

Adalimumab-induced autoimmune hepatitis in a patient with Crohn's disease



Hepatitis autoinmune causada por adalimumab en un paciente con enfermedad de Crohn

Biological therapies are increasingly being used for immune-mediated, inflammatory disorders. Minor side effects of treatment with TNF α blockers agents are common, including upper respiratory tract infections, asthenia, fever and headache. More serious side effects are less common. The following case report shows an autoimmune hepatitis (AIH) after beginning of adalimumab, to our knowledge, the first case described in a patient with Crohn's disease.

A 54-year-old male patient was diagnosed with ileo-colonic Crohn's disease (Montreal Classification A3, L3, B1), and due to steroid and azathioprine refractory disease, TNF α blockers agent therapy was considered. Cutaneous tuberculin (Mantoux) test was positive, without signs of active tuberculosis infection on chest X-ray, so prophylactic treatment with isoniazide was started. After one month of prophylaxis, infliximab (IFX) was started with standard dose (intravenously 5 mg/kg of weight at weeks 0, 2 and 6). Due to a "serum sickness-like" reaction after the second dose, it was switched to subcutaneous adalimumab (ADA) (160 mg on day 0, 80 mg on day 14 and 40 mg each for 14 days). The presence of antinuclear antibodies was not assessed during infliximab therapy. Liver tests performed before starting azathioprine, isoniazide and infliximab, as well as periodically during such treatments, were normal. After 9 months, isoniazide was stopped. As clinical manifestations persisted, adalimumab dose was escalated up to 40 mg every 7 days, achieving clinical and biochemical (C reactive protein) remission. After six months of adalimumab therapy, blood test showed elevated liver enzymes (ALT 70 UI/mL, normal range up to 35; AST 102 UI/mL, normal range up to 37); results were confirmed two weeks later. Patient denied alcohol intake. Hepatitis C antibodies, Hepatitis B surface antigen and Hepatitis B DNA were negative. Ferritin, transferrin saturation index, ceruloplasmin, serum copper, alfa-1-antitrypsin, HFE mutations were also negative; antinuclear autoantibodies were positive (1/320), with homogeneous pattern; liver ultrasound examination and abdominal CT scan did not show any abnormalities. Percutaneous liver biopsy showed portal areas with inflammatory infiltrate of lymphocytes and plasmatic cells, with no periportal affection. Histiocytes and lymphocytes infiltrate the acini, with cytolysis foci, focal necrosis and mild steatosis. Simplified criteria for the diagnosis of autoimmune hepatitis revealed a score of 6, allowing the diagnosis of "probable autoimmune hepatitis". Adalimumab was interrupted, and after one month liver tests and autoantibodies became normal. Clinical activity led us to start methotrexate, however ileo-hemicolectomy was necessary three years later because of obstructive symptoms. Azathioprine was not sufficient to prevent anastomotic recurrence so certolizumab was started in standard doses (400 mg subcutaneously at weeks 0, 2 and 4, and 400 mg every 4 weeks thereafter). No relevant liver test abnormality was observed after 3 years of follow up.

Drug induced autoimmune hepatitis (DIAIH) is only documented in the literature as case reports and case series. Differentiation between AIH, DIAIH, and drug-induced liver injury (DILI) can be extremely difficult; chronologically correlation between liver test and initiation and withdrawal of drugs and liver biopsy may help. As explained in our case, normalization of antinuclear antibodies and transaminase levels after etiological agent removal is highly suggestive of adalimumab induced-AIH, although we cannot confirm the absence of antinuclear antibodies after first biological therapy, infliximab. Moreover, non-immune-mediated liver injury has been described during TNF α blockers therapy.

Autoimmune disorders are documented side effects of TNF α blockers agents, and they are increasing as these agents become more frequently used. Autoimmune hepatitis is one of the most recently described adverse event. Twenty-five cases of TNF α blocker-AIH have been described in the literature, 19 IFX-induced, 4 ADA-induced and 2 etanercept-induced, predominantly in patients with seronegative spondyloarthropathies. Rodrigues et al.¹ reported eight cases of DIAIH among inflammatory bowel disease, rheumatoid arthritis and ankylosing spondylitis patients under antiTNF α treatment; all of them received successful corticosteroid therapy. There are four biopsy-proven ADA-induced AIH cases reported in the literature.¹⁻⁴ All of them arise in patients diagnosed with rheumatic disease patients and need for corticosteroids to reach remission. As in the present case, it has been previously described absence of recurrence of antiTNF α induced-AIH after switching of antiTNF α agent,⁵ suggesting that AIH is not a class effect of antiTNF α .

In conclusion, DIAIH is a rare adverse event that should be taken into account by all physicians using antiTNF α drugs. High degree of suspicion should promptly drive us to perform a liver biopsy and withdraw the drug. Corticosteroid and other immunosuppressant may be useful, and monitor liver laboratory tests is recommended in case of substitution of the drug by a same-class therapy, although relapse has not yet been described.

Conflict of interest

None.

References

- Rodrigues S, Lopes S, Magro F, Cardoso H, Horta e Vale AM, Marques M, et al. Autoimmune hepatitis and anti-tumor necrosis factor alpha therapy: a single center report of 8 cases. *World J Gastroenterol*. 2015;21:7584-8.
- Adar T, Mizrahi M, Pappo O, Scheiman-Elazary A, Shibolet O. Adalimumab-induced autoimmune hepatitis. *J Clin Gastroenterol*. 2010;44:e20-2.
- Grasland A, Sterpu R, Boussoukaya S, Mahe I. Autoimmune hepatitis induced by adalimumab with successful switch to abatacept. *Eur J Clin Pharmacol*. 2012;68:895-8.
- Petrikova J, Jarcuska P, Svajdlar M, Pella D, Macejova Z. Autoimmune hepatitis triggered by adalimumab and allergic reactions after various anti-TNF α therapy agents in a patient with rheumatoid arthritis. *Isr Med Assoc J*. 2015;17:256-8.

5. Cravo M, Silva R, Serrano M. Autoimmune hepatitis induced by infliximab in a patient with Crohn's disease with no relapse after switching to adalimumab. *BioDrugs*. 2010;24 Suppl 1:25–7.

José Miranda-Bautista^a, Luis Menchén^{a,b,c,*}

^a *Servicios de Aparato Digestivo Hospital General Universitario Gregorio Marañón - Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain*

^b *Centro de Investigación en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Instituto de Salud Carlos III Spain*

^c *Departamento de Medicina, Universidad Complutense de Madrid, Spain*

* Corresponding author.

E-mail address: lamenchen.hgugm@salud.madrid.org (L. Menchén).

2444-3824/

© 2018 Elsevier España, S.L.U. All rights reserved.

Severe upper gastrointestinal bleeding due to eosinophilic gastritis



Hemorragia digestiva alta severa por gastritis eosinofílica

Eosinophilic gastritis (EG) is an uncommon disease that may manifest itself with dyspeptic symptoms, nausea, vomiting and epigastric pain. At onset, digestive hemorrhage is atypical. The incidence of EG has increased in the past few years. The infiltration of eosinophils can affect any part of the digestive tract. The presence of at least 15 eosinophils per high-power field (HPF) is essential for diagnosis. Here, we present a patient with recurrent epigastric pain that started with severe upper gastrointestinal bleeding due to EG.

Our patient, a 15-year-old female, had been studied since she was 9 years old due to a recurrent abdominal pain and severe anemia. Prior tests included the results of 6 gastroscopies with biopsies and 1 colonoscopy. They showed chronic gastritis, a nodular pattern in the gastric antrum, and infection by *Helicobacter pylori*, which was later treated and eradicated. Only one gastric biopsy showed an increase in eosinophils, no specific treatment was carried out. Furthermore, the colonoscopy results presented were normal. Additional studies for coeliac disease were tested and the results came negative (antitransglutaminase antibodies, HLA DQ2 DQ8 and normal duodenal biopsies).

At 14 she was hospitalized due to dizziness and hematemesis. Laboratory tests showed a normocytic-hypochromic anemia (hemoglobin 6.7 g/dL and hematocrit 21%). Metabolic profile, lipase, and clotting test were normal. She was treated with proton pump inhibitors (PPIs), intravenous iron and blood transfusions. A gastroscopy was performed and red blood remains were found with an ulcer Forrest IIA in the gastric body. She was then treated with adrenaline, ethoxy-sclerol and hemostatic clips.

After 6 days, another gastroscopy was performed. The results revealed a nodular pattern in the fundus and gastric body (Fig. 1A). Biopsies were taken and a chronic inflammatory infiltrate was observed. No other pathology was seen. The rapid urease test for *H. pylori* was repeated and came out negative.

Laboratory findings were repeated 3 months later and showed hemoglobin values of 12.8 g/dL, a hematocrit of 38.7%, no peripheral blood eosinophilia, pepsinogen of 74 ng/mL, gastrin of 68.8 pg/mL, Calprotectin of 11 mg/kg,

negative antinuclear antibodies and stool culture. Studies of food allergies were positive on nuts, skin and blood.

A gastroscopy was repeated one year later. It showed the previously observed nodular pattern. The biopsies of the gastric fundus and body showed an acute marked eosinophilia in the lamina propria and muscularis mucosa. The eosinophile count was of 40 HPF (Fig. 1B).

After the tests, she was treated with ranitidine 300 mg/day, ebastine 10 mg/day and a diet free of nuts. No abdominal pain, anemia, or recurrence of bleeding were observed in the following 18 months. A control gastroscopy was performed that showed a marked improvement in eosinophile infiltrate (count below 10 eosinophils).

The incidence of EG is estimated as 1–30/100,000. The most common symptom is abdominal pain. Other “severe” signs, such as digestive hemorrhage, is uncommon. Three similar cases have been reported.^{1,2} It should be noted that our case is the only one that presented an episode of severe bleeding with hemodynamic repercussion. When the gastroscopy was performed, our patient had blood in the stomach and an ulcer. The entire colon was checked, no other lesions were found and a test of eosinophilia in peripheral blood came out negative.

The suspicion of the disease becomes essential in its diagnosis. Our patient required more than 4 years and 10 gastroscopies before diagnosed. Multiple gastric biopsies should be taken and the pathologist should be aware about EG. Apparently EG is not as uncommon as previously thought and missed diagnosis are high.^{3,4}

Although eosinophilia or leukocytosis are usually found,⁴ they are not essential for the diagnosis of EG. In our case eosinophil count was normal. The most common endoscopic presentation is mucosal edema and hyperemia, followed by mucosal erosion and hemorrhage. Our patient presented erythema, erosions, lymphonodular hyperplasia and granular mucosal changes at the antrum, fundus, and pyloric regions.

The treatment is based on diet control and systemic or enteral administration of corticosteroids. Other therapies as histamine blockers, mast cell stabilizers, or leukotriene inhibitors can also be used. Current therapies include monoclonal antibody against IgE and IL-5. In this case, the treatment with diet, oral antihistamines and anti-H2, the patient became asymptomatic.

In summary, when a patient presents peptic ulcer not related to *H. pylori* or non-steroidal anti-inflammatory drug use, the presence of EG disease should be considered and biopsies should be performed for the diagnosis.