World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.3748/wjg.v20.i13.3716

World J Gastroenterol 2014 April 7; 20(13): 3716-3718
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

CASE REPORT

Ulcerative colitis flair induced by mesalamine suppositories hypersensitivity

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Received: September 15, 2013 Revised: November 5, 2013
Accepted: December 12, 2013
Published online: April 7, 2014

Abstract

Mesalamine suppositories have been used widely for the treatment of distal ulcerative colitis and considered to be safer than systemic administration for its limited systemic absorption. However, previous studies have shown that mesalamine suppository occasionally causes severe hypersensitivity reactions including fever, rashes, colitis exacerbation and acute eosinophilic pneumonia. Here we present a 25-year-old woman with ulcerative colitis with bloody diarrhea accompanied by abdominal pain and fever which were aggravated after introduction of mesalamine suppositories. In light of symptom exacerbation of ulcerative colitis, increased inflammatory injury of colon mucosa shown by colonoscopy and elevated peripheral eosinophil count after mesalamine suppositories administration, and the Naranjo algorithm score of 10, the possibility of hypersensitivity reaction to mesalamine suppositories should be considered, warning us to be aware of this potential reaction after administration of mesalamine formulations even if it is the suppositories.

Key words: Mesalamine suppositories; Hypersensitivity; Ulcerative colitis; Surgery; Sulfasalazine

Core tip: Mesalamine suppository, a kind of newly designed 5-aminosalicylic acid formulations, is considered safe and effective and is widely used in the treatment of distal ulcerative colitis. Few cases concerning its side effect of hypersensitivity have been reported. Herein, we report a case of ulcerative colitis flare induced by mesalamine suppository hypersensitivity in an attempt to improve our understandings of the rare side effect of mesalamine suppositories.

Ding H, Liu XC, Mei Q, Xu JM, Hu XY, Hu J. Ulcerative colitis flair induced by mesalamine suppositories hypersensitivity. *World J Gastroenterol* 2014; 20(13): 3716-3718 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i13/3716.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i13.3716

INTRODUCTION

Mesalamine suppository is a kind of newly designed 5-aminosalicylic acid formulations, it is supposed to be safe for its limited systemic absorption and lack of sulphapyridine moiety that has been implicated in many of the adverse reactions associated with sulfasalazine (SASP)[1], thus is widely used in the treatment of distal ulcerative colitis (UC). Hypersensitivity to mesalamine suppositories is very rare, there are only 3 cases documented worldwide so far. Here, we present a first case of symptomatic exacerbation of UC induced by mesalamine suppositories in China.

CASE REPORT

A 25-year-old woman experienced abdominal discomfort and diarrhea (3-5 per day) with no blood or purulence 8 months ago. Because of continuous bloody stools (1-2 per day) accompanied with crampy abdominal pain for 2 mo, she presented to the local health clinic where a pancolonoscopy was obtained which revealed erythema, edema, and shallow ulcers in rectum, she was diagnosed with UC of proctitis and treated with SASP 0.5 g *tid* for 20 d which seemed to aggravate bloody diarrhea (7-8 per day containing purulence), abdominal pain and high fever (up to 39 ℃) and generalized erythematous rashes. She was immediately admitted to the gastroenterology department of a local hospital, symptoms were improved with reduction of bloody purulent diarrhea (1-2 per day with reduced blood) and partial regression of skin lesions by comprehensive treatment including hydrocortisone, the patient then was referred to our hospital for further treatment.

On admission, physical examination revealed high temperature (37.8 ℃) and erythematous rashes all over the body with partial desquamation, a repeat pancolonoscopy confirmed previous endoscopic findings, laboratory examinations showed abnormal liver biochemical changes [alanine aminotransferase (ALT) 245 U/L, normal range: 5-40 U/L; aspartate aminotransferase (AST) 336 U/L, normal range: 8-40 U/L; alkaline phosphatase (ALP) 216 U/L, normal range: 40-150 U/L; gamma glutamyl transferase (GGT) 217 U/L, normal range: 0-50 U/L; lactate dehydrogenase (LDH) 806 U/L, normal range: 109-245 U/L]. Hepatitis serology was negative. C-reactive protein (CRP) (4.96 mg/L, normal range: 0-3 mg/L) and erythrocyte sedimentation rate (ESR) (23 mmHg, normal range: 0-20 mmHg) were slightly elevated. Peripheral white blood cell count (14.97 × 10^3/μL, normal range: 3.69-9.16 × 10^3/μL) and neutrophil count (8.35 × 10^3/μL, normal range: 2.0-7.5 × 10^3/μL) was significantly elevated, and hemoglobin was decreased slightly (9.8 g/dL, normal range: 11.3-15.1 g/dL). She was diagnosed with moderately active UC based on her symptoms and endoscopic findings, for her severe systemic symptoms and ineffectiveness of SASP treatment. Corticosteroids therapy (intravenous hydrocortisone 200 mg/d for the first 5 d and oral prednisone 40 mg/d for subsequent 3 d) was applied, resulting in significant improvement of her fever (36-37 ℃), skin rashes (basically subsided) and liver biochemical abnormalities (ALT 47 U/L, AST 18 U/L, ALP 111 U/L, GGT 101 U/L, LDH 347 U/L). While the obvious rectal irritation symptoms were still bothering her, mesalamine suppositories (0.5 g QN) were prescribed. After taking only 3 suppositories, the patient developed a temperature of 37.6 ℃, and experienced new rash in the face and aggravation of bloody purulent diarrhea (up to 10 per day with evident blood and mucosal exfoliation). Blood tests showed an increase of peripheral white blood cell count (12.31 × 10^3/μL) with normal neutrophil count, of particular note, the eosinophil count was increased to 0.71 × 10^3/μL (normal range: 0.02-0.35 × 10^3/μL). ESR and CRP were in the normal range. Stool studies were negative for infection. A proctosigmoidoscopy revealed diffuse erythema, edema, shallow ulcers and contact hemorrhage with purulent exudate beyond the view of scope, mesalamine suppositories were immediately discontinued and a 5-d steroid treatment was administered. The patient had remained symptomatic (bloody purulent diarrhea and fever), a rescue therapy of infliximab or cyclosporine A was proposed, but she refused it for her poor economic condition and severe illness at that time. She had to accept surgery eventually which removed the whole colon and the upper part of rectum. Postoperative pathology showed chronic inflammation cell infiltration with local ulceration and scattered distribution of eosinophils. For her persistent rectal irritation symptoms, a mesalamine suppository was prescribed, resulting in the recurrent bloody stool, abdominal pain and fever which were improved as soon as mesalamine suppository was discontinued, thus by an unintentional repeated medication, her intolerance of mesalamine suppositories was confirmed objectively.

DISCUSSION

SASP has been the first-line therapy to induce and maintain remission in mild to moderately active UC[2,3]. However, up to 30% of patients cannot take it due to intolerance or hypersensitivity reactions which are often attributed to the sulphapyridine moiety[4]. Mesalamine formulations, due to their less frequent causation of sulfa-related adverse events, have replaced SASP as the first-choice treatment of UC. Adverse events from hypersensitivity and intolerance can occur. Skin rash, fever, and systemic reactions have been described[5]. More severe reactions associated with use of mesalamine occur infrequently, such as pancreatic, renal, myo-pericardial and pulmonary toxicity, as well as hematological disorders[6].

In this case report, it was surprising and skeptical when the patient reported fever and rash after mesalamine suppository administration, for at least 80% of patients intolerant of SASP can tolerate mesalamine preparations[7]. However, in light of twice symptom exacerbation of UC and increased peripheral eosinophil count after mesalamine suppository administration, and the Naranjo algorithm score[6] of 10, the patient's hypersensitivity to mesalamine suppositories was confirmed.

Intolerance to SASP is not rare which are often attributed to the sulphapyridine moiety. Bousseaden *et al*[8] reported a patient intolerant to SASP (fever and skin rash), who developed a severe hypersensitivity reaction to oral mesalamine characterized by abdominal pain and blood-stained diarrhea and had to receive coloproctectomy eventually. In this case, we speculated that SASP hypersensitivity was responsible for the first symptom aggravation of UC, rashes and abnormalities of liver function. The similar adverse event after both SASP and mesalamine suppository administration in this patient suggests that this pattern of SASP intolerance may in fact be caused by the 5-aminosalicylic acid moiety of the molecule[8].

The precise mechanism of colitis exacerbation induced

by mesalamine is not clear. Scheurlen *et al*[9] mentioned that the mechanism of diarrhea caused by mesalamine was attributed to a secretory mechanism secondary to the inhibition of ileal and colonic Na^+K^+ATPase. Another proposed mechanism was an alteration of arachidonic acid metabolism which was manifested mainly with secretory diarrhea and malabsorption[10]. Both mechanisms, however, can not explain the bloody diarrhea or the endoscopic and pathological evidence of inflammation seen in this case.

Mesalamine suppositories are considered to be safer than systemic administration by bypassing the threat of small bowel absorption[11]. Three cases concerning the hypersensitivity reactions after mesalazine suppositories administration were well documented[12-14], and it is demonstrated that small amounts of enema or suppository can be absorbed when administered topically[15]. Therefore, in this case, we speculated that the hypersensitivity reactions were probably due to hematogenous spread of mesalazine absorbed by the rectal mucosa. Further investigation with blood, luminal fluid and tissue cytokine determination is required to elucidate the mechanism for this sensitivity reaction. Clinicians must keep in mind the possibility of salicylate sensitivity and colitis exacerbation, especially in atopic individuals and in patients who failed to respond appropriately to SASP.

COMMENTS

Case characteristics

This report a case of ulcerative colitis flare induced by mesalamine suppository hypersensitivity.

Clinical diagnosis

She was diagnosed with moderately active ulcerative colitis (UC) based on her severe systemic symptoms, endoscopic findings and ineffectiveness of sulfasalazine (SASP) treatment.

Differential diagnosis

In light of twice symptom exacerbation of UC and increased peripheral eosinophil count after mesalamine suppository administration, and the Naranjo algorithm score of 10, the patient's hypersensitivity to mesalamine suppositories was confirmed.

Laboratory diagnosis

Laboratory tests including peripheral neutrophil count, erythrocyte sedimentation rate, C-reactive protein and fecal pathogenic examination were nearly normal in addition to a significant increased peripheral eosinophil count. Antibiotic and intravenous steroid treatment was ineffective, and the Naranjo algorithm score was 10, the patient eventually underwent surgery. The postoperative pathology showed chronic inflammation cell infiltration with local ulceration and scattered distribution of eosinophils, and hypersensitivity to mesalamine suppositories was confirmed finally.

Experiences and lessons

Only three similar cases have been documented worldwide so far, not including this one. Clinicians must keep in mind the possibility of salicylate sensitivity and colitis exacerbation, especially in atopic individuals and in patients who failed to respond appropriately to SASP.

Peer review

Authors described a case of systemic hypersensitivity reaction on mesalamine suppository in ulcerative colitis. The description is clear and concise.

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P- Reviewers: Andus T, Bassotti G, De Silva AP
S- Editor: Gou SX **L- Editor**: Ma JY **E- Editor**: Wang CH

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ISSN 1007-9327
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9 771007 932045