Clinical Case Report

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Severe enteropathy with villous atrophy in prolonged mefenamic acid users – a currently under-recognized in previously well-recognized complication

Case report and review of literature

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Abstract

Rationale: Mefenamic acid-induced enteropathy may be an under-recognized condition because few reported cases and no review of literature to comprehensively describe all reported cases exist. From inception until February 2017, a systematic literature search identified twenty original reports of cases of mefenamic acid-induced enteropathy. Additional five cases were identified at our hospital. All cases were included in the analyses.

Patient concerns: Most patients had been regularly taking therapeutic dosages of mefenamic acid for at least three months before symptoms developed. All patients presented with chronic diarrhea with significant weight loss. Approximately one-third of the cases had some degree of anemia and hypoalbuminemia.

Diagnoses: Endoscopic findings could range from very mild abnormalities, such as mild atrophic mucosa, to marked abnormalities, such as blunted villi with scalloping appearance in the small intestine and inflamed mucosa with a few superficial ulcers in the ileum and colon. Pathological findings included flattened small intestinal villi and mixed inflammatory infiltrates including eosinophils in lamina propria.

Intervention: After identifying history of prolong mefenamic acid exposure, all patients were prescribed to stop this medication. Nutritional support and substitutional treatment for mefenamic acid were provided as well.

Outcomes: All symptoms responded dramatically to drug withdrawal. Some patients could change to use other nonsteroidal anti-inflammatory drugs (NSAIDs) without symptoms reoccurring.

Lessons: Unlike other traditional NSAIDs, mefenamic acid could induce intestinal villous atrophy. An adequate drug history is crucial to identifying the condition. Protracted diarrhea occurring during treatment should be the indication to cease the medicine promptly.

Abbreviations: BMI = body mass index, GI = gastrointestinal, NSAID = nonsteroidal antiinflammatory drug.

Keywords: chronic diarrhea, enteropathy, mefenamic acid, nonsteroidal antiinflammatory agents, villous atrophy

1. Introduction

Nonsteroidal antiinflammatory drugs (NSAIDs) are commonly used for relieving pain and treating arthritis worldwide. Gastrointestinal (GI) complications of NSAIDs are well recognized, particularly the effect on the upper GI tract.[1] However, the deleterious effects of NSAIDs on the lower GI tract may not be perceived as a significant clinical problem. Previous studies have shown that up to 70% of NSAID users might have some degree of intestinal damage, but it is usually subclinical.[2,3] Clinically, diarrhea has been reported in only 3% of more than 3000 chronic NSAID users.[4] Furthermore, among the lower GI complications, development of diaphragm-like stricture in the intestine causing intestinal obstruction is quite well recognized as a complication of NSAIDs.[5–9] In contrast, NSAIDs-induced small intestinal villous atrophy has rarely been reported.[10–12]

Mefenamic acid is an NSAID that has been reported to cause serious GI problems, including intestinal ulcers and colitis as other traditional NSAIDs, and severe flattened small intestinal villi resulting in severe protracted diarrhea, which is an uncommon presentation of NSAID-induced enteropathy.[10–22] Because mefenamic acid-induced enteropathy can manifest atypically, and all reported cases were reported many years ago, this condition may be overlooked. Herein, we report 5 patients with this unusual GI complication of mefenamic acid and perform a review of literature of mefenamic acid-induced enteropathy.

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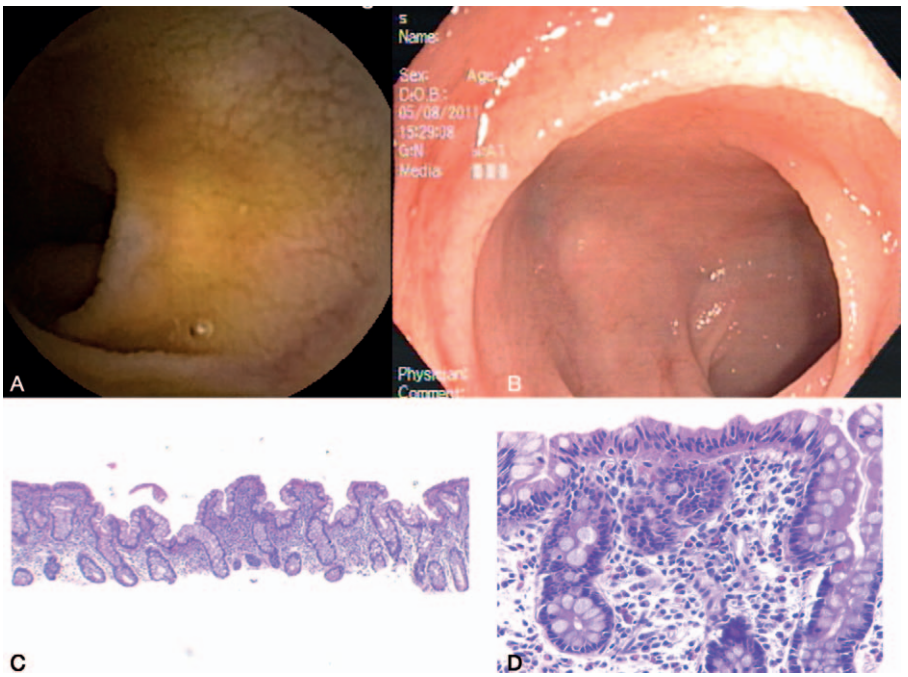

Figure 1. The findings of case 1. (A) Mosaic pattern of ileal mucosa and scalloped mucosal folds from video capsule endoscopy. (B) Flattened villi with scalloped mucosal folds at terminal ileum on colonoscopy. (C, D) Biopsy specimens show blunted villi, slightly increased eosinophils in the lamina propria, and increased intraepithelial lymphocytes of the terminal ileum.

2. Case 1

A 40-year-old woman suffering from a chronic migraine headache was given mefenamic acid at 500 mg 3 times per day for 7 years. Her history of medications included omeprazole at 20 mg once per day, tramadol at 50 mg 3 times per day, and lorazepam at 1 mg once per day before bedtime. In 2011, she developed watery diarrhea consisting of 5 to 6 bowel movements per day with nausea and vomiting in the absence of abdominal pain for 3 years. She underwent colonoscopy at a local hospital, which revealed scattered small erosions at the cecum. The histologic examination of her colonic biopsy specimens demonstrated moderate acute erosive colitis with increased eosinophilic infiltration. A diagnosis of eosinophilic colitis was made, and the patient was treated with prednisolone at 30 mg per day for 1 month. However, her symptoms were not improved. Further evaluation with magnetic resonance imaging of the upper abdomen and urine 5-hydroxyindoleacetic acid were unremarkable. She required blood transfusion intermittently and had lost 25 kg of body weight over the previous 3 years. The patient was then referred to our gastroenterology unit.

On admission, physical examination revealed signs of malnutrition such as generalized xerosis, glossitis, Beau line, and leukonychia. Her body weight was 41 kg and body mass index (BMI) was 18.44 kg/m^2.[2] The hemoglobin level was 10.2 g/dL; white blood cell count was 7340 cells/μL with 7.8% of eosinophils; creatinine level was 1.15 mg/dL (normal range 0.67–1.17 mg/dL); albumin level was 2.9 g/dL (normal range 3.5–5.2 g/dL); and serum electrolytes were normal. Stool examination revealed 5 to 10 white blood cells per high power field but was negative for the infectious organism. Quantitative analysis of fecal fat with a Sudan III stain was positive. Based on these clinical features, wireless capsule endoscopy was performed to evaluate the small bowel for the cause of the intestinal malabsorption, which revealed generalized villous flattening with scalloped mucosal folds along with a mosaic pattern of mucosa beginning at the jejunum, and becoming progressively severe toward the ileum (Fig. 1A). To obtain tissue samples of the terminal ileum, a repeat colonoscopy was done. Flattened villi with scalloping mucosal folds of the ileal mucosa (Fig. 1B) and multiple small geographic, clean-based ulcers were observed at the terminal ileum. The histology of bowel biopsy specimens showed blunted villi, slightly increased eosinophils in lamina propria, and increased intraepithelial lymphocytes of the terminal ileum in the absence of parasitic infections (Fig. 1C and D). Biopsy from one of the ileal ulcers showed one aphthous ulcer characterized by a shallow ulcer on top of a lymphoid nodule. Biopsies of the colon showed moderate acute colitis with eosinophil infiltration.

During admission, we discovered that she had been continuing to take mefenamic acid by herself. The analgesic was then withdrawn, and the diarrhea ceased within 1 week. She could eat well and gained 20 kg in body weight over the next 3 months. Her hemoglobin and serum albumin returned to normal levels in 2 months.

3. Case 2

A 58-year-old woman with a long history of migraine headache and 4 years of regular mefenamic acid usage at 500 mg 3 times per day presented in 2012, with chronic watery diarrhea and body weight loss of 14 kg in 8 months. She was initially investigated at a local hospital. Her stool examination was negative for erythrocyte, leukocyte, ova, and parasites. Gastroscopy and colonoscopy observed mild diffuse edematous mucosa of the entire stomach, sigmoid colon, and rectum. Multiple biopsy specimens demonstrated moderate eosinophilic infiltration in both gastric and colonic mucosa. The patient was diagnosed with eosinophilic gastroenteritis and started on prednisolone at 40 mg daily. After an initial dose of corticosteroids, she was clinically

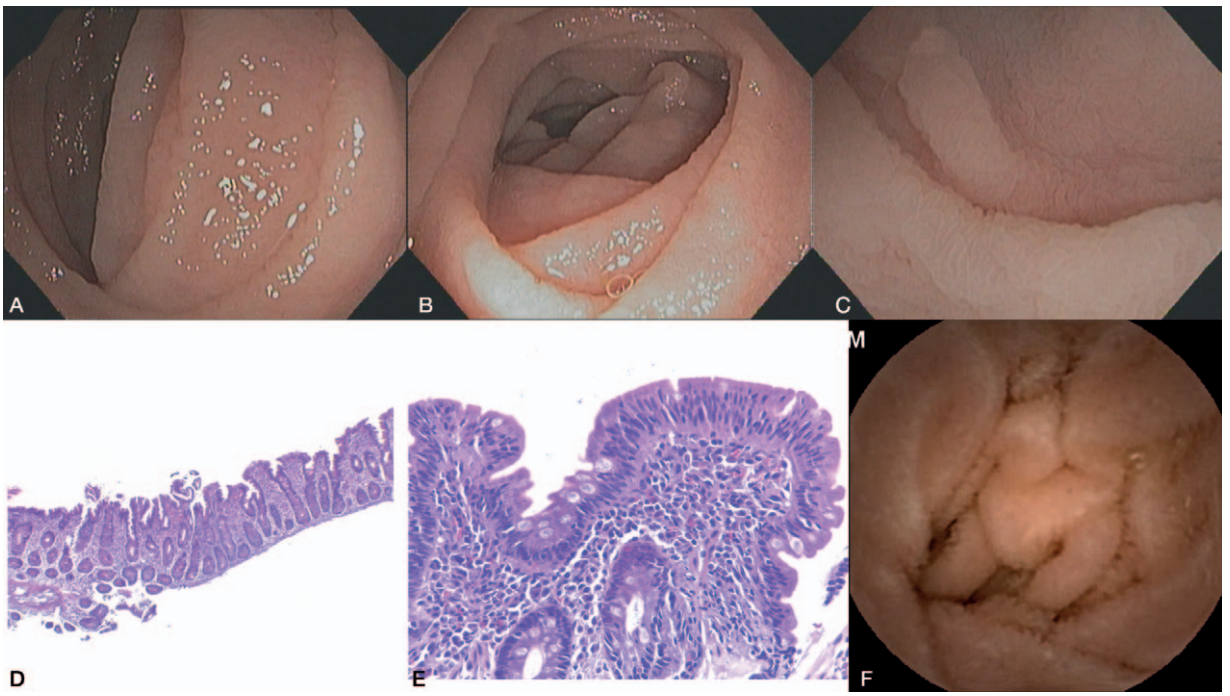

Figure 2. The findings of case 2. (A, B) Endoscopic view from the 3rd part of the duodenum and proximal jejunum show diffusely edematous bowel mucosa with mild degree of scalloping of the small intestinal folds. (C) Underwater view of intestinal mucosa demonstrated loss of intestinal villi. (D, E) Pathological specimens show moderate to severe villous blunting and crypt hyperplasia with increased intraepithelial lymphocytes and lamina propria eosinophils. (F) Jejunal mucosa reverts to normal at 3 months after drug cessation.

improved. Unfortunately, her symptoms of diarrhea recurred 1 week later and did not respond further to prednisolone.

She was referred to us with a suspected eosinophilic gastroenteritis that was refractory to treatment. At our hospital, her physical examination was only significant for cachexia, xerosis, and pitting edema of both legs. Her body weight was 43.8 kg and BMI was 18.9 kg/m^2. Pertinent laboratories showed hemoglobin of 11.3 g/dL, mean corpuscular volume of 90.3 fL, white blood cell count of 4220 cells/μL with an absolute eosinophil count of 139 cells/μL (3.3%), erythrocyte sedimentation rate of 40 mm/hour, albumin of 3.6 g/dL, and normal electrolyte levels. To evaluate the response to corticosteroids therapy for eosinophilic gastroenteritis, a follow-up colonoscopy and push enteroscopy were performed and disclosed diffusely edematous bowel mucosa with mild degree of scalloping of the small intestinal folds (Fig. 2A–C). Biopsies from the duodenum and jejunum showed moderate to severe villous blunting and crypt hyperplasia. Intraepithelial lymphocytes and lamina propria eosinophils were increased (Fig. 2D and E). Biopsies from the ileum showed mild active inflammation with slightly blunted villi. Biopsies from the colon showed few intraepithelial eosinophils with surface epithelial cell injury.

A diagnosis of NSAID-induced enteropathy was suspected, and mefenamic acid treatment was discontinued. The patient's condition steadily improved in nutritional status with the resolution of the diarrhea. Three months later, the appearance of small bowel mucosa had returned to normal on follow-up evaluation with wireless capsule endoscopy (Fig. 2F).

4. Case 3

A 47-year-old woman was referred to our hospital in 2013 with abdominal pain and watery diarrhea up to 10 times per day for 1 year. Her diarrhea was treated initially with metronidazole at 400 mg 3 times per day and albendazole at 400 mg 2 times per day for 7 days by a primary physician. However, the bowel symptoms were not improved, and the patient developed fatigue and lost 14 kg in body weight in 1 year. Afterwards, she was admitted to a local hospital for evaluating the cause of chronic diarrhea. Laboratory studies disclosed hypochromic microcytic anemia with a hemoglobin level of 7.0 g/dL; an absolute eosinophil count of 1530 cells/μL; and an albumin level of 3.8 g/dL. The stool was positive for occult blood. The patient received a transfusion of 2 units of packed red cells. Colonoscopy revealed mild edematous and erythematous mucosa of the terminal ileum. The pathological examination demonstrated moderate acute and chronic ileitis without granuloma or parasites.

Physical examination in our gastroenterology unit revealed moderate pallor and pedal edema. Her body weight was 68 kg and BMI was 28.4 kg/m^2. The patient underwent assessment of small bowel disease with push enteroscopy, which showed normal intestinal mucosa at both the duodenum and proximal jejunum. Colonoscopy disclosed focal granularity of ileal mucosa (Fig. 3A). The gross appearance of the colon was normal. Biopsy specimens from the ileum showed moderate to severe villous atrophy and crypt hyperplasia with moderately increased eosinophilic infiltrates. The ileal surface epithelium was injured, which was demonstrated by cytoplasmic vacuolation with irregular arrangement of their nuclei and infiltration of inflammatory cells. Biopsies from the colon also showed surface epithelial injury that was evidenced by inflammatory cell infiltration with increased eosinophilic infiltrates in lamina propria (Fig. 3B–D). During the investigation, the patient reported a 5-year history of a chronic migraine, and she had been continuing to take mefenamic acid at 500 mg 3 times per day

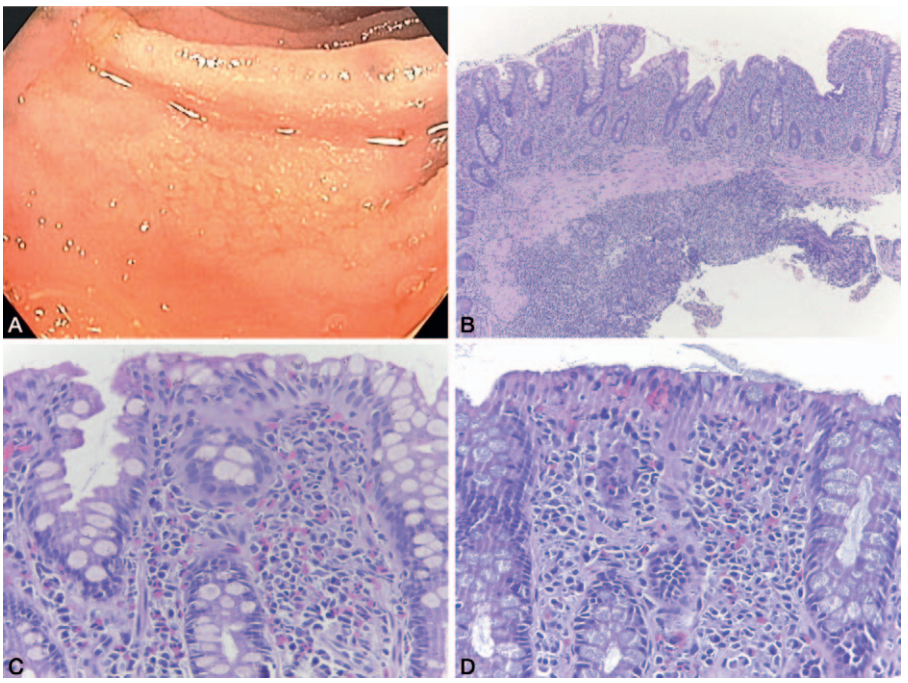

Figure 3. The findings of case 3. (A) Focal granularity of terminal ileum. (B, C) Ileal mucosa with moderate to severe villous atrophy and crypt hyperplasia, moderately increase eosinophilic infiltrates, and cytoplasmic vacuolation with irregularity arrangement of epithelial cell nuclei. (D) Colonic mucosa with surface epithelial injury evidenced by inflammatory cell infiltration, and increased eosinophilic infiltrations in the lamina propria.

even while she was in the hospital. A diagnosis of NSAID-induced enteropathy was suspected, and then mefenamic acid was discontinued. Her diarrhea dramatically improved with the resolution of diarrhea and abdominal pain within 3 days. The hemoglobin level rose to 12.2 g/dL. She never had recurrent diarrhea after discharged.

5. Case 4

A 46-year-old woman presented with chronic watery diarrhea 5 to 6 times per day and body weight loss of 10 kg over 1 year. She visited a general practice doctor and was treated with antibiotics, which did not improve her symptoms. Her stool was checked, and a barium study was done, both of which were unremarkable. She received only antidiarrheal agents to control her symptoms.

She came to our hospital in 2013 due to a concern of her indefinite diagnosis. Physical examination revealed moderate anemia. Her body weight was 72 kg and BMI was 28.1 kg/m^2. Tests on admission showed a hemoglobin of 6.8 g/dL with an mean corpuscular volume of 60.6 fL; white blood cell count of 8940 cells/μL with an absolute eosinophil count of 358 cells/μL; serum iron of 5.5 μmol/L (normal range 9–29 μmol/L), transferrin saturation of 8.7% (normal range 30–50%); and normal values of liver function test, thyroid function test, as well as electrolytes. The result of an HIV test was nonreactive. Colonoscopy showed a normal appearance of the entire colon and mild atrophic change of ileal mucosa (Fig. 4A). Biopsies showed flattened villi and 1 aphthous ulcer at the ileal mucosa. The lamina propria of both the ileum and colon had increased inflammatory infiltrates including eosinophils and neutrophils (Fig. 4B). At next visit, a 1-year history of mefenamic acid use for muscle pain from daily activities was disclosed, and the medication was discontinued. Her bowel habit returned to normal in 1 month without recurrence of diarrhea.

6. Case 5

A 65-year-old woman presented in 2011 with a 2-month history of watery diarrhea with up to 10 bowel movements per day, anorexia, and body weight loss of 5 kg. She had been taking mefenamic acid at 500 mg 2 times per day intermittently for knee pain due to osteoarthritis over 3 years.

Physical examination was unremarkable. Her body weight was 69 kg and BMI was 28.7 kg/m^2. The stool tests were negative for occult blood and parasites. The hemoglobin level was 12.0 g/dL, and white blood cell was 6350 cells/μL with an absolute eosinophil count of 197 cells/μL (3.1%). The results of a thyroid function test and liver function test were normal. Colonoscopy revealed normal colonic mucosa with mild villous blunting of the ileal mucosa, but no biopsy specimen was taken. Gastroduodenoscopy revealed blunting of the duodenal folds and some mucosal erosions at the body of the stomach that was thought to be due to NSAIDs. Therefore, mefenamic acid was withdrawn, and her diarrhea settled immediately. Two weeks later, her primary physician again gave her mefenamic acid; diarrhea recurred within the same day. A diagnosis of mefenamic acid-induced enteropathy was made. The patient did not take this drug for the following year and was free of symptom. She was taking acetaminophen, tramadol, and selective cyclooxygenase-2 inhibitors as needed for her osteoarthritis.

7. Methods

A PubMed search was performed from the inception to February 2017 to describe the characteristics associated with mefenamic acid-induced enteropathy. Only articles in English were included. The medical subject heading descriptors used for our search were: ("mefenamic" OR "mefenamate") AND ("enteropathy" OR

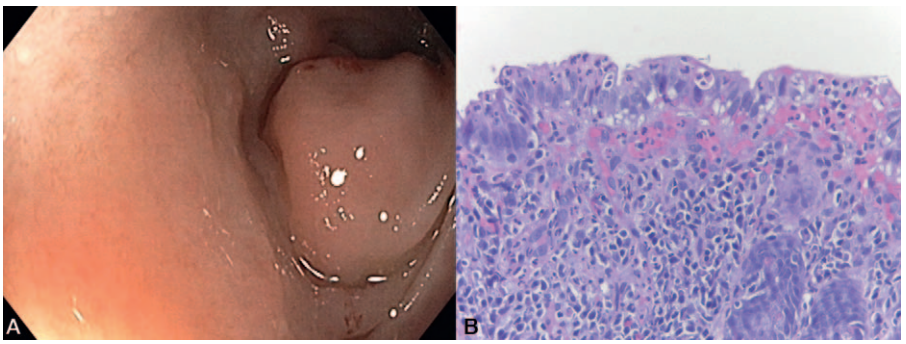

Figure 4. The findings of case 4. (A) Mild atrophic change of ileal mucosa. (B) Ileal mucosa with flattened villi and increased inflammatory infiltrates including eosinophils and neutrophils.

"enteritis" OR "colitis" OR "gastrointestinal" OR "diarrhea" OR "villous" OR "villi"). We also did the same systematic searches but used "ibuprofen", "naproxen," "indomethacin", and "diclofenac" instead of mefenamic acid to investigate if other common NSAIDs were associated with the same type of enteropathy.

Eligible articles were reviewed independently by 2 investigators (JL and UK). Disagreements were resolved by consensus and, as necessary, involvement of a 3rd reviewer (PC). All case reports and case series of mefenamic acid-induced enteropathy were included. Demographic data, mefenamic acid dosage and duration, clinical manifestations, laboratory findings, endoscopic findings, radiologic findings, pathological findings, and response to cessation of mefenamic acid were recorded. The findings of the cases from the literature and our cases were included in the analyses. This study was approved by the institutional review board of Siriraj Hospital, Mahidol University.

Table 1

Summary of mefenamic acid-induced enteropathy findings.

Characteristic	Previously reported cases		Our cases	
	Number of patients with available data	Results	Number of patients with available data	Results
Age (mean ± SD, range)	20	59.6 ± 11.4 (39–73)	5	51.2 ± 10.1 (40–65)
Gender	20	Male 8, female 12	5	Female 5
Mefenamic acid dose	16	1500 mg/d (500–1500)	5	1500 mg/d (1000–1500)
Duration of medication usage before developing symptoms	17	6 mo (0.25–72)	5	36 mo (24–60)
Duration of symptoms before diagnosis	17	5 mo (0.25–96)	5	11 mo (2–36)
Diarrhea	20		5	
Watery		8 (40%)		4 (80%)
Bloody		7 (35%)		1 (20%)
Frank steatorrhea		5 (25%)		0
Number of bowel movements/day	11	12 (6–20)	5	10 (4–10)
Weight loss	14	14 (100%), Median 9.5 kg (1–30)	5	5 (100%), Median 14 kg (5–25)
Anemia	17	4 (23.5%)	5	4 (80%)
Hemoglobin levels at presentation	12	12.7 ± 1.9 g/dL	5	10.0 ± 2 g/dL
Hypoalbuminemia	12	3 (25%)	5	2 (40%)
Albumin levels at presentation	5	3.5 ± 1.0 g/dL	5	3.5 ± 0.5 g/dL
Fecal fat	8	15.85 g/d (6.5–27.4)	0	
Bowel involvement (only documented by endoscopy or pathology) (15 patients had small bowel investigations, and 20 had colonic investigations)				
Small bowel		9/10		5/5
Large bowel		14/15*		4/5
Unknown		1†		0
Significant endoscopic/pathological findings				
Ulceration on endoscopy		3/15 (20%)		1/5 (20%)
Villous blunting		6/10 (60%)		4/4 (100%)
Eosinophil infiltration		1/19 (5.3%)		4/4 (100%)

SD = standard deviation.

* Two patients without large bowel involvement did not have pathological results.

† This patient had only his small bowel biopsy findings reported, which were normal.

Continuous variables were expressed in median and range or mean ± standard deviation whereas categorical variables were expressed in the number of subjects and percentages.

8. Results

The systematic search yielded 20 cases from 7 case reports and 6 case series during 1975 to 2007. To the best of our knowledge, a review of literature of mefenamic acid-induced enteropathy has never been performed. The systematic search for the association between other common NSAIDs, of those including ibuprofen, naproxen, indomethacin, and diclofenac, with small intestinal villous atrophy did not find any reports. We summarize the findings from all previously reported cases and our cases in Table 1. The full details of all 25 patients are available in Table S1, http://links.lww.com/MD/B926 in the supplementary document.[10–22]

Mefenamic acid-induced enteropathy was reported in the age range from 39 to 73 years and in both genders. All cases regularly took therapeutic dosages of mefenamic acid. The duration of medication usage before developing diarrhea was quite long, with the median of 6 months among the cases in the literature and 36 months in our cases. Nineteen of 22 cases had been taking the drugs for more than 3 months.

The onset was often gradual; however, a few cases have reported acute onset. Notably, most cases were delayed in diagnosis. The median duration of clinical presentation before diagnosis was 5 months in the previously reported cases and 11 months in our cases, with the longest of 8 years. Many cases, particularly our cases, presented with voluminous watery diarrhea. Some patients had recurrent bleeding. Clinically reported steatorrhea was infrequent, but abnormal stool fat content was more frequently observed, particularly in cases with extensive enteritis. Other GI symptoms could be present, for example, colicky abdominal pain, nausea, and vomiting. Malabsorption features were observed in severe cases. Body weight loss was common and severe. The median body weight loss was 9.5 and 14 kg in the reported cases and our cases, respectively. Approximately one-third of the cases had some degree of anemia and hypoalbuminemia. In our case series, 2 of 5 patients had peripheral eosinophilia.

The disease could affect both small bowel and large bowel. However, unlike other NSAIDs, ulceration was not a prominent feature in endoscopic findings. Only 4 of 20 cases who underwent endoscopy were reported to have ulcers. In contrast, villous blunting was reported in 10 of 14 cases who had small intestinal biopsies, and this is uncommon in classic NSAID-induced bowel injury. Eosinophilic infiltration in intestinal mucosa was infrequently reported in the past but was reported in all of our cases. This caused a misdiagnosis of eosinophilic enterocolitis in 2 of our cases.

Response to drug discontinuation was dramatic without recurrence in all reported cases. More than half of them stopped having diarrhea within 1 week after discontinuation of the offending agent.

9. Discussion

In the present study, we performed a review of literature, including in the analysis of 5 additional cases of mefenamic acid-induced enteropathy that we had diagnosed. This particular type of NSAID-induced bowel injury may have been well recognized in the past. Nevertheless, because the most recent previously reported case was many years ago, many physicians who are currently in clinical practice may be unaware of this condition. Our patients had been suffering from undiagnosed chronic diarrhea for 1 to 3 years and had undergone extensive investigations before obtaining their definite diagnoses. Earlier recognition of this condition should have precluded them from the disease morbidity and unnecessary investigations.

Mefenamic acid can cause both enteritis and colitis. Clinical manifestations include chronic nonspecific diarrhea, frank colitis as in ulcerative colitis, and severe enteropathy from flattened jejunal mucosa as in celiac disease. Villous atrophy is possibly unique to mefenamic acid among NSAID-induced enteropathy. The literature review did not reveal this complication occurring in other commonly-used NSAIDs, such as ibuprofen, naproxen, indomethacin, and diclofenac. Furthermore, some patients in our literature review could switch to taking other NSAIDs, for example, ibuprofen, without disease recurrence (Table S1, http://links.lww.com/MD/B926).[10,14]

Continuous and prolonged usage of mefenamic acid is an important key to the development of severe enteropathy induced by the medication. This serious complication has not been reported in many trials using cycling regimens in the treatment of menorrhagia and dysmenorrhea even though the medication was used for more than 1 year.[23–26] Furthermore, diarrhea was reported in only 3% of patients with acute mefenamic acid overdosage.[27] The lag of the occurrence of symptoms after the initiation of the drug may have caused failure to recognize its causative role.

Endoscopic findings in the previous case reports have included inflamed colorectal mucosa, and only a few cases have had superficial ulcerations. Our case series firstly reports the features of the small intestine, which varied from mild atrophic change of the mucosa to severe mucosal atrophy with scalloped mucosal folds. As mention above, ulceration is less prominent and was found in only 1 of 5 of our patients. These small bowel findings are quite similar to the findings in celiac disease. However, the location of involvement may be different. Although celiac disease mostly involves the duodenum and jejunum and is less pronounced in the ileum, mefenamic acid-induced enteropathy can involve any part of the small intestine and colon. In our series, 2 patients had lesions predominantly in the terminal ileum, and 4 patients had microscopic abnormalities in the colonic mucosa.

Pathological findings in the small intestine show villous atrophy, crypt elongation, mixed inflammatory infiltrates in lamina propria, presence of intraepithelial lymphocytes, and vacuolated epithelial cell cytoplasm. The findings mimic the findings in celiac disease.[28] However, the severity of villous atrophy may be less severe in mefenamic acid-induced enteropathy, and this condition can involve the colon as mentioned above. The finding of eosinophilic infiltration at the mucosa can be found in both the small intestine and large intestine, and can mislead to the diagnosis of eosinophilic gastroenteritis. Two of our patients had been treated incorrectly with corticosteroids, and one had a temporary partial response. Some pathological findings may differentiate these 2 conditions. In mefenamic acid-induced enteropathy, the inflammatory responses are mixed including neutrophils, eosinophils, plasma cells, and lymphocytes whereas eosinophils are very dominant in eosinophilic gastroenteritis. Furthermore, eosinophils in eosinophilic gastroenteritis can infiltrate not only in the lamina propria, but also into the crypts or surface epithelium, or even deep into the submucosa.

The response to drug discontinuation is usually rapid, dramatic, and sustained, which contrasts to its gradual onset

after the initiation of the drug. Recognition of this condition, prompt withdrawal of the medicine, and observation of symptoms are the most important approaches in the diagnosis and management of mefenamic acid-induced enteropathy.

The pathogenesis of mefenamic acid-induced diarrhea is not well understood. Gullikson et al[29] studied the effects of NSAIDs in the fenamate chemical class, indomethacin, and aspirin. They found that all NSAIDs except aspirin had dose-related effects to increase mucosal permeability and block net fluid absorption similar to stimulant laxatives. These effects were caused by villous cell damage. Interestingly, the diarrheagenic effect was inversely correlated with their antiinflammatory activity and ulcerogenic potential. Fenamates had a higher potential for inhibitory fluid absorption than indomethacin but caused fewer ulcers.[29] This result is compatible with the endoscopic findings in our report in that most cases had blunted intestinal villi but did not have ulcers. Another factor that appears to be essential in pathogenesis is repeated injuries. Generally, NSAIDs with high enterohepatic circulation have more potential to cause intestinal damage because of more repeated exposure to the intestinal epithelium.[30] Enterohepatic circulation is less than 5% for mefenamic acid.[11] This could be the reason why severe enteropathy occurred mostly in chronic and persistent mefenamic acid users. Proton pump inhibitors have been reported to be associated with NSAID-induced small bowel injuries by alteration of intestinal microbiota.[31] However, they may not play a key role in the pathogenesis of mefenamic acid-induced enteropathy. All previously reported cases were before the proton pump inhibitor era, and there has been no report of this form of enteropathy after acid suppressive therapy became widely used. In our review of literature, only one case was reported as taking cimetidine before diarrhea developed, and only one was taking omeprazole in our cases.[11] All of the above suggest that mefenamic acid-induced enteropathy is unique and differs from enteropathy caused by other types of NSAIDs.

There are some limitations in this study. First, none of the previous case reports provided the information for celiac serology. It is possible that the celiac serological tests were not widely used during the time of the previously reported cases. Thus, celiac disease might not have been excluded. However, some authors mentioned about the response to gluten-free diet in their patients. Two patients reported by Isaacs et al[10] in 1987 and Batt[11] in 1989 did not respond to restriction of gluten, and the case reported by Isaacs had clinical improvement after stopping mefenamic acid in 3 weeks although continuing to take a normal diet. The diarrhea in another patient reported by Peacey and Walls[12] in 1992 began to settle in 1 week, and normal bowel habit had returned in 3 weeks after stopping mefenamic acid even though continuing normal diet. For our patients, unfortunately, we did not test for celiac serology. However, because of the rarity of celiac disease in Asia with a pooled sero-prevalence and a biopsy-proven prevalence of 1.6% and 0.5%, respectively, and the very good response to cessation of mefenamic acid in all of our patients, we believed that diarrhea in our patients was associated with mefenamic acid usage.[32] Second, we have described mefenamic acid-induced enteropathy based on the details from few cases; therefore, these could not be generalized and may not reflect the accurate clinical characteristics of this condition. Describing a larger number of cases should better characterize this complication. However, we believe that very few cases having been reported may be due to the under-recognition of this condition. This emphasizes the importance of reporting this complication. In this study, we have described mefenamic acid-induced enteropathy based on the all available cases. We hope that our report will increase number of case recognition, which should result in better characterizing this condition. Third, the causal inference may be difficult because causality cannot be inferred from an uncontrolled observation. However, all patients in this case series and literature review resolved dramatically after mefenamic acid was discontinued. Some patients were confirmed resolution of the lesions by endoscopy or tissue biopsy.[10–12,14,15,18,20–22] Some patients had recurrence of symptoms when mefenamic acid was re-challenged.[14,15,20,21] These evidences suggest that mefenamic acid was the cause of diarrhea in the patients in this study.

Our case series emphasizes the need for an adequate drug history in chronic diarrhea patients as recommended in many clinical guidelines.[33,34] NSAIDs are over-the-counter medication and are commonly misused. The lack of recognition of this unusual form of complication is dangerous and raising awareness in the general public, pharmacists, and physicians is crucial. This condition must be ruled out before making the diagnosis of celiac disease, tropical sprue, or eosinophilic enterocolitis. Protracted diarrhea occurring during treatment with mefenamic acid should be the indication to cease the medicine promptly. Furthermore, mefenamic acid use should be restricted to short courses, for example, for the treatment of dysmenorrhea. Other NSAIDs should be considered in the long-term treatment of chronic rheumatologic disorders or other chronic conditions.

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