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【 ORIGINAL ARTICLE 】

Zinc Acetate Dihydrate Tablet-associated Gastric Lesions

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Abstract:

Objective This study aimed to determine the prevalence and endoscopic features of zinc acetate dihydrate tablet-associated gastric lesions.

Methods We retrospectively examined the endoscopic features of 47 patients taking zinc acetate dihydrate tablets who underwent esophagogastroduodenoscopy.

Results Gastric mucosal alterations, including redness, erosions, ulcers, and adhesion of the white coat, were observed in 29 of 47 patients (61.7%). Among patients with gastric lesions (group A), there was a significantly higher percentage of symptomatic patients in comparison to patients without lesions (group B) (65.5% vs. 22.2%; $p<0.01$). The background characteristics of the two groups did not differ to a statistically significant extent. On esophagogastroduodenoscopy, mucosal redness (n=27, 93.1%), erosions (n=26, 90.0%), adhesion of the white coat (n=25, 86.2%), and ulcers (n=9, 31.0%) were observed. None of the 19 patients who previously underwent esophagogastroduodenoscopy had gastric lesions before starting zinc acetate dihydrate. Esophagogastroduodenoscopy was performed after the cessation of zinc acetate dihydrate intake in six patients, and revealed the resolution of gastric lesions.

Conclusion Gastric lesions were observed in 29 of 47 patients who were taking zinc acetate dihydrate tablets. The most common endoscopic findings were mucosal redness (93.1%), erosions (90.0%), adhesion of the white coat (86.2%), and ulcers (31.0%). Although the exact pathogenesis is uncertain, we believe that understanding the unique manifestations of this gastric lesion will help physicians manage adverse events in patients taking zinc acetate dihydrate tablets.

Key words: esophagogastroduodenoscopy, gastric erosion, gastric ulcer, zinc acetate dihydrate

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Introduction

Zinc acetate dihydrate tablets (Nobelzin®) are prescribed for patients with Wilson's disease and hypozincemia (1-4). Since the oral administration of zinc acetate dihydrate suppresses the absorption of copper contained in foods, it has been used for the treatment of Wilson's disease, alone or in combination with chelating drugs. Meanwhile, zinc deficiency can lead to a variety of disorders, including dysgeusia, loss of appetite, diarrhea, dermatitis, mouth ulcers, anemia, delayed wound healing, and even failure to thrive. Thus, zinc acetate dihydrate tablets are also used for zinc supplementation in these patients. Although the administration of zinc acetate dihydrate tablets is generally safe and tolerable (3, 4), we observed that some patients taking this medication developed gastric erosions and/or ulcers with characteristic endoscopic features.

In this study, we retrospectively investigated the prevalence and features of gastric mucosal lesions occurring in

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patients taking zinc acetate dihydrate tablets. The clinical courses of representative patients are also presented.

Materials and Methods

A database search of electronic medical records at Okayama University Hospital identified 525 patients who were prescribed zinc acetate dihydrate tablets. Among them, 47 patients underwent esophagogastroduodenoscopy examinations between February 2018 and June 2021, and were included in the present study.

According to the endoscopy results, patients were subdivided into two groups: patients with gastric mucosal alterations, such as mucosal redness, erosions, ulcers, and adhesion of the white coat (Group A); and patients without gastric mucosal alterations (Group B). We retrospectively reviewed the patients' clinical records and investigated the data of each subgroup regarding the medication history and endoscopic and pathological examinations.

This retrospective study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the ethics committee of Okayama University Hospital. For comparisons of the two groups, statistical analyses, including *t*-tests, chi-squared tests, and F-tests were performed using the JMP Pro software program (version 14.0.0, SAS Institute, Cary, USA). P values of <0.05 were considered statistically significant.

Results

The characteristics of the enrolled patients are presented in Table 1. Gastric mucosal alterations, including redness, erosions, ulcers, and adhesion of the white coat, were observed in 29 of 47 patients (61.7%); these patients were classified into Group A [male, n=24; female, n=5; mean age, 61.7 years (25-85 years)]. The remaining 18 patients were classified into Group B [male, n=11; female, n=7; mean age, 59.8 years (18-80 years)]. The sex and age of the groups did not differ to a statistically significant extent. In addition, the body mass index on endoscopy examination did not differ between the two groups to a statistically significant extent (mean ± SD: 22.3±4.7 kg/m^2 vs. 22.5±5.9 kg/m^2). The underlying diseases in Group A patients were Wilson's disease (n=3); liver diseases other than Wilson's disease (n=10); neoplasms (n=8) including liver cancer (n=2), laryngeal cancer (n=1), pancreatic cancer (n=1), lung cancer (n=1), bladder cancer (n=1), lymphoma (n=1), and leukemia (n=1); inflammatory bowel disease (n=3); chronic kidney disease (n=2); and rheumatoid arthritis (n=1). The underlying diseases in Group B patients were Wilson's disease (n=2); liver diseases other than Wilson's disease (n=5); neoplasms (n=7) including esophageal cancer (n=5), pancreatic cancer (n=1), and mesothelioma (n=1); and inflammatory bowel disease (n =1). Thus, zinc acetate dihydrate tablets were prescribed for Wilson's disease (Group A, n=3; Group B, n=2) or hypozincemia (Group A, n=26; Group B, n=16).

Data on the duration of zinc acetate dihydrate tablet administration were available for 25 patients in Group A and 16 patients in Group B. In Groups A and B, esophagogastroduodenoscopy was performed 300±782 days and 95±142 days (mean ± SD) after zinc acetate dihydrate tablet administration, respectively. Notably, 5 patients in Group A were diagnosed with gastric lesions within 14 days after zinc acetate dihydrate tablet administration. The serum zinc concentration before zinc acetate dihydrate tablet administration was measured in 25 patients in Group A and 13 patients in Group B, while that on endoscopy examination was measured in 22 patients in Group A and 15 patients in Group B. The serum zinc concentration before zinc acetate dihydrate tablet administration did not differ between Groups A and B (68.1±34.3 μg/dL vs. 58.2±13.4 μg/dL). However, although the difference was not statistically significant (p=0.07), the serum zinc concentration at the time of the endoscopy examination was higher in Group A (107.6±43.0 μg/dL) than in Group B (84.0±33.8 μg/dL).

No differences were observed in terms of the patients' medications other than zinc acetate dihydrate tablets, including proton pump inhibitors or vonoprazan (Group A, 72.4% vs. Group B, 61.1%), diuretics (37.9% vs. 38.9%), nonsteroidal anti-inflammatory drugs (20.7% vs. 5.6%), and steroids (24.1% vs. 27.8%). The *Helicobacter pylori* (*H. pylori*) infection status was only available for 7 patients in Group A and in 3 patients in Group B. All 7 patients in Group A were negative for *H. pylori*. In Group B, 1 patient was positive, 1 was negative for *H. pylori*, and the other patient had previously undergone *H. pylori* eradication. In Group A, 16 patients did not have gastric mucosal atrophy, 3 patients had closed-type atrophy, and 10 patients had open-type atrophy. In Group B, 13 patients did not have gastric mucosal atrophy, 2 patients had closed-type atrophy, and 3 patients had open-type atrophy. There were no differences between the groups in terms of the presence or absence of gastric mucosal atrophy.

The indications for esophagogastroduodenoscopy in Group A patients were for screening (n=8), anemia (n=7), hematemesis (n=4), epigastric pain (n=4), melena (n=3), investigation of other diseases (n=2), difficulty in swallowing (n=1), nausea (n=1), vomiting (n=1), and appetite loss (n=1). On the other hand, in Group B, the indications included screening (n=8), investigation of other diseases (n=6), hematemesis (n=1), throat pain (n=1), heartburn (n=1), and appetite loss (n=1). Group B patients who initially presented symptoms of hematemesis were diagnosed with rupture of esophageal varices. When patients were classified as asymptomatic (i.e., screening purposes and investigation of other diseases) and symptomatic, Group A included a greater number of symptomatic patients (n=19, 65.5%) than Group B (n=4, 22.2%) (p<0.01).

On esophagogastroduodenoscopy, with the exception of one patient, all patients in Group A had gastric lesions in the middle third of the stomach (96.6%; Table 2). The upper and lower thirds of the stomach were affected in 65.5% (19/

Table 1. Clinical Characteristics of the Study Population.

	Group A (n)	Group B (n)	p value
Sex			0.17
Men	24	11	
Women	5	7	
Mean age, years (range)	61.7 (25-85)	59.8 (18-80)	0.72
Mean body mass index, kg/m^2 (range)	22.3 (14.3-38.0)	22.5 (13.6-36.4)	0.94
Underlying diseases			
Wilson's disease	3	2	
Liver disease*	10	5	
Neoplasms	8	7	
Inflammatory bowel disease	3	1	
Chronic kidney disease	2	0	
Rheumatoid arthritis	1	0	
Mean days after administration of ZAD (range)	300 (2-3,969)	95 (4-525)	0.21
Mean serum zinc concentration, μg/dL (range)			
Before administration of ZAD	68.4 (22-169)	58.2 (37-77)	0.20
On endoscopy examination	107.6 (65-226)	84.0 (49-163)	0.07
Use of PPI or vonoprazan			0.28
Positive	21	11	
Negative	8	7	
Use of diuretics			0.57
Positive	11	7	
Negative	18	11	
Use of NSAIDs			0.23
Positive	6	1	
Negative	23	17	
Use of steroids			1.00
Positive	7	5	
Negative	22	13	
Helicobacter pylori infection			NA
Positive	0	1	
Negative	7	1	
Eradicated	0	1	
Not available	22	15	
Gastric mucosal atrophy			0.36**
Absent	16	13	
Closed-type atrophy	3	2	
Open-type atrophy	10	3	
Symptoms			<0.01
Positive	19	4	
Negative	10	14	

ZAD: zinc acetate dihydrate, PPI: proton pump inhibitor, NSAIDs: non-steroidal anti-inflammatory drugs
*Liver diseases other than Wilson's disease. **Absent vs. present.

29) and 46.4% (13/28) patients, respectively. Group A patients had mucosal redness (n=27, 93.1%), erosions (n=26, 90.0%), adhesion of the white coat (n=25, 86.2%), and ulcers (n=9, 31.0%). A combination of plural erosions/ulcerations and a sticky white coat surrounded by substantially reddish mucosa was observed in 23 (79.3%) patients. The representative endoscopic features observed in Group A patients are shown in Fig. 1. Nineteen of the Group A patients (65.5%) underwent esophagogastroduodenoscopy before the initiation of zinc acetate dehydrate therapy, and none had the aforementioned mucosal alterations before their intake of this medicine. Esophagogastroduodenoscopy was performed after the cessation of zinc acetate dihydrate intake in six patients, which revealed resolution of the gastric mucosal alterations.

Endoscopic biopsy was performed for gastric lesions in 20 patients, and histopathological examination revealed mucosal edema (n=11, 55.0%), erosion with infarct-like necrosis of epithelial cells (n=13, 65.0%), and/or fibrin exudation (n=11, 55.0%) (Fig. 2, Table 3).

In the following section, we present two representative cases of patients with zinc acetate dihydrate-induced gastric lesions.

Case Presentation

Case 1

A Japanese man underwent endoscopic submucosal dissection for early gastric cancer at 70 years of age. He had been undergoing esophagogastroduodenoscopy annually after receiving endoscopic treatment. At 76 years of age, esophagogastroduodenoscopy revealed multiple ulcers and erosions with mucosal redness and adhesion of the white coat (Fig. 3A, 3B), which had not previously been observed. The patient had chronic kidney disease, hypertension, hyperuricemia, constipation, dementia, obstructive sleep apnea, and allergic dermatitis, and had been taking aspirin, lansoprazole, telmisartan, bisoprolol, benidipine, valproic acid, memantine, magnesium oxide, furosemide, febuxostat, trichlormethiazide, and ramelteon. Since the patient had dysgeusia and hypozincemia (60 μg/dL), zinc acetate dihydrate tablets were prescribed 7 weeks before esophagogastroduodenoscopy. As the etiology of the gastric lesions was not determined, we repeated esophagogastroduodenoscopy 5, 8, and 14 months later, which showed multiple ulcers and erosions with mucosal redness and adhesion of the white coat (Fig. 3C, 3D). The locations of ulcers and erosions were different in each examination. Although endoscopic biopsy was performed each time, the histopathological diagnosis was inconclusive, showing erosion with infarct-like necrosis of epithelial cells and neutrophil infiltration. Since we suspected that zinc acetate dihydrate tablets were the cause of the gastric lesions, we advised the patient and his attending physician to discontinue the drug. Esophagogastroduodenoscopy performed 5 weeks after the cessation of zinc acetate dihydrate tablets revealed that the gastric lesions had disappeared (Fig. 3E).

Table 2. Endoscopic Features of Group A Patients.

	Positive	Negative
Involved site		
Upper third	19	10
Middle third	28	1
Lower third	13	15*
Endoscopic feature		
Mucosal redness	27	2
Erosions	25	4
Adhesion of the white coat	26	3
Ulcers	9	20

*The lower third of the stomach was not evaluated in one patient due to post-distal gastrectomy.

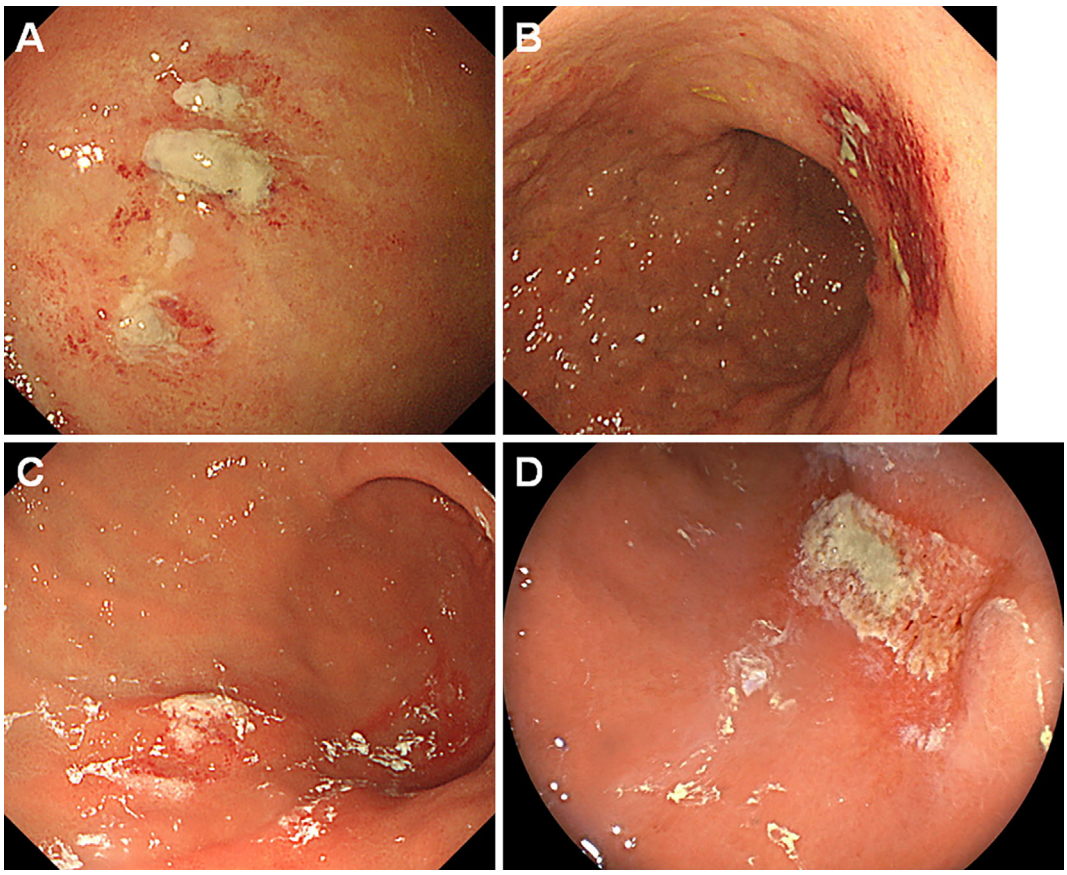

Figure 1. Representative endoscopic images of the gastric lesions observed in patients taking zinc acetate dihydrate tablets. A 64-year-old man had multiple erosions with a thick white coat in the gastric fornix (A) and reddish, erosive mucosa in the gastric body (B). In a 25-year-old man, the white coat showed linear adhesion to the folds of the gastric body, accompanied by a reddish mucosa (C). A 48-year-old woman had a shallow ulcer with the adhesion of the white coat in the gastric antrum (D).

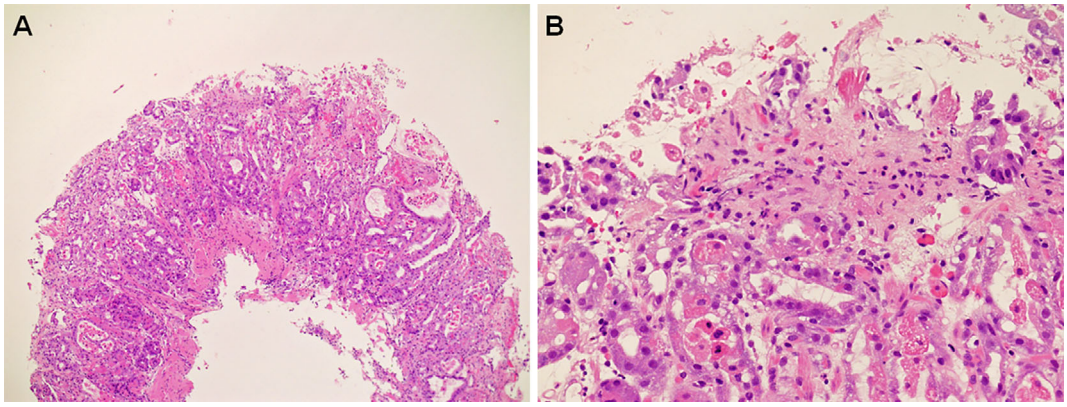

Figure 2. **Representative histopathology image of the gastric lesions observed in patients taking zinc acetate dihydrate tablets. A biopsy specimen from the gastric lesion of a 48-year-old woman (same patient as Fig. 1D) shows mucosal edema, erosion with infarct-like necrosis of epithelial cells, and fibrin exudation.**

Table 3. **Pathological Features of Group A Patients.**

	Mucosal edema	Erosion with infarct-like necrosis of epithelial cells	Fibrin exudation
Positive	11	13	11
Negative	9	7	9

Case 2

A 63-year-old Japanese man was admitted to our hospital with acute pyelonephritis. He had a history of whole-brain radiotherapy for diffuse large B-cell lymphoma of the brain. After admission, zinc acetate dihydrate tablets were prescribed for hypozincemia (22 μg/dL) and loss of appetite. The patient had hematemesis 2 days after starting the zinc acetate dihydrate tablets. Although esophagogastroduodenoscopy showed blood and multiple ulcers in the stomach (Fig. 4A, arrows), endoscopic hemostasis was not performed because there was no active bleeding from the gastric ulcers. The patient was treated with proton pump inhibitors and nothing by mouth. Esophagogastroduodenoscopy performed 2 days later revealed multiple ulcers and erosions with mucosal redness and adhesion of the white coat (Fig. 4B-D). Endoscopic biopsy showed small erosions with atypical epithelial regeneration. Considering the possibility of zinc acetate dihydrate tablet-induced gastric lesions, the medication was discontinued. Esophagogastroduodenoscopy performed 7 weeks after the episode of hematemesis revealed multiple ulcer scars in the stomach and the absence of active ulcers, erosions, mucosal redness, and adhesion of the white coat (Fig. 4E).

Discussion

We herein present the reports of 29 cases in which gastric lesions occurred in patients taking zinc acetate dihydrate tablets. We consider zinc acetate dihydrate tablets to be the cause of the gastric lesions based on the following reasons: i) patients had common endoscopic features showing gastric mucosal redness, erosions, adhesion of white coat, and/or ulcers; ii) such gastric lesions did not exist before the administration of zinc acetate dihydrate tablets and they appeared after administration; and iii) the gastric lesions improved after the cessation of zinc acetate dihydrate tablets. Although the gastric lesions observed in the Group A patients may have had other causes, the high prevalence of gastric mucosal redness (93.1%), erosions (90.0%), and adhesion of the white coat (86.2%) suggest that these occurred due to a single cause, possibly the intake of zinc acetate dihydrate tablets.

In the field of gastroenterology, zinc has long been prescribed as polaprezinc to treat gastric ulcers and gastritis (5, 6). Polaprezinc, a complex of zinc and L-carnosine, has a high affinity for gastric mucosal injuries, exhibits a direct cytoprotective effect via antioxidant and membrane-stabilizing effects, and promotes gastric wound healing. Thus, the fact that zinc-containing agents damage the gastric mucosa is a blind spot for gastroenterologists. In fact, there have been few reports on zinc-induced gastric lesions. In 2013, Wiernicka et al. retrospectively analyzed 53 pediatric patients with Wilson's disease treated with zinc sulfate (7). Esophagogastroduodenoscopy was performed for 7 patients with abdominal pain, and revealed gastrointestinal ulcerations or erosions. Furthermore, in 2014, Mirjana et al. reported two patients with Wilson's disease who presented with gastric ulceration a few months after the initiation of zinc acetate treatment (8). The endoscopic images reported by Wiernicka et al. and Mirjana et al. demonstrated gastric mucosal redness, erosions, and ulcers with adhesion of the white coat, which were quite similar to the endoscopic findings of the present study. In 2016, Gilbert et al. reported the case of a patient with Wilson's disease who had gastric ulcer perforation (9). The patient was then treated with zinc sulfate and diclofenac. In 2020, Antczak-Kowalska et al. reviewed 115 patients with Wilson's disease, and 75 patients (65.2%) were diagnosed with gastropathy (10), and 11 (9.6%) had gastric or duodenal ulcers. The authors also re-

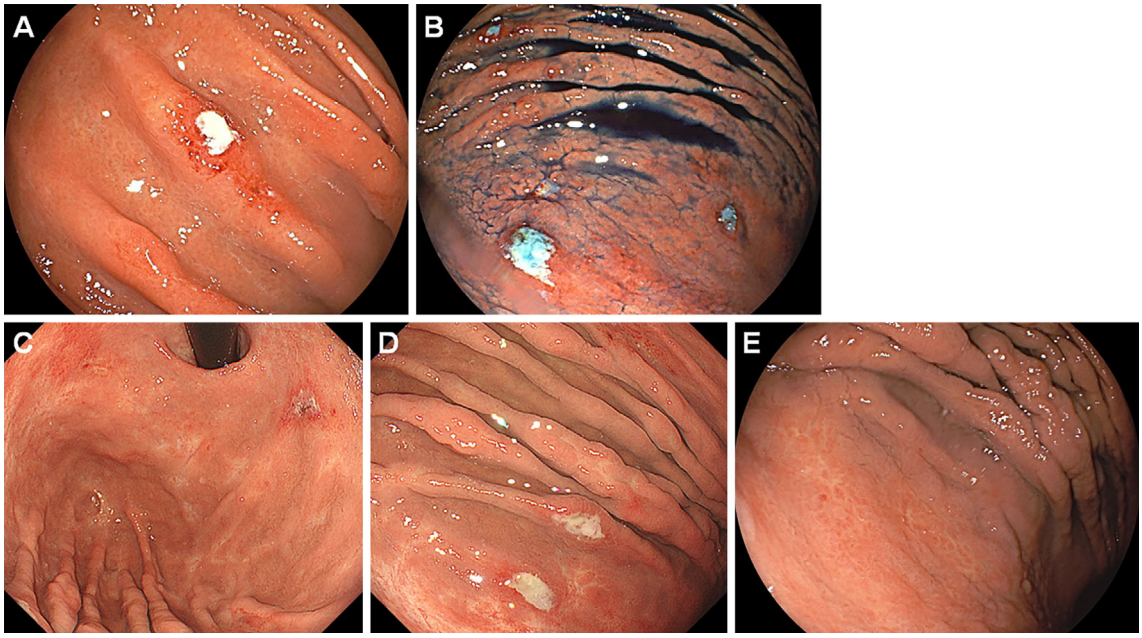

Figure 3. **Endoscopic images of Case 1. Esophagogastroduodenoscopy performed 7 weeks after the administration of zinc acetate dihydrate tablets revealing multiple ulcers and erosions with mucosal redness and adhesion of the white coat (A, B). Esophagogastroduodenoscopy performed 5 weeks later also showing multiple ulcers and erosions with mucosal redness and adhesion of the white coat (C, D). The locations of the ulcers and erosions were different from those in the initial endoscopy. The gastric lesions disappeared 5 weeks after the cessation of zinc acetate dihydrate tablets (E).**

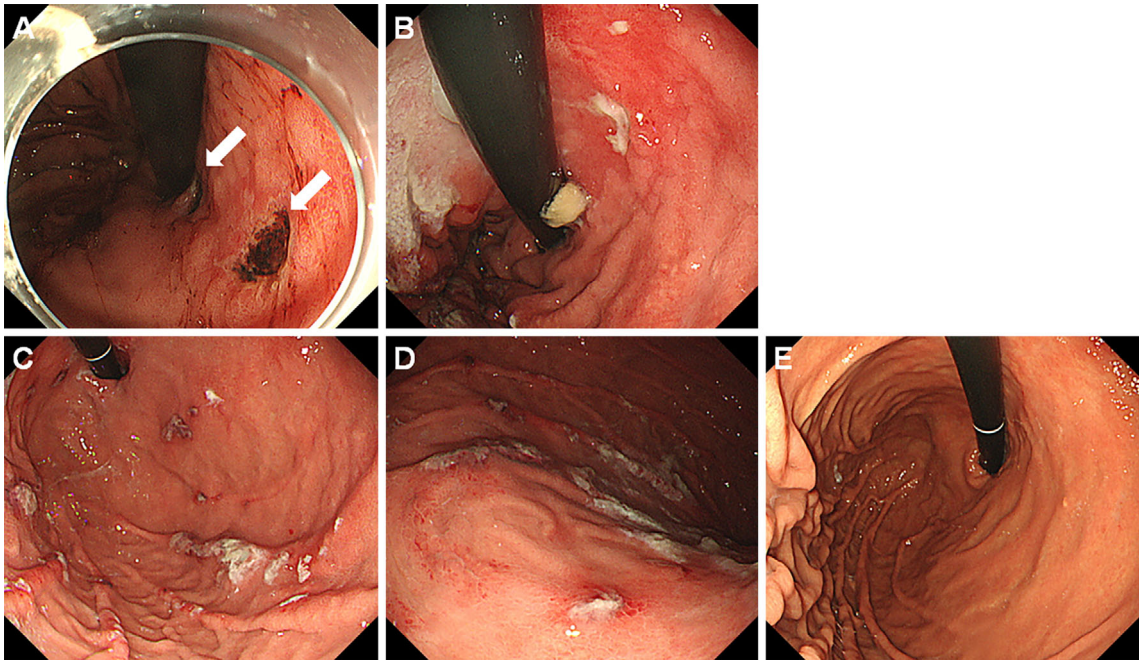

Figure 4. **Endoscopic images of Case 2. A 63-year-old man presented with hematemesis 2 days after he started taking zinc acetate dihydrate tablets. Esophagogastroduodenoscopy shows blood and multiple ulcers in the stomach (A, arrows). Esophagogastroduodenoscopy performed 2 days later revealing multiple ulcers and erosions with mucosal redness and adhesion of the white coat (B-D). Esophagogastroduodenoscopy performed after the cessation of zinc acetate dihydrate tablets showing multiple gastric ulcer scars (E).**

ported that zinc sulfate use was associated with gastropathy (p=0.03). To our knowledge, no reports have demonstrated firm evidence that zinc-containing drugs can damage the gastric mucosa. As such, the present study, which included the largest number of patients with zinc-containing drug-induced gastric lesions, was the first to report a probable as-

sociation.

In this study, 5 patients in Group A were diagnosed with gastric lesions within 14 days of the administration of zinc acetate dihydrate tablets. Thus, zinc acetate dihydrate tablet-associated gastric lesions can develop in both short-term and long-term users. Several hypotheses may explain the pathogenesis of zinc acetate dihydrate tablet-associated gastric lesions. First, some inorganic substances cause severe damage to the gastrointestinal tract, such as iron pills, which are known to induce erosion, ulcers, and gastritis in some patients (11-14). Iron pills are considered to be injurious in a concentration-dependent manner through direct corrosive effects (12) from the oxidation of iron from the ferrous to ferric form (13). Thus, contact with a high concentration of zinc may also induce gastric lesions. However, there have been no reports of gastric mucosal damage caused by polaprezinc, another form of zinc-containing medication. In addition, zinc oxide is safely used to treat or prevent skin diseases, such as burns, cuts, and diaper rash. Thus, it is possible that zinc itself directly causes gastric mucosal damage, but it is not probable. Second, the other ingredients contained in zinc acetate dihydrate tablets, such as acetate, may be harmful to the gastric mucosa. For instance, it is well known that acetic acid causes irritation, erosion, and ulcers in the stomach (15). Third, other drugs or underlying diseases may have induced or enhanced gastric mucosal damage in association with zinc acetate dihydrate tablets in a synergistic manner. In particular, despite the statistically insignificant difference, there were more non-steroidal anti-inflammatory drug users in Group A (20.7%) than in Group B (5.6%). Further investigations are required to determine the etiology of gastric lesions in patients treated with zinc acetate dihydrate tablets.

In our institution, the prevalence of gastric lesions among patients who underwent esophagogastroduodenoscopy was 61.7%. We revealed that patients with gastric lesions included a higher percentage of symptomatic patients (65.5%) in comparison to patients without gastric lesions (22.2%). Gastric irritation is listed as a possible side effect of zinc acetate dihydrate that occurs in 1-10% of users, particularly at the beginning of treatment (16). In addition, nausea, vomiting, and dizziness have been reported as possible symptoms after the intake of excessive doses of zinc acetate dihydrate. Wiernicka et al. reported that 21 of 53 of children with Wilson's disease (39.6%) experienced adverse effects with zinc sulfate (7), and all symptoms were of gastrointestinal origin, including abdominal pain, nausea, and vomiting. In the present study, the symptoms observed in the patients from Group A included hematemesis, epigastric pain, melena, difficulty in swallowing, nausea, vomiting, and appetite loss. Although some of these might have been associated with underlying diseases or medications other than zinc acetate dihydrate tablets, the results suggest that esophagogastroduodenoscopy should be recommended for symptomatic patients who are taking this drug. Simultaneously, physicians should be aware of the risk of gastric mucosal damage in all users of zinc acetate dihydrate, since gastric lesions may occur even in asymptomatic patients.

It is noteworthy that some patients in the present study underwent multiple endoscopic examinations, with or without biopsy, to investigate and identify the etiology of their gastric lesions. In this context, the recognition of this disease entity is important for all physicians who prescribe zinc acetate dihydrate tablets and endoscopists to avoid unnecessary examinations as these lesions improve after the cessation of the medication.

We consider that cessation of medication is a priority when clinicians identify gastric lesions that are suspected to be related to zinc acetate dihydrate tablet use. In this study, six patients underwent esophagogastroduodenoscopy after zinc acetate dihydrate tablet cessation, and the resolution of gastric mucosal alterations was observed in all patients. However, some patients, particularly those with Wilson's disease, may have no choice but to continue zinc acetate dihydrate tablet treatment when other copper chelating agents are ineffective. Proton pump inhibitors or vonoprazan are probably not effective for the prevention of zinc acetate dihydrate tablet-associated gastric lesions, as the lesions occurred even in patients who had been receiving these acid suppressors. In fact, 72.4% of Group A patients had been receiving proton pump inhibitors or vonoprazan. Although medications that coat the gastric mucosa, such as sucralfate and sodium alginate, may have the potential to prevent gastric lesions, this concept requires further investigation.

The present study was associated with several limitations. First, this was a retrospective study performed in a single institution, and the number of enrolled patients was relatively small. Second, there was no direct evidence that zinc acetate hydrate tablets induced gastric lesions. However, we believe that a definite association exists between the development of gastric lesions and the use of zinc acetate dihydrate tablets because the characteristic endoscopic features were observed in many of the patients. Third, the patient information was incomplete due to the retrospective nature of this study, including the unavailability of the *H. pylori* infection status in most patients. Future studies incorporating such patient information and a larger number of patients may reveal the pathophysiology of these gastric lesions in greater detail.

In conclusion, we observed gastric lesions in 29 patients who were taking zinc acetate dihydrate tablets. The most common endoscopic findings were mucosal redness (93.1%), erosions (90.0%), adhesion of the white coat (86.2%), and ulcers (31.0%). Although the exact pathogenesis is uncertain, we believe that understanding the unique manifestations of this gastric lesion will help physicians manage adverse events in patients taking this drug.

The authors state that they have no Conflict of Interest (COI).

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