

## Isolated fever induced by mesalamine treatment

Rita Slim, Joseph Amara, Roy Nasnas, Khalil Honein, Joseph Bou Jaoude, Cesar Yaghi, Fady Daniel, Raymond Sayegh

Rita Slim, Joseph Amara, Khalil Honein, Joseph Bou Jaoude, Cesar Yaghi, Fady Daniel, Raymond Sayegh, Department of Gastroenterology, Hotel Dieu de France University Hospital, Saint Joseph University, Beirut 94010, Lebanon

Roy Nasnas, Department of Infectious Diseases, Hotel Dieu de France University Hospital, Saint Joseph University, Beirut 94010, Lebanon

Author contributions: Slim R and Amara J designed the paper; Nasnas R, Honein K, Jaoude JB, Yaghi C, Daniel F and Sayegh R revised the paper.

Correspondence to: Rita Slim, MD, Department of Gastroenterology, Hotel Dieu de France University Hospital, Saint Joseph University, Beirut 94010, Lebanon. [rslmkaram@hotmail.com](mailto:rslmkaram@hotmail.com)

Telephone: +961-1-615300 Fax: +961-1-615300

Received: September 23, 2012 Revised: December 17, 2012

Accepted: December 22, 2012

Published online: February 21, 2013

### Abstract

Adverse reactions to mesalamine, a treatment used to induce and maintain remission in inflammatory bowel diseases, particularly ulcerative colitis, have been described in the literature as case reports. This case illustrates an unusual adverse reaction. Our patient developed an isolated fever of unexplained etiology, which was found to be related to mesalamine treatment. A 22-year-old patient diagnosed with ulcerative colitis developed a fever with rigors and anorexia 10 d after starting oral mesalamine while his colitis was clinically resolving. Testing revealed no infection. A mesalamine-induced fever was considered, and treatment was stopped, which led to spontaneous resolution of the fever. The diagnosis was confirmed by reintroducing the mesalamine. One year later, this side effect was noticed again in the same patient after he was administered topical mesalamine. This reaction to mesalamine seems to be idiosyncratic, and the mechanism that induces fever remains unclear. Fever encountered in the course of a mesalamine treatment in ulcerative colitis must be considered a mesalamine-induced fever when it cannot

be explained by the disease activity, an associated extraintestinal manifestation, or an infectious etiology.

© 2013 Baishideng. All rights reserved.

**Key words:** Mesalamine; 5-aminosalicylic acid; Side effects; Adverse reactions; Fever

Slim R, Amara J, Nasnas R, Honein K, Jaoude JB, Yaghi C, Daniel F, Sayegh R. Isolated fever induced by mesalamine treatment. *World J Gastroenterol* 2013; 19(7): 1147-1149 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v19/i7/1147.htm> DOI: <http://dx.doi.org/10.3748/wjg.v19.i7.1147>

### INTRODUCTION

Mesalamine is a well-known treatment for inflammatory bowel diseases (IBDs), particularly ulcerative colitis (UC), in which it is used for remission induction and maintenance therapy. Mesalamine is considered a safe drug, but some side effects have been described in the literature. We report a case of mesalamine-induced isolated fever in a patient with UC.

### CASE REPORT

A 22-year-old-man presented with a 1 wk history of apyretic acute bloody diarrhea, which was treated with 500 mg of metronidazole three times a day (TID) without clinical improvement. At this stage, flexible sigmoidoscopy showed diffuse hyperemic mucosa with few erosions. The biopsies indicated infectious colitis. The blood analysis and stool exam were normal. Treatment with 500 mg of ciprofloxacin twice a day and 500 mg of metronidazole TID was prescribed. Ten days later, the patient's clinical condition worsened, with passage of 5 stools per day with mucus and blood. A complete colonoscopy was performed, which demonstrated diffuse pancolitis with superficial ulcerations, loss of vascular

pattern and easy contact bleeding from the mucosa. The terminal ileum was normal. The colonic biopsies were consistent with UC. The blood analysis at this time was also unremarkable except for the C reactive protein (CRP) level, which was 17 mg/dL. Treatment with 4 g of pH-dependent release mesalamine (Asacol<sup>®</sup>) was started, and a significant clinical improvement was noted, with resolution of the bloody diarrhea and passage of 2 normal stools per day. Ten days later, while the patient was doing well, he presented with a 39 °C fever with rigor, myalgia and anorexia. Upon admission, 6 d after the fever onset, his physical examination was normal.

A blood analysis showed a hemoglobin level of 12.2 g/dL, a white blood cell count of 8600/mL (of which 77% were granulocytes), a platelet count of 264 000/mL, and a CRP level of 104 mg/dL, with normal levels of liver and pancreatic enzymes. Serologies for typhoid fever, brucellosis, parvovirus, Epstein Barr virus and cytomegalovirus were negative. Stool, blood and urine cultures were also negative. The tuberculosis skin test was normal as well as the chest X-ray and cardiac ultrasound. The mesalamine was discontinued, and the fever was treated symptomatically with paracetamol. Two days later, the patient's clinical condition improved, with the disappearance of the febrile syndrome and a decrease in the CRP level to 62 mg/dL. After discussing the matter with the patient and because a reactivation of the colitis was feared, particularly after the rapid remission that was obtained with the use of 5-aminosalicylic acid (5-ASA), we decided to reintroduce another time-dependent release mesalamine (Pentasa<sup>®</sup>) under medical surveillance. After administering the second dose, the patient presented with a 38.5 °C fever with rigors. Mesalamine was stopped, and the fever resolved the following day without any intervention. The diagnosis of fever related to mesalamine was confirmed. Two days later, the patient presented with bloody diarrhea, and a treatment with 40 mg of prednisone and 150 mg of azathioprine was started, with rapid improvement. The patient was discharged in good condition. Two months later, the prednisone was stopped after tapering, and the patient was maintained in clinical remission with azathioprine. Eight months later, the patient presented with a flare-up of his colitis. He consulted another gastroenterologist, who treated him with suppositories of Asacol because the rectosigmoidoscopy showed an active proctitis. Two days later, the patient presented with the same symptoms encountered with oral mesalamine (*i.e.*, fever and rigors), which spontaneously resolved after stopping the topical treatment.

## DISCUSSION

The 5-ASA agents are known to be safe and remain among the first-line approaches for inducing remission and preventing relapse in UC<sup>[1]</sup>. These benefits of 5-ASA agents are less impressive in the treatment of mild to moderate Crohn's disease. Their possible role in chemo-

prevention of colon cancer strengthens the indication for the long-term use of 5-ASA<sup>[2]</sup>.

The efficacy of sulfasalazine in UC has been known since 1940, but the use of this drug was problematic because of its side effects, either dose related or idiosyncratic reactions, such as headache, dyspepsia, nausea, hypersensitivity rash, hemolytic or aplastic anemia, and pulmonary or hepatic dysfunction<sup>[3]</sup>. The identification in sulfasalazine of the 5-ASA moiety, which is responsible for the therapeutic effects, led to the development of new drugs that delivered 5-ASA directly to the colonic mucosa with fewer side effects.

These new drugs included mesalamine or 5-ASA itself, olsalazine (Dipentum; a dimer of 5-ASA) and balsalazide (Colazal or Colazide; a pro-drug of 5-ASA). In their systematic review of the safety of 5-ASA-based agents, Loftus *et al*<sup>[3]</sup> concluded that all of these agents appeared to be safe and that the fraction of patients experiencing adverse events was similar to that seen in patients treated with placebo.

However, severe adverse events encountered with mesalamine therapy have been reported as isolated cases. A French pharmacovigilance study of mesalamine microgranules (Pentasa) reported between 6.6 and 9.0 adverse events per million treatment days over a 2-year period, including cases of pancreatitis, hepatitis, pericarditis and hematological disturbances<sup>[4,5]</sup>. Other side effects have also been reported, such as worsening colitis, renal toxicity (interstitial nephritis and nephrotic syndrome), pulmonary toxicity (interstitial lung disease and fibrosis, bronchiolitis obliterans, pulmonary granulomatosis and eosinophilic pleural effusion) hair loss and Stevens-Johnson syndrome<sup>[6]</sup>. Some of these drug-related complications must be distinguished from the extraintestinal manifestations of IBD, and they may arise independently of disease activity. The causal relationship between mesalamine administration and the occurrence of the adverse event is established by the appearance of the symptoms after the administration of the 5-ASA compound, the rapid resolution of the symptoms after discontinuation and the reoccurrence of the same symptoms if the treatment is restarted<sup>[6]</sup>.

The mechanism by which mesalamine induces side effects remains unclear. In some cases, the occurrence of a complication seems to be dose related, whereas in other cases it appears to be more of an idiosyncratic reaction<sup>[7]</sup>. Moreover, the pathogenesis of the fever induced by mesalamine remains unknown.

In cases of acute pancreatitis, the suggested mechanism is an increased permeability of the pancreatic duct directly due to the effects of salicylic acid<sup>[8]</sup>. In cases of mesalamine-induced exacerbation of UC<sup>[9]</sup> or myocarditis<sup>[10]</sup>, eosinophilic infiltration of the colon and the myocardium point to an allergic drug reaction.

Mesalamine-related complications are known to occur with oral and topical preparations. Some reports have claimed an absence of cross reactivity among different 5-ASA-based drugs<sup>[11]</sup>.

Our patient presented with an isolated fever while his bloody diarrhea was improving. Mesalamine-induced isolated fever has been reported by Gonzalo *et al*<sup>[12]</sup> and the causal relationship was proved by a placebo-controlled challenge test and a protocol of desensitization, which was realized successfully. We realized, under medical surveillance, a challenge test with a different 5-ASA drug, and the fever reappeared earlier than the first time (1 d *vs* 10 d). On both occasions, no other causes of fever could be identified, and the fever disappeared spontaneously after stopping the drug. Moreover, reintroducing the mesalamine in suppository form one year later led to the same side effect: an isolated fever that also resolved after stopping the treatment. Although mesalamine seemed to be efficacious, we did not choose to adopt a desensitization protocol at that time because the patient feared a more severe reaction, and we needed another strategy to treat the reactivated colitis.

In conclusion, mesalamine appears to be safe and to achieve good results in IBD patients, particularly those with UC. Side effects of 5-ASA-based drugs are rare, but they should be distinguished from extraintestinal manifestations and should be suspected when the symptoms resolve with the discontinuation of the treatment and reappear with its reintroduction. An isolated fever can reappear on multiple occasions after the reintroduction of various formulations of mesalamine, as illustrated in our case report.

## REFERENCES

- 1 **Ford AC**, Achkar JP, Khan KJ, Kane SV, Talley NJ, Marshall JK, Moayyedi P. Efficacy of 5-aminosalicylates in ulcerative colitis: systematic review and meta-analysis. *Am J Gastroenterol* 2011; **106**: 601-616 [PMID: 21407188 DOI: 10.1038/ajg.2011.67]
- 2 **Cheng Y**, Desreumaux P. 5-aminosalicylic acid is an attractive candidate agent for chemoprevention of colon cancer in patients with inflammatory bowel disease. *World J Gastroenterol* 2005; **11**: 309-314 [PMID: 156377333]
- 3 **Loftus EV**, Kane SV, Bjorkman D. Systematic review: short-term adverse effects of 5-aminosalicylic acid agents in the treatment of ulcerative colitis. *Aliment Pharmacol Ther* 2004; **19**: 179-189 [PMID: 14723609]
- 4 **Marteau P**, Nelet F, Le Lu M, Devaux C. Adverse events in patients treated with 5-aminosalicylic acid: 1993-1994 pharmacovigilance report for Pentasa in France. *Aliment Pharmacol Ther* 1996; **10**: 949-956 [PMID: 8971293 DOI: 10.1046/j.1365-2036.1996.92264000.x]
- 5 **Rogler G**. Gastrointestinal and liver adverse effects of drugs used for treating IBD. *Best Pract Res Clin Gastroenterol* 2010; **24**: 157-165 [PMID: 20227029 DOI: 10.1016/j.bpg.2009.10.011]
- 6 **Schroeder KW**. Is mesalamine safe? *Gastroenterol Hepatol (NY)* 2007; **3**: 878-879 [PMID: 21960801]
- 7 **Sossai P**, Cappellato MG, Stefani S. Can a drug-induced pulmonary hypersensitivity reaction be dose-dependent? A case with mesalamine. *Mt Sinai J Med* 2001; **68**: 389-395 [PMID: 11687867]
- 8 **Arai Y**, Arihiro S, Ide D, Odagi I, Itagaki M, Komoike N, Nakao Y, Takakura K, Saruta M, Matsuoka M, Kato T, Tajiri H. Acute Pancreatitis due to pH-Dependent Mesalazine That Occurred in the Course of Ulcerative Colitis. *Case Rep Gastroenterol* 2011; **5**: 610-616 [PMID: 22110423 DOI: 10.1159/000333605]
- 9 **Gupta MK**, Pollack S, Hutchings JJ. Mesalamine induced symptom exacerbation of ulcerative colitis: Case report and brief discussion. *World J Gastrointest Pharmacol Ther* 2010; **1**: 132-134 [PMID: 21577308 DOI: 10.4292/wjgpt.v1.i6.132]
- 10 **Stelts S**, Taylor MH, Nappi J, Van Bakel AB. Mesalamine-associated hypersensitivity myocarditis in ulcerative colitis. *Ann Pharmacother* 2008; **42**: 904-905 [PMID: 18430794 DOI: 10.1345/aph.1K288]
- 11 **Kung SJ**, Choudhary C, McGeady SJ, Cohn JR. Lack of cross-reactivity between 5-aminosalicylic acid-based drugs: a case report and review of the literature. *Ann Allergy Asthma Immunol* 2006; **97**: 284-287 [PMID: 17042131]
- 12 **Gonzalo MA**, Alcalde MM, Garcia JM, Alvarado MI, Fernandez L. Desensitization after fever induced by mesalazine. *Allergy* 1999; **54**: 1224-1225 [PMID: 10604561 DOI: 10.1034/j.1398-9995.1999.00298.x]

P- Reviewers Slomiany BL, Kane SV

S- Editor Huang XZ L- Editor A E- Editor Xiong L

