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【 ORIGINAL ARTICLE 】

Clinical Characteristics of Seven Patients with Lanthanum Phosphate Deposition in the Stomach

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Abstract:

Objective To analyze the clinical characteristics and endoscopic features of patients with lanthanum deposition in the stomach.

Patients We retrospectively reviewed seven patients with lanthanum deposition in the stomach who were diagnosed at Okayama Saiseikai General Hospital. We investigated the patient sex, age at diagnosis, medical and medication histories, gastrointestinal symptoms, complications, presence or absence of gastric atrophy, and outcome. We also investigated any changes in the endoscopic features if previous endoscopic images were available.

Results Seven patients (six males and one female) had lanthanum deposition. The median age was 65 years (range, 50-79 years). All patients had been undergoing dialysis (continuous ambulatory peritoneal dialysis in one patient, hemodialysis in six patients). The dialysis period ranged from 16 to 73 months (median, 52 months). The patients had all been taking lanthanum carbonate for a period ranging from 5 to 45 months (median, 27 months). Gastric atrophy was noted in 6 patients (85.7%). One patient had difficulty swallowing, and 1 other patient had appetite loss. The other 5 patients were asymptomatic. Endoscopic features included annular whitish mucosa (n = 4), diffuse whitish mucosa (n = 3), and whitish spots (n = 2). Five patients underwent multiple esophagogastroduodenoscopy. The endoscopic features were unchanged in 2 patients, whereas the whitish mucosa became apparent and spread during the course in 3 patients.

Conclusion We identified 7 patients with lanthanum deposition in the stomach. All patients showed whitish lesions macroscopically. Although the pathogenicity of gastric lanthanum deposition is uncertain, lanthanum-related lesions in the stomach progressed during continuous lanthanum phosphate intake in several patients.

Key words: lanthanum carbonate, hyperphosphatemia, chronic kidney disease

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Introduction

Lanthanum carbonate, $La_2(CO_3)_3$, has been widely used to treat hyperphosphatemia in patients with chronic kidney disease because this agent has a higher efficacy and tolerability compared to other conventional phosphate binders (1-5). After consuming lanthanum carbonate with meals, lanthanum binds with dietary phosphate. As a result, the formation of highly insoluble complexes, such as lanthanum phosphate, occurs, and prevents phosphate absorption via the intestine. The gastrointestinal tract minimally absorbs lanthanum phosphate complexes; therefore, most of the lanthanum phosphate is excreted via the feces (6, 7). Despite its low bioavailability, accumulating evidence shows that lanthanum can be deposited in the gastrointestinal mucosa, particularly in the stomach (8-15). However, the endoscopic features of gastric lanthanum deposition have not yet been fully eluci-

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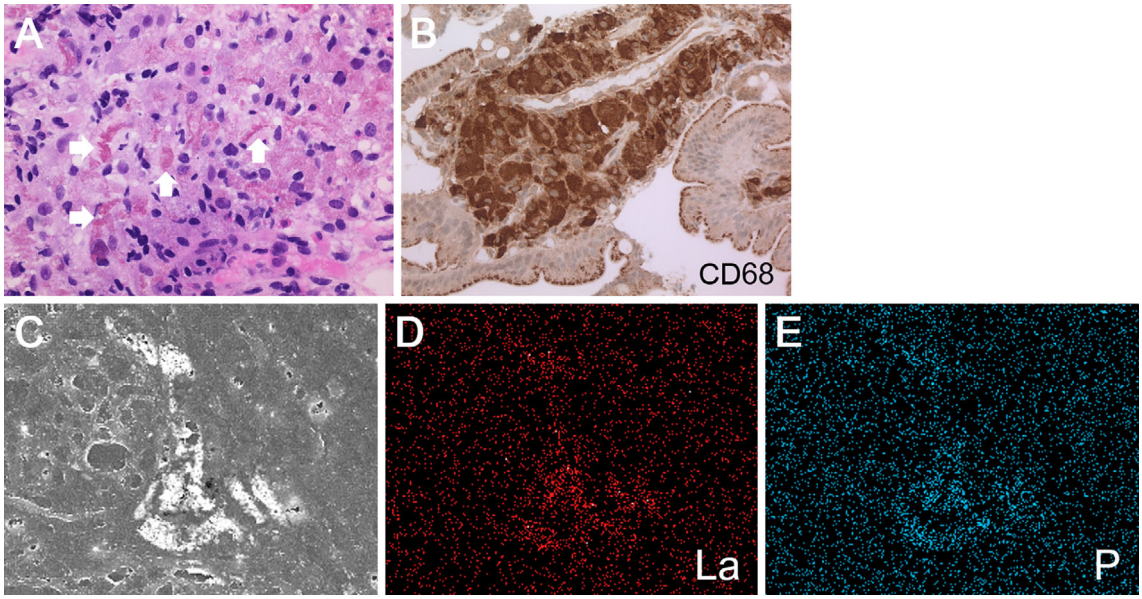

Figure 1. **Pathological images of lanthanum deposition in the stomach. Hematoxylin and Eosin staining shows fine, amorphous, eosinophilic material (A). CD68 staining confirms the existence of histiocytes in all cases (B). On scanning electron microscopy, the deposited material appears bright (C). Energy-dispersive X-ray spectroscopy shows that lanthanum (D) and phosphate (E) distribution is identical to that of the bright areas.**

dated.

The purpose of this study was to investigate the macroscopic features of lanthanum phosphate deposition in the stomach, with a particular focus on the sequential changes of the gastric mucosa over the course of continuous lanthanum carbonate use.

Materials and Methods

A database search of medical charts at Okayama Saiseikai General Hospital found 90 patients prescribed with lanthanum carbonate between January 2013 and February 2016. Biopsy was performed in 9 of the 90 patients during esophagogastroduodenoscopy examinations to investigate the possible presence of neoplasms, amyloid deposition, or lanthanum deposition. As a result, lanthanum deposition was histologically diagnosed in 7 patients. Thus, 7 patients were retrospectively registered in this study. Lanthanum deposition was histologically diagnosed based on the presence of fine, amorphous, eosinophilic material on hematoxylin and eosin-stained tissue slides (Fig. 1A). The presence of histiocytes was also identified by CD68 staining (Fig. 1B) in all cases. In 1 patient, scanning electron microscopy and energy-dispersive X-ray spectroscopy were used for the chemical analysis, as described in a previous study (16). Briefly, the deposited material on osmium-coated samples appeared bright in the scanning electron microscopy observation (Fig. 1C). We confirmed lanthanum (Fig. 1D) and phosphate distribution (Fig. 1E), which was identical to that of the bright areas, in elemental mapping images by using energy-dispersive X-ray spectroscopy.

We retrospectively examined the following to determine each patient's background: patient sex, age at diagnosis, medical, and medication histories including lanthanum carbonate intake, the infection status of *Helicobacter pylori*, gastrointestinal symptoms, gastrointestinal complications possibly related to lanthanum deposition, and the outcome. The presence or absence of gastric atrophy was endoscopically evaluated based on the mucosal color and structure of the stomach. Each patient's endoscopic images in the database were reviewed and analyzed by two board-certified endoscopists (NM and MY). We subdivided each patient's endoscopic features into three types as follows: (i) whitish spot (s) (whitish lesion ≤2 cm in diameter with a uniform white color) (Fig. 2A and B), (ii) annular whitish mucosa (lesion ≤ 2 cm in diameter with a white color in the periphery) (Fig. 2C and D), and (iii) a diffuse whitish mucosa (>2 cm in diameter, reddish areas may be intermixed in this lesion) (Fig. 2E). Sequential changes of the endoscopic features were also investigated in patients with multiple histories of undergoing endoscopic examinations.

Results

The patients' characteristics are shown in Table 1. Six males and 1 female were included in the study. The median age was 65 years, ranging from 50 to 79 years. All patients were on dialysis: continuous ambulatory peritoneal dialysis (n=4), hemodialysis converted from continuous ambulatory peritoneal dialysis (n=2), and hemodialysis (n=1). The median length of dialysis treatment was 4 years (range, 1-6 years). The median administration period of lanthanum

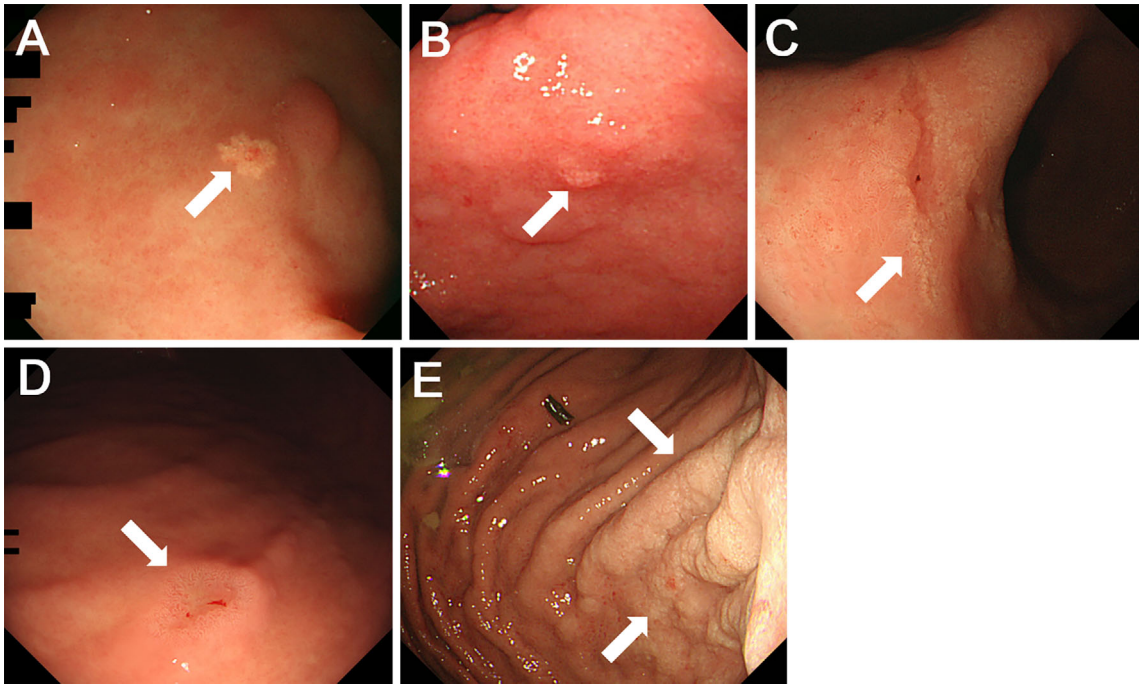

Figure 2. Endoscopy images. Representative endoscopy images of whitish spots (A, B), an annular whitish mucosa (C, D), and a diffuse whitish mucosa (E). Case 3 has whitish spots (A, arrow), which resemble gastric xanthoma, in addition to a diffuse whitish mucosa (Fig. 5). Similar whitish spots are seen in case 7 (B, arrow). An annular whitish mucosa is seen in case 4 (C, arrow) and case 5 (D, arrow). Case 1 has a diffuse whitish mucosa (E).

Table 1. Clinical Background of the Study Subjects with Lanthanum Deposition in the Stomach.

No.	Age at diagnosis (years)	Sex	Type of dialysis	Dialysis history (months)	Period of taking lanthanum carbonate (months)	*Helicobacter pylori* infection	Gastric atrophy	Gastrointestinal symptoms
1	50	M	CAPD	36	20	Positive (serology)	Present	Difficulty swallowing
2	50	F	HD	73	36	Positive (histology)	Present	None
3	65	M	CAPD, HD	59	40	NA	Present	None
4	73	M	CAPD	16	5	NA	Present	Appetite loss
5	79	M	CAPD	52	25	NA	Absent	None
6	67	M	CAPD	29	27	NA	Present	None
7	56	M	CAPD, HD	68	45	NA	Present	None

CAPD: continuous ambulatory peritoneal dialysis, HD: hemodialysis, NA: not available

phosphate was 27 months, ranging from 5 to 45 months. The *H. pylori* infection status was examined in only two patients. Both patients were positive for *H. pylori*, which was confirmed by serum antibodies against *H. pylori* in one patient and by a pathological analysis of gastric biopsy samples in the other patient. Gastric atrophy was endoscopically present in 6 of the 7 cases (85.7%). With regard to the gastrointestinal symptoms, difficulty in swallowing was documented in one patient, and one other patient had appetite loss. The other 5 patients were asymptomatic.

An annular whitish mucosa was identified in 4 patients, diffuse whitish mucosa in 3 patients, and whitish spots in 2 patients (Fig. 2-5) (Table 2). Five patients underwent esophagogastroduodenoscopy twice or more. The endoscopic features were unchanged in 2 patients. The interval of esophagogastroduodenoscopy was 9 months in these 2 patients. In the remaining 3 patients, a whitish mucosa became apparent and spread during the course in a time-dependent manner.

In case 1, esophagogastroduodenoscopy performed 4 months before the start of lanthanum carbonate prescription showed no whitish lesions in the stomach (Fig. 3A and B). After lanthanum carbonate intake for 20 months, a diffuse whitish mucosa was seen in the gastric cardia (Fig. 3C). Multiple round, slightly elevated areas with reddish part in its center and whitish part in its periphery were also identified in the gastric antrum (Fig. 3D). Thirty-eight months after the start of lanthanum phosphate administration, the dif-

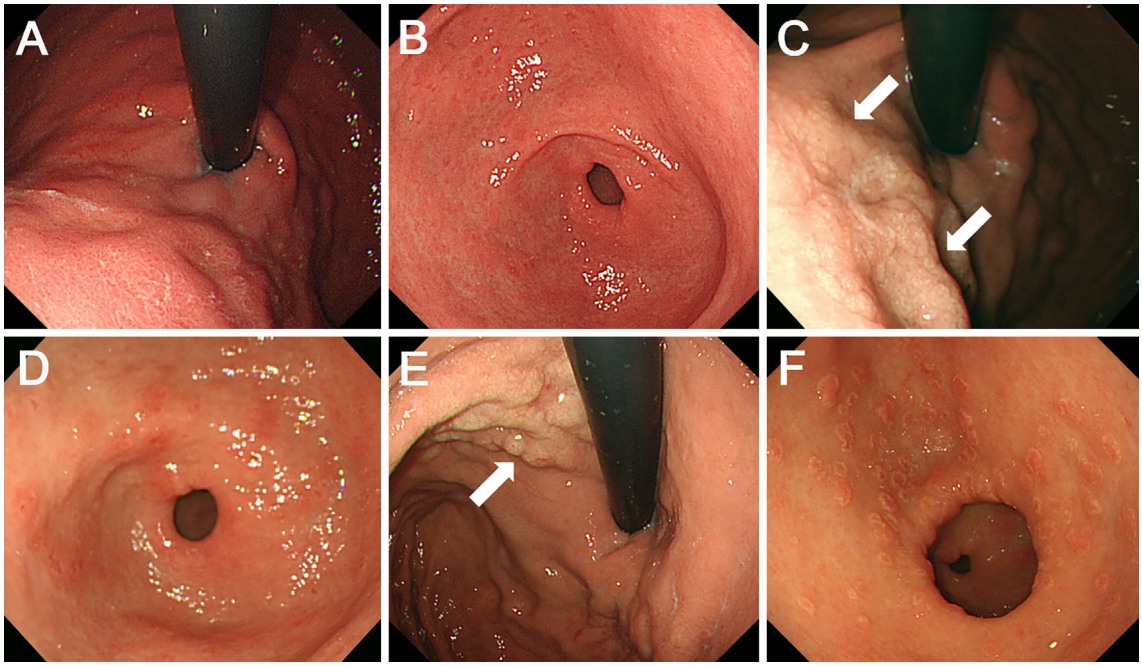

Figure 3. **Endoscopic images of case 1. Esophagogastroduodenoscopy performed four months before the start of lanthanum carbonate administration shows no whitish lesions (A, B). After lanthanum carbonate intake for 20 months, a diffuse whitish mucosa appeared in the gastric cardia (C). Round, slightly elevated areas with a reddish part in its center and a whitish part in its periphery are also identified in the antrum (D). Thirty-eight months after the start of lanthanum phosphate prescription, a diffuse whitish mucosa appears to have spread (E) and annular whitish lesions are evident (F).**

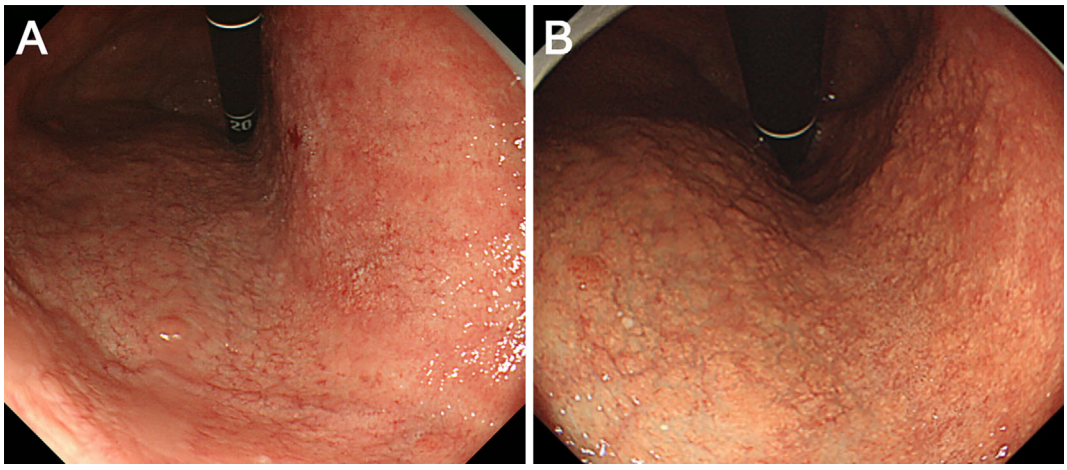

Figure 4. **Endoscopic images of case 2. Esophagogastroduodenoscopy performed 36 months after the start of lanthanum carbonate intake shows a whitish mucosa in the lesser curvature of the gastric body (A). A diffuse whitish mucosa is more apparent 56 months after lanthanum carbonate intake (B).**

fuse whitish mucosa in the gastric cardia seemed to have expanded (Fig. 3E). Moreover, multiple round lesions in the gastric antrum became apparent (Fig. 3F).

In case 2, a 50-year-old female, who had been taking lanthanum carbonate for 36 months was diagnosed with lanthanum deposition in the stomach (Fig. 4A). Fifty-six months after taking lanthanum carbonate, a diffuse whitish mucosa with partial redness was seen predominantly in the lesser curvature of the gastric body, which became more apparent and spread during the course (Fig. 4B).

In case 3, esophagogastroduodenoscopy performed 4 months after lanthanum carbonate intake showed a slightly whitish area in the posterior wall of the gastric body, which seemed to have resulted from intestinal metaplasia (Fig. 5A). Biopsy sampling was not performed at that time. Apparent whitish lesions emerged, which were intermingled with reddish areas, 32 months later (Fig. 5B). Lanthanum deposition was detected in the biopsy samples of the diffuse whitish mucosa.

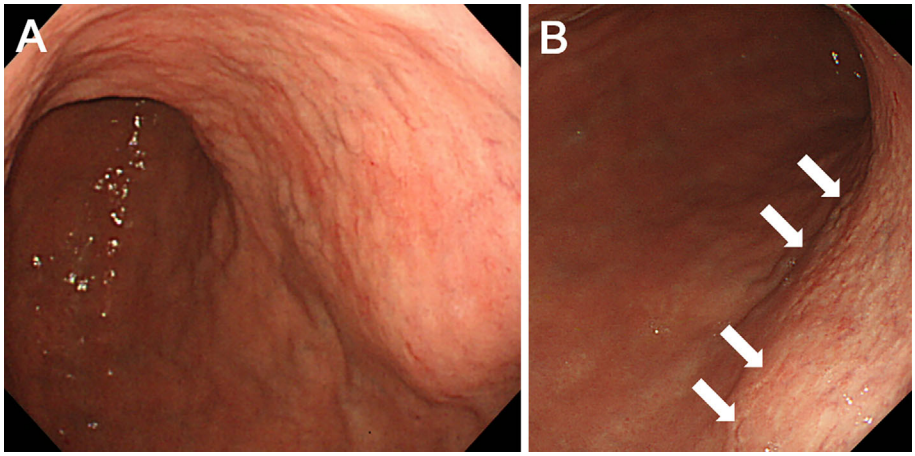

Figure 5. **Endoscopic images of case 3. Intestinal metaplasia is seen in the posterior wall of the gastric body (A). Whitish lesions emerged 32 months after lanthanum carbonate intake (B).**

Table 2. **Endoscopic Features of the Study Subjects with Lanthanum Deposition in the Stomach.**

No.	Endoscopic features	Interval of endoscopy examinations	Change of endoscopic features
1	Diffuse whitish mucosa and annular whitish mucosa	18	Progressed
2	Diffuse whitish mucosa	20	Progressed
3	Diffuse whitish mucosa and whitish spots	62	Progressed
4	Annular whitish mucosa	9	Unchanged
5	Annular whitish mucosa	NA	NA
6	Annular whitish mucosa	NA	NA
7	Whitish spots	9	Unchanged

NA: not available because only a single endoscopy examination was performed.

Discussion

In Japan, a chewable tablet form of lanthanum carbonate was released to the market in March 2009. In addition, lanthanum carbonate granules have been marketed since May 2012. Other phosphate-binding modulators include calcium carbonate, sevelamer hydrochloride, bixalomer, and ferric citrate. The phosphorus removal effect of calcium carbonate decreases as the intragastric pH increases. In contrast, lanthanum carbonate shows a high phosphorus removal effect irrespective of the intragastric pH levels (17). Therefore, lanthanum carbonate is effective for treating hyperphosphatemia even under acid secretion inhibitor administration. Although gastrointestinal symptoms, such as nausea, vomiting, and constipation, may appear as side effects, lanthanum carbonate has been widely used based on its safety and tolerability as described above.

Orally administered lanthanum binds with phosphorus in the diet and forms lanthanum phosphate, finally being excreted via the feces, as described in the Introduction section. However, since 2015, lanthanum has been reported to be phagocytosed by macrophages and deposited in the gastric mucosa as lanthanum phosphate (8-16). Previous reports described gastric and duodenal lesions associated with lanthanum phosphate deposition as white lesions, which were found during esophagogastroduodenoscopy. The white color may be caused by the aggregated particles of lanthanum phosphate itself, as demonstrated by microscopy and scanning electron microscopy (Fig. 1). Another hypothesis is that the white color reflects histiocytes entrapping lanthanum phosphate. The similarity in the color between the lanthanum deposition and gastric xanthoma, which consists of clusters of foamy histiocytes, supports the latter hypothesis. Differential diagnoses of whitish lesions in the stomach include extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) (18), plasmacytoma (19), and crystal-storing histiocytosis (20), in addition to xanthoma. Intestinal metaplasia is often visible as whitish plaques as well. Magnifying observations may be helpful to distinguish these disorders from lanthanum phosphate deposition. However, the value of magnifying observation for diagnosing this entity is beyond the scope of this study and thus will requires further investigation. At the present time, endoscopic biopsy and appropriate pathological analyses are essential.

In the present study, lanthanum deposition in the stomach was observed as an annular whitish mucosa (n=4), diffuse whitish mucosa (n=3), and whitish spots (n=2). Although we determined the presence of gastric atrophy based on endoscopic features alone rather than based on pathological evaluations, all but one patient had atrophic gastritis. Consequently, one possible explanation of such a multifarious presentation of lanthanum induced gastric lesions is that

these lesions reflect underlying gastric mucosal alterations caused by chronic gastritis. Tonooka et al. reported a patient with lanthanum deposition in the stomach, in whom lanthanum trapped in macrophages was found mainly in the atrophic mucosa with metaplastic epithelia (8). They also mentioned another patient who had taken lanthanum carbonate for years and showed no atrophy, intestinal metaplasia, or lanthanum deposition in the stomach. The authors speculated that differences in the tight junction structure and increased permeability of the intestinal metaplasia may lead to lanthanum deposition or absorption in the gastric mucosa. However, because of the small number of reported patients, the primary factor affecting the macroscopic features of lanthanum-induced gastric lesions still remains unknown.

This is the first study showing the chronologic changes of lanthanum-related lesions in the stomach over the course of lanthanum carbonate administration. Repeat esophagogastroduodenoscopy examinations revealed that whitish lesions in the stomach became apparent and had spread during the course in three patients (Fig. 2-4). Although the endoscopic features were unchanged in the other 2 patients, the interval between endoscopy examinations was 9 months in both patients. Therefore, if endoscopic examinations had been performed after a longer time interval, then the macroscopic features of gastric lesions in these 2 patients might have changed. Our study results indicate that lanthanum deposition in the gastric mucosa probably progresses in a time-dependent manner, as long as this agent is prescribed.

Several components of various drugs have been known to be deposited in the gastroduodenal mucosa in patients with chronic kidney disease. A change in the mucosal color to black in patients taking diuretics or antihypertensive agents is known to be associated with pseudomelanosis (21, 22). Pseudomelanosis is generally not considered a contraindication for any administered drug, because this occurrence is considered to be harmless. In contrast, the pathological significance of lanthanum deposition in the gastrointestinal mucosa has not yet been elucidated. In the present study, one patient complained of difficulty in swallowing, while another patient had appetite loss before undergoing esophagogastroduodenoscopy. However, the relationship between their symptoms and lanthanum deposition remains uncertain, because such symptoms are non-specific and can occur after the ingestion of lanthanum carbonate itself or due to some other causes. No known treatment or specific follow-up protocols have yet been established in previously described cases as well.

Rothenberg et al. reported a histological improvement of lanthanum deposition in the stomach and duodenum 3 months after discontinuing lanthanum carbonate intake (10). Yabuki et al. reported that lanthanum deposition was identified in the gastric mucosa in 3 patients with chronic renal failure who had undergone gastrectomy and lymph node dissection due to gastric cancer. They also detected lanthanum deposition in the peripheral lymph nodes, suggesting that lanthanum deposited on the gastrointestinal mucosa may be removed via the lymphatic flow (15). Meanwhile, Namie et al. reported that the endoscopic findings remained unchanged even 8 months after the discontinuing lanthanum carbonate administration (23), thus indicating that lanthanum-related lesions may be irreversible once deposited in the gastrointestinal mucosa. Further investigation is required to determine whether lanthanum deposition decreases or remains unchanged after the cessation of lanthanum carbonate intake.

In summary, we retrospectively investigated 7 patients with lanthanum phosphate deposition in the stomach. Lanthanum-related gastric lesions were observed as an annular whitish mucosa (n=4), diffuse whitish mucosa (n=3), and whitish spots (n=2). The progression of such lesions over time was observed in 3 patients. Although the clinical significance and long-term sequelae of this entity are unclear, endoscopists and gastroenterologists should include lanthanum deposition in the differential diagnosis when whitish lesions are found during esophagogastroduodenoscopy.

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

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