



Mesalazine formulation intolerance due to suspected excipient allergy in the treatment of ulcerative colitis: a case report

Yoshinori Arai¹ · Maiko Ogawa¹ · Fumitsugu Yamane¹ · Natsuki Sumiyoshi¹ · Rikako Arimoto¹ · Yoshitaka Ando¹ · Daisuke Endo¹ · Tatsuya Nakada¹ · Ichiro Sugawara¹ · Hiroshi Yokoyama¹ · Keiko Shimoyama² · Hiroko Inomata² · Yosuke Kawahara² · Masayuki Kato² · Seiji Arihiro¹ · Atsushi Hokari¹ · Masayuki Saruta³

Received: 14 July 2020 / Accepted: 18 August 2020 / Published online: 3 September 2020
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Abstract

Mesalazine formulations are essential for treating ulcerative colitis (UC), and intolerance to these formulations complicates the treatment of this condition. Some cases of mesalazine formulation intolerance are caused by the excipients rather than the active ingredient mesalazine. Therefore, mesalazine administration can be continued in such cases by changing the mesalazine formulation. This report describes a case of intolerance to mesalazine in which UC was effectively treated by switching mesalazine formulations. A drug-induced lymphocyte stimulation test suggested that allergy to the additive povidone was the cause of mesalazine formulation intolerance. This is the first case study to identify an additive that caused mesalazine formulation intolerance.

Keywords Ulcerative colitis · Mesalazine formulation intolerance · Excipient · Drug-induced lymphocyte stimulation test

Introduction

Ulcerative colitis (UC) is an inflammatory disorder of unknown etiology that causes colonic inflammation [1–3]. If left untreated, the condition follows a remitting and recurring course throughout the patient's lifetime, and the number of cases around the world is increasing [4]. Maintaining remission improves quality of life (QOL) and decreases the risk of carcinogenesis [5, 6]. Mesalazine formulations are essential for treating UC [7, 8]; however, intolerance to these drugs complicates the maintenance of remission, promoting recurrence and increasing the risk of carcinogenesis. Some cases of intolerance to mesalazine formulations are caused

by excipients, rather than the active ingredient mesalazine, and treatment can be continued by changing the mesalazine formulation.

This report describes a case of mesalazine formulation intolerance, where a drug-induced lymphocyte stimulation test (DLST) suggested that allergy to the additive povidone was the cause of the intolerance. To our knowledge, this is the first report to identify an additive that caused mesalazine formulation intolerance. Switching mesalazine formulations was effective in this case.

Case report

The patient was a 35-year-old woman who had been treated for diarrhea and bloody stool by her local doctor. A loss of vascular pattern and granular mucosal appearance limited to the rectum were observed on colonoscopy, and she was diagnosed with UC (Fig. 1a, b) and started on pH-dependent mesalazine at a dose of 2400 mg/day. The bloody stool resolved after a few days. However, she developed a fever of 38 °C on day 9 of treatment and bloody stool recurred on day 11. She was referred to our hospital for detailed investigation due to intense abdominal pain on day 13 and was emergently admitted.

✉ Yoshinori Arai
yoshinori.a1@gmail.com

¹ Division of Gastroenterology and Hepatology, Department of Internal Medicine, The Jikei University Katsushika Medical Center, -41-2 Aoto, Katsushika-ku, Tokyo 105-8461, Japan

² Department of Endoscopy, The Jikei University Katsushika Medical Center, Tokyo, Japan

³ Division of Gastroenterology and Hepatology, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan

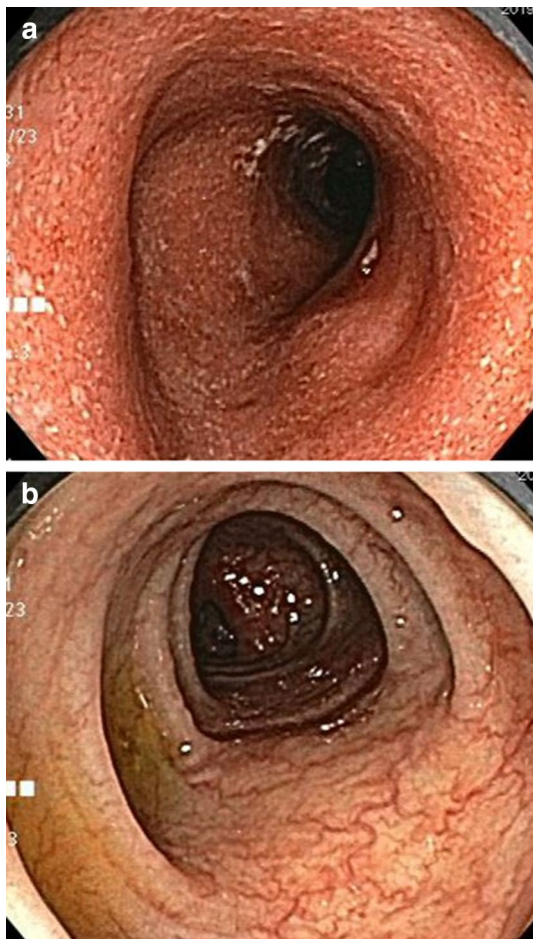


Fig. 1 Endoscopy findings at diagnosis of UC. **a** Rectum: loss of vascular pattern and granular mucosal appearance limited to the rectum (MES 2). **b** Transverse colon: visible vascular pattern and no signs of inflammation (MES 0). MES, Mayo endoscopic score

Physical examination showed body temperature 39.4 °C, blood pressure 118/71 mmHg, heart rate of 113 beats per minute, and generalized abdominal tenderness. Diarrheal frequency was up to about 20 episodes of bloody and watery stool per day. Blood tests showed a white blood cell of 6300/ μ L, C-reactive protein level of 4.48 mg/dL, and erythrocyte sedimentation rate of 24 mm/h, indicating elevated inflammatory response (Table 1). Stool culture yielded no growth.

Withdrawal of the mesalazine formulation upon admission resulted in a decreased fever (36.9 °C), with resolution of the watery and bloody stool the following day (hospital day 1). The number of bowel movements decreased from 20 to 8 times per day, with only 2 episodes on hospital day 3. The patient was diagnosed with mesalazine formulation intolerance based on the clinical course. We performed colonoscopy on hospital day 3. There was conspicuous erosion and adhesion to purulent mucosa in the rectum with loss of vascular pattern and erythema throughout the colon, indicating exacerbation of inflammation and increasing extent of

Table 1 Blood test findings on admission

Blood count		Blood biochemistry			
WBC (μ L)	6300	AST (IU/L)	8	Na (mEq/L)	139
Gran	72.6%	ALT (IU/L)	9	K (mEq/L)	3.4
Lymph	14.0%	LDH (IU/L)	160	Cl (mEq/L)	104
Mono	7.3%	T-Bil (mg/dL)	0.5	CRP (mg/dL)	4.48
Eosino	5.9%	ALP (IU/L)	144	ESR (mm/h)	24
Baso	0.2%	γ -GTP (IU/L)	16	C7-HRP	negative
RBC (μ L)	446×10^4	TP (g/dL)	6.7		
Hb (g/dL)	13.2	Alb (g/dL)	3.8		
MCV (fL)	87.7	CK (IU/L)	27		
Ht	39.1%	BUN (mg/dL)	6		
Plt (μ L)	21.7×10^4	Cr (mg/dL)	0.43		

ALP alkaline phosphatase, AST aspartate aminotransferase, BUN blood urea nitrogen, CK creatine kinase, CRP C-reactive protein, ESR erythrocyte sedimentation rate, LDH lactate dehydrogenase, MCV mean corpuscular volume, RBC red blood cell count, TP total protein, WBC white blood cell count

the lesions (Fig. 2a, b). She was diagnosed with mesalazine formulation intolerance associated with exacerbation of UC and was started on intravenous steroid therapy (prednisolone at a dose of 40 mg/day) on hospital day 4. We informed the patient that mesalazine treatment was necessary and that the symptoms of intolerance might recur. The patient provided informed consent, and we switched her medication to Multi Matrix System (MMX) mesalazine at a dose of 4800 mg/day on hospital day 11. The symptoms of intolerance did not recur, the clinical course was favorable, and she was discharged on hospital day 21. DLST was performed on hospital day 20. The DLST results were positive for pH-dependent mesalazine and negative for MMX mesalazine. Given the positive DLST for the previous formulation and the negative DLST for the new formulation, we believe the patient was allergic to an excipient in the pH-dependent mesalazine formulation.

Colonoscopy 12 weeks after discharge showed complete mucosal healing (Fig. 3a, b). The patient has been treated with MMX mesalazine alone for 1 year and remains in clinical and endoscopic remission.

Discussion

Intolerance to mesalazine formulations causes physical disease following administration, and the causes of this intolerance are divided into allergic and non-allergic mechanisms. Allergic intolerance is an abnormal immune-mediated reaction, while non-allergic intolerance is a

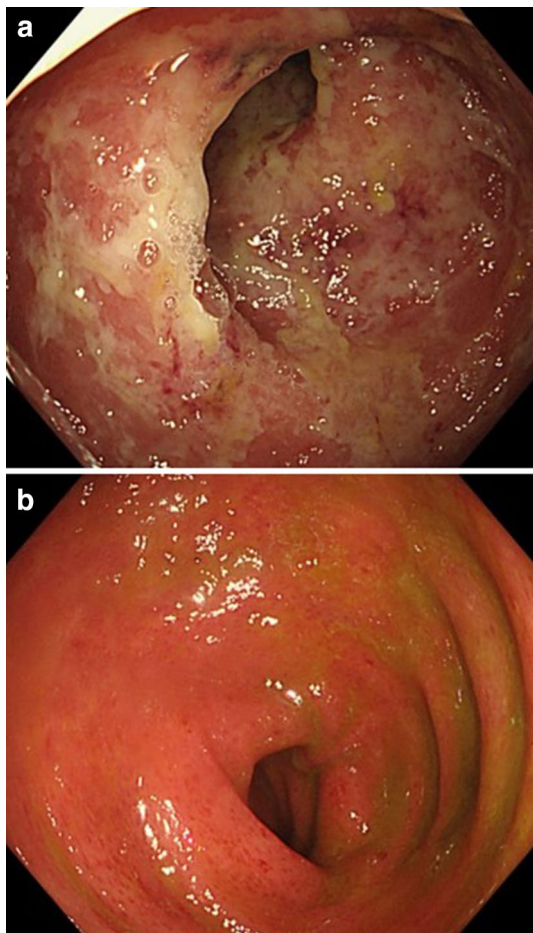


Fig. 2 Endoscopy findings at onset of mesalazine formulation intolerance. **a** Rectum: conspicuous adhesions in purulent mucosa (MES 2). **b** Transverse colon: loss of vascular pattern and erythema throughout the colon, indicating exacerbation of inflammation and increasing extent of the lesions (MES 2). MES, Mayo endoscopic score

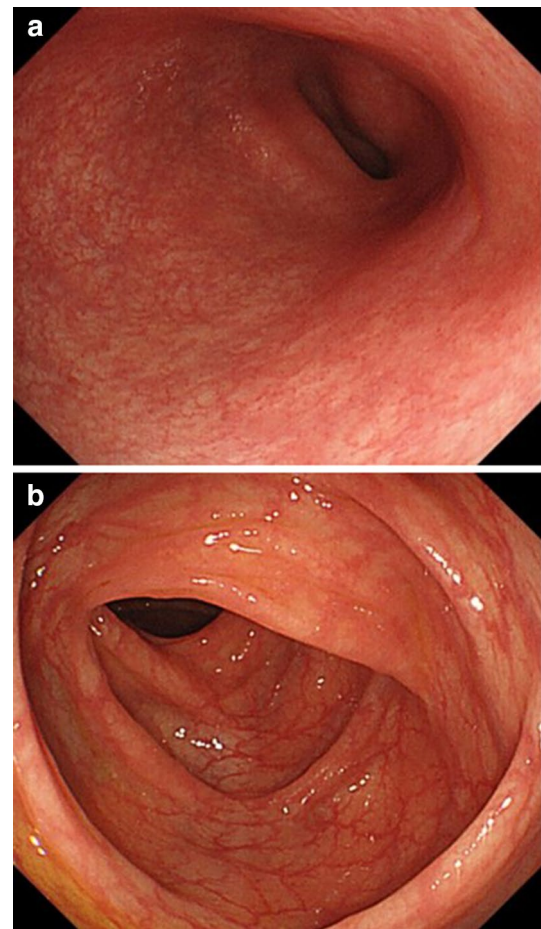


Fig. 3 Endoscopy findings 12 weeks after switching mesalazine formulations. **a** Rectum: visible vascular pattern and no signs of inflammation (MES 0). **b** Transverse colon: visible vascular pattern and no signs of inflammation (MES 0). Obvious endoscopic features of mucosal healing are apparent. MES, Mayo endoscopic score

non-immune-mediated reaction to mesalazine due to diminished ability to metabolize the drug; both forms result in adverse drug reactions. Intolerance occurs in 2% of cases, and onset usually occurs within the first 4 weeks of administration of the mesalazine formulation [9, 10]. Symptoms including fever, headache, arthralgia, fatigue, and abdominal symptoms such as diarrhea, bloody stool, and abdominal pain [10–12] are observed. Intolerance is diagnosed based on the clinical course, and specifically symptom onset soon after mesalazine administration commences (particularly within 4 weeks) and rapid improvement within a few days after mesalazine withdrawal. The DLST provides a supplementary diagnosis and is used to diagnose drug allergy, so intolerance unrelated to allergic reactions will result in a negative DLST. Conversely, the DLST will be positive in cases of allergic intolerance. The diagnostic accuracy of the DLST for mesalazine formulation intolerance is reported as follows: sensitivity 0.24, specificity 0.805, false positive

rate 0.195, and false negative rate 0.76 [13]. A negative DLST cannot completely rule out mesalazine intolerance. The most important point in treating mesalazine formulation intolerance is detecting the etiology when the abdominal symptoms are exacerbated and clarifying whether this exacerbation is due to intolerance, exacerbation of UC, or both. It is, therefore, important to take a detailed history about (1) whether a new mesalazine formulation was administered or the formulation was modified within the 4 weeks prior to abdominal symptom with frequent watery diarrhea and (2) whether extraintestinal manifestations such as fever, arthralgia, or malaise occurred after administration of the mesalazine formulation. At the slightest suspicion of intolerance, the mesalazine formulations should be stopped. If symptoms improve within a few days, then the cause may be mesalazine formulation intolerance. However, if symptoms do not readily improve, exacerbation of UC should be suspected, colonoscopy performed, and additional treatment

Table 2 Intolerance to mesalazine formulation excipients

Mesalazine formulation	DLST (%)	Excipients
pH-dependent mesalazine	405	Povidone, lactose hydrate, sodium starch glycolate, magnesium stearate, talc, methacrylic acid copolymer S, triethyl citrate, yellow ferric oxide, ferric oxide, macrogol 6000EP
MMX mesalazine	97	Carmellose sodium, carnauba wax, stearic acid, hydrous silicon dioxide, sodium starch glycolate, talc, magnesium stearate, methacrylic acid copolymer L, methacrylic acid copolymer S, triethyl citrate, titanium oxide, ferric oxide, macrogol 6000
Time-dependent mesalazine	213	Povidone, ethyl cellulose, crystalline cellulose, carmellose calcium, talc, magnesium stearate, dried aluminum hydroxide gel
Salazosulfapyridine	304	Povidone, light anhydrous silicic acid, magnesium stearate, corn starch

A positive DLST result was defined as a stimulation index above 180%

DLST drug-induced lymphocyte stimulation test, MMX multi matrix system

for UC given as required. If a diagnosis cannot be made despite intolerance to mesalazine formulations, then there will be inadvertent administration of further UC treatment that may, in turn, exacerbate the adverse drug reactions to potent drugs, such as systemic steroids or biologics. For this reason, it is extremely important to determine the etiology, as discussed above.

Treatment of UC should also be attempted in cases of mesalazine formulation intolerance accompanied by exacerbation of UC. Characteristic findings in cases of intolerance are the presence of severe clinical symptoms or conspicuous elevation of serum inflammatory markers on blood tests, contrary to findings of mild-to-moderate inflammation observed on endoscopy. If symptoms do not readily improve after mesalazine withdrawal and there are moderate to severe signs of inflammation on endoscopy, it is also necessary to attempt treatment to induce UC remission.

Our patient was allergic to an excipient of a mesalazine formulation. We performed the DLST for four formulations, pH-dependent mesalazine to which the patient was intolerant, MMX mesalazine to which the patient was not intolerant, time-dependent mesalazine, and salazosulfapyridine. The patient tested positive for pH-dependent mesalazine, time-dependent mesalazine, and salazosulfapyridine and tested negative for MMX mesalazine alone (Table 2). All mesalazine formulations except MMX mesalazine contain povidone. We, therefore, believe that our patient is allergic to povidone and this caused the mesalazine intolerance. Povidone is an allergic agent present in numerous substances, including food and medicine. Povidone is a polymer with a molecular weight ranging from 10,000 to 700,000 Da, comparable to plasma proteins, and is used as excipient in multiple pharmaceutical products [14, 15]. It is reported that povidone causes mainly type I allergy. A few cases of anaphylactic shock, urticaria, and wheezing have been also reported with povidone [14–16]. In the present case, an allergic reaction to povidone was suspected based on the DLST result but symptoms of type I allergy were not detected. The reason for this is not known. In our case,

DLST was performed on hospital day 20, the administration of MMX mesalazine was started on hospital day 11. In consideration of concerns about drug intolerance, we should have started MMX mesalazine from smaller doses after the DLST results were found. In the future, should the patient develop recurrence of UC, we will switch from MMX mesalazine to another mesalazine formulation that use a drug-delivery system without povidone. Mesalazine formulations are essential for treating UC, because they are useful for maintenance therapy as well as induction therapy, and therefore, their administration has a major impact on the clinical course of UC. Some cases of intolerance are caused by excipients rather than mesalazine, so it is important to carefully consider alternative mesalazine formulations if the situation allows.

Acknowledgements This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest Yoshinori Arai, Maiko Ogawa, Fumitsugu Yamane, Natsuki Sumiyoshi, Rikako Arimoto, Yoshitaka Ando, Daisuke Endo, Tatsuya Nakada, Ichiro Sugawara, Hiroshi Yokoyama, Keiko Shimoyama, Hiroko Inomata, Yosuke Kawahara, Masayuki Kato, Seiji Arihiro, Atsushi Hokari, and Masayuki Saruta declare that they have no conflict of interest.

Human rights All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from the patient for being included in the study.

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