 4 g/dl, albumin 2.1 g/dl, creatinine 1.2 mg/dl. The 24-hour urinary protein was over 9 g/day. Crohn's disease activity index was 53. Colonoscopic examinations confirmed the underlying disease activity. Renal biopsy was performed and Congo red staining showed the presence of characteristic (AA type) amyloid deposition. The patient was confirmed with secondary amyloidosis (SA) due to CD and treated with adequate diet, ACE inhibitors, colchicine, azathioprine and adalimumab.

Chronic active inflammation is generally accepted as a cause of SA. However, the time it takes for this to occur is unknown. Secondary amyloidosis is a rare complication in early CD and this situation could be dependent on the underlying chronic silent disease [2]. Hypoalbuminemia in patients with CD can be defined as a reduction in albumin levels in response to the secondary acute phase or protein-losing enteropathy. Therefore, we believe that in these patients especially in whom disease was controlled, a routine 24-hour urine investigation can be beneficial for the early diagnosis of nephropathy prior to the appearance of oedema. Also, renal biopsy is a legitimate approach for proteinuria (over 1g/day) in eliminating nephropathic processes.

Finally, the goal of therapy in patients with SA is to treat the underlying inflammatory process. TNF alpha inhibitors are useful for the treatment of amyloidosis secondary to CD [1, 3, 4]. However, most patients with SA are candidates for renal transplantation due to long term progression of end-stage renal failure.

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