Intrahepatic cholestasis in Bruton's agammaglobulinemia receiving mesalamine for co-morbid Crohn's disease

Sir,

The salicylate derivatives mesalamines are used to treat both ulcerative colitis and Crohn's disease.[1] Mesalamines are almost devoid of toxicity, apart from very low figures of nephrotoxicity as derived from large population surveys.[2] Indeed, meticulous analysis of the literature reveals some almost anecdotal cases of cholestatic hepatitis in inflammatory bowel disease (IBD) patients receiving these drugs. We recently encountered one of such patients and we thought it worth describing him, owing to the presence of a peculiar co-morbidity.

A Caucasian male patient born in 1986, seen at another center in 1989 for eczemas and recurrent infection, was found frankly hypogammaglobulinemic, with the absence of CD19 + B-lymphocytes from peripheral blood. The clinical diagnosis of X-linked agammaglobulinemia (Bruton's) was confirmed by sequencing of gene BTK (1610-11TC > AG) in March 1997. On monthly infusions of gamma-globulins ever since, the patient experienced control of his infectious episodes. Erythema nodosum and pericarditis developed in September 2008 and June 2009 respectively: The former subsided spontaneously, the latter responded to non-steroidal anti-inflammatory drugs (NSAIDs) and colchicines. Beginning January 2010, patient's serum gamma globulin levels were falling leading to an increase in the infusion frequency. There was onset of abdominal malaise and diarrhea accompanied by hypoalbuminemia, with sharp increase of serum C-reactive protein and fecal calprotectin. Because the family history reported a brother with a confirmed diagnosis of gastro-esophageal Crohn's disease, the patient was referred to us for work-up. At our Center, clinical examination and biochemical data were consistent. In a patient with an impaired humoral immunity by definition, determination of anti-Saccharomyces cerevisiae antibodies was omitted. Colonoscopy revealed confluent ulcers of the valve, with the accompaniment of aphthous lesions of the distal loop. Having set the diagnosis of ileocolonic Crohn's disease on this basis, the patient was provisionally begun on mesalamine 500 mg thrice a day in May 16, 2012, with subjective remission; check-up in June 14, revealed mild aminotransferase elevation, accompanied, yet, by a significant increment of cholestastic enzymes: aspartate transaminase (AST)/alanine aminotransferase (ALT) 48/45 (normal value [n.v.] 10-40 U/l); alkaline phosphatase/gamma-glutamil transferase 231/227 (n.v. <90 and <50 U/l respectively). The patient was symptomless and an ultrasound ruled out biliary stones or bile duct dilation. Autoimmune hepatitis was ruled out by a negative autoantibody profile, including antinuclear antibody and anti-liver/kidney microsomal-1 antibodies; being under the supervision of a hematology unit for his myelodysplastic syndrome, the patient was being routinely monitored for hepatitis virus markers negativity. Mesalamine was immediately discontinued and 1 month later (July 13) the liver enzymes had dropped to normal: AST/ALT 41/12; alkaline phosphatase/gamma-glutamil transferase 73/21. By contrast, the need for gamma globulin infusions to keep the least but still protective level had increased again. To further scrutinize the hypothesis of a mesalamine-related hepatitis-like cholestatic reaction, we entered the patient's data into the 10-point Naranjo's algorithm.[3] This patient's case scored 8 ("probable likelihood"), with 4 points being due to the existence of similar claims in the literature and to the onset and improvement of the reaction on starting and withdrawing the drug respectively. We subsequently decided to switch the patient to budesonide, in order to attempt

to control what looked like a protein-losing enteropathy linked to his unchecked Crohn's disease. Most recently, budesonide was changed for balsalazide, which transports mesalamine to the colon, after breakage of the azo bond with its carrier. Follow-up after a month has failed enzyme changes and we are now keeping the patient on balsalazide capsules bid which deliver the equivalent of 525 mg of mesalamine daily.

This is a young man developing biochemical cholestasis shortly after therapeutic doses of mesalamine for his ileocolonic Crohn's. Speculation of the existence of a cause-effect relationship between this drug prescription and the liver reaction is warranted by the prompt normalization of the data upon drug withdrawal and is rendered reasonable by the knowledge that aminosalicylates become concentrated in the liver to undergo acetylation. The "likelihood" score yielded by the Naranjo algorithm may represent a further formal validation of our hypothesis. On the other hand, rapid normalization of all abnormality contraindicated a liver biopsy. Besides an interesting claim that mesalamines can cause granulomatous hepatitides,[4] we found five reports by matching the terms "mesalazines" with cholestasis in the Medline. Of them, in fact, only two turn out to be relevant: Of the two described individual patients, one case of Crohn's disease, normalizing his liver enzymes some 40 days after mesalamine discontinuation, seems to closely duplicate our own observation.[5] Manual elaboration of the references in another report disclosed an emphasis on the presence of accompanying hypersensitivity phenomena,[6] a feature which we failed to observe. Several circumstances of various orders support the diagnosis of Crohn's disease for this patient: A positive family history; the clinical, laboratorial and endoscopic data; the onset of two among the typical extra-intestinal manifestations (erythema nodosum and pericarditis) of the IBDs, the response to mesalamine. Interestingly enough, Crohn's or, if one prefers, Crohn's like pictures, are being increasingly described in conjunction with myelo-hematological disorders affecting both the adaptive and the innate arms of the immune response.[7] Though the Bruton's variant is most frequently associated with gastric adenocarcinoma, a few cases of co-morbid Crohn's – like are not lacking[8] thus negating the primacy to the current observation. To the best of our knowledge, by contrast, this is the first description of a mesalamine-dependent cholestatic reaction in a Crohn's-like disease associated to Bruton's defect. Failure to provoke a re-challenge liver reaction on balsalazide can be explained, on the simplest ground, by the fact that the mesalamine dose released by balsalazide is one-third that released by the previous prescription. On these premises, this reaction would be dose-dependent rather than allergic, a reasonable hypothesis in an immunoglobulin-deficient subject. Further explanations, of a speculative nature, would concentrate on a role of the balsalazide carrier allowing different blood levels or a modified drug release to the liver. The next relevant question is why mesalamine, a molecule that has proven poorly effective for Crohn's disease,[9] at least initially seems to have controlled the ileocolonic lesions of this patient. One possible explanation may rely with the absence of adjunctive risk factors (smoke, NSAIDs) and by the fact that often these Crohn's-like syndromes in co-morbidity with myelodyspastic disease might behave differently from "idiopathic" Crohn's.

Though an extremely rare event, clinicians should remain aware of the hepatotoxic potential of mesalamine and be prompt in its withdrawal and replacement, particularly in patients with co-morbid Crohn's such as the individual that is described herein. Circumstantially, the present findings suggest that it might be possible to circumvent the problem by simple replacement of the mesalamine formulation.

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