CASE REPORT

Lanthanum Deposition in the Stomach in the Absence of Helicobacter pylori Infection

Masaya Iwamuro¹, Haruo Urata², Takehiro Tanaka³, Seiji Kawano¹, Yoshiro Kawahara¹, Katsuhiro Kimoto⁵ and Hiroyuki Okada¹

Abstract:
In this case report, we describe two patients who showed a diffusely whitish mucosa in the posterior wall and the lesser curvature of the gastric body. The patients were serologically- and histopathologically-negative for Helicobacter pylori. Random biopsy specimens from the stomach revealed no regenerative changes, intestinal metaplasia, and/or foveolar hyperplasia in either of the patients. Although lanthanum deposition in the gastric mucosa has been reported to occur in close association with H. pylori-associated gastritis, our patients tested negative for H. pylori. These cases suggest that lanthanum deposition presents as whitish lesions in the gastric body in H. pylori-negative patients.

Key words: hyperphosphatemia, lanthanum carbonate, scanning electron microscopy analysis, Helicobacter pylori, atrophic gastritis

(Intern Med 57: 801-806, 2018) (DOI: 10.2169/internalmedicine.9665-17)

Introduction

Phosphorus excretion is generally decreased in patients with end-stage renal disease, which induces hyperphosphatemia. Thus, the treatment of increased blood levels of phosphorus becomes necessary to prevent osteoporosis and arteriosclerosis (1-4). Although lanthanum carbonate, which is widely prescribed to treat hyperphosphatemia in patients with end-stage renal disease, is generally safe and well tolerated by most patients, an increasing body of evidence suggests that lanthanum deposition can be observed in the gastroduodenal mucosa during esophagogastroduodenoscopy (EGD) (5-13). Moreover, several reports have revealed that lanthanum deposition tends to occur in the gastric mucosa in association with regenerative change, intestinal metaplasia, and/or foveolar hyperplasia (14); all of these histopathological features indicate that lanthanum is detected in the gastric mucosa in close association with Helicobacter pylori infection.

However, we encountered two patients with lanthanum deposition in the stomach who were serologically and histopathologically negative for H. pylori. Random biopsy specimens revealed no regenerative changes, intestinal metaplasia, and/or foveolar hyperplasia. To the best of our knowledge, this is the first report to describe the detailed endoscopic features of gastric mucosal lanthanum deposition in patients without H. pylori infection.

Case Reports

Case 1
A 73-year-old Japanese man underwent EGD for screening purposes. He had been undergoing hemodialysis for chronic kidney disease for 14 years, and had received oral lanthanum carbonate to treat hyperphosphatemia for 25 months. He had also been consuming rebamipide, celecoxib, nalfurafine, cinacalcet, nicorandil, esomeprazole, carvedilol, warfarin, clonazepam, and flunitrazepam for associated atrial fibrillation, spinal canal stenosis, and insomnia among other comorbidities, but had no history of gastroduodenal disease.

¹Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Japan, ²Central Research Laboratory, Okayama University Medical School, Japan, ³Department of Pathology, Okayama University Hospital, Japan, ⁴Department of Endoscopy, Okayama University Hospital, Japan and ⁵Kimoto Naika Clinic, Japan

Received: June 14, 2017; Accepted: July 22, 2017; Advance Publication by J-STAGE: December 8, 2017
Correspondence to Dr. Masaya Iwamuro, iwamuromasaya@yahoo.co.jp
A physical examination revealed no abnormalities, and no evidence of peripheral lymphadenopathy. The laboratory findings demonstrated elevated levels of phosphate (9.3 mg/dL, reference range: 2.3-4.5 mg/dL), creatinine (13.14 mg/dL), blood urea nitrogen (59.4 mg/dL), uric acid (9.6 mg/dL), and a low hemoglobin level (10.2 g/dL). The patient’s serum was negative for anti-*Helicobacter pylori* immunoglobulin G antibodies (3 U/mL).

EGD showed a diffusely whitish mucosa in the posterior wall and lesser curvature of the gastric body (Fig. 1A and B). Examination under magnification revealed fine, whitish deposits within the mucosa (Fig. 1C), which were more prominently noted using narrow-band imaging (Fig. 1D). The whitish mucosa was not detected in other parts of the stomach, including the antrum (Fig. 1E), and regenerative changes, intestinal metaplasia, and/or mucosal atrophy were not observed endoscopically. A biopsy specimen from part of the white deposits revealed the accumulation of fine, amorphous eosinophilic material within the lamina propria (Fig. 2A and B). These areas of deposition were positive for CD68 (C).

**Figure 1.** EGD images from Case 1. A diffusely whitish mucosa is seen in the posterior wall and the lesser curvature of the gastric body (A, B). Observation under magnification reveals fine, whitish deposits within the mucosa (C). The whitish deposits are more prominently seen under narrow-band imaging (D). The antral mucosa shows no whitish lesions (E).

**Figure 2.** Pathological images from Case 1. A biopsy specimen from the gastric mucosa with white deposits containing the accumulation of fine, amorphous eosinophilic material within the lamina propria (A, B). These areas of deposition were positive for CD68 (C).
Figure 3. Scanning electron microscopy images. The deposited material appears bright (A). The deposits are seen as aggregates of microparticles (B). Elemental mapping by energy dispersive X-ray spectroscopy shows that the distribution of lanthanum (C) and phosphate (D) corresponds to the areas that appeared bright (A).

Figure 4. Spectra obtained by energy dispersive X-ray spectroscopy. Spectra obtained from the bright areas (A) demonstrate lanthanum (arrow) and phosphate (arrowheads). These elements are almost completely absent in the background mucosa (B).

(Fig. 3A), and were seen as aggregates of microparticles (Fig. 3B). Elemental mapping using energy dispersive X-ray spectroscopy confirmed that the distribution of lanthanum (Fig. 3C) and phosphate (Fig. 3D) corresponded to the distribution of bright areas that was noted on X-ray spectroscopy (Fig. 3A). A comparative analysis of the spectra between the bright areas and the background also demonstrated that lanthanum and phosphate were present in the bright areas, but were almost completely absent in the background mucosa (Fig. 4). Consequently, we diagnosed the gastric lesion as lanthanum phosphate deposition. Random biopsy specimens taken from the greater and lesser curvatures of the gastric body and the greater curvature of the gastric antrum did not show regenerative change, intestinal metaplasia, and/or foveolar hyperplasia.

Case 2
A 42-year-old Japanese man underwent EGD for routine
checkup of esophageal varices. He had been undergoing hemodialysis for 7 years for chronic kidney disease, and had been treated with oral lanthanum carbonate for 69 months. In addition, he had been consuming lansoprazole, ethyl icosapentate, bixalomer, furosemide, teneligliptin, and voglibose. A physical examination revealed no abnormalities. The laboratory findings demonstrated elevated levels of phosphate (5.8 mg/dL), creatinine (10.18 mg/dL), blood urea nitrogen (28.6 mg/dL), hemoglobin A1c (6.6%), and a decreased hemoglobin level (13.4 g/dL). A test for serum anti-
H. pylori immunoglobulin G antibodies was negative (<3 U/mL).

EGD showed a diffusely whitish mucosa in the posterior wall and the lesser curvature of the gastric body (Fig. 5A and B). An examination under linked color imaging emphasized the whitish mucosa (Fig. 5C and D). The whitish mucosa was not detected in other parts of the stomach, including the antrum; endoscopy revealed no regenerative changes, intestinal metaplasia, and/or mucosal atrophy. Whitish deposition was also observed in the duodenal villi (Fig. 5E). Biopsy specimens from the gastric and duodenal whitish mucosa contained lanthanum phosphate, which was confirmed by electron microscopy. Random biopsy specimens obtained from the greater and lesser curvatures of the gastric body, and the greater curvature of the gastric antrum did not show regenerative change, intestinal metaplasia, and/or foveolar hyperplasia.

**Discussion**

The deposition of lanthanum in the gastroduodenal mucosa has been reported since 2015 (5-14). As described above, recent studies have reported a correlation between underlying gastric mucosal alterations and susceptibility to lanthanum deposition. Ban et al. investigated 121 biopsy specimens of the gastric mucosa obtained from 22 patients who had been treated with lanthanum carbonate. These authors identified lanthanum deposition in 86 gastric biopsies (71.1%), and gastric mucosal alterations such as intestinal metaplasia, regenerative changes, and foveolar hyperplasia were more frequently observed in the mucosa with numerous lanthanum deposits (14). Some authors have reported an association between the mucosal distribution of the lanthanum deposits and intestinal metaplasia (5, 11, 13). Ji, et al. evaluated epithelial paracellular permeability using the lanthanum tracer method (15). While lanthanum nitrate did not permeate the normal gastric epithelium, it did penetrate the lateral intercellular space of the gastric epithelium that showed intestinal metaplasia. This result indicates that lanthanum is able to cross the tight junctions of gastric epithelium in the presence of intestinal metaplasia, because the epithelial barriers are impaired under this condition. Consequently, there is a close relationship between lanthanum deposition and 
H. pylori-associated gastric mucosal alterations such as intestinal metaplasia, regenerative changes, and/or foveolar hyperplasia.

In our patients, EGD revealed that the gastric mucosa with lanthanum deposition had a whitish appearance. The two patients were serologically and histopathologically negative for 
H. pylori. Moreover, regenerative changes, intestinal metaplasia, and foveolar hyperplasia were not detected, indicating that neither of the patients had 
H. pylori infection. To the best of our knowledge, this is the first report to describe the detailed endoscopic features of lanthanum deposition in the gastric mucosa of patients without 
H. pylori infection. In our previous work, we retrospectively investigated the endoscopic features of lanthanum deposition in the stomach of seven patients (16). All lesions had a whitish appearance and were further classified as an annular whitish mucosa (n=...
4), diffusely whitish mucosa (n=3), or whitish spots (n=2). Similarly, in another set of 10 patients with lanthanum deposition in the stomach, all cases presented with white lesions (17). Observation under endoscopic magnification demonstrated the deposition of white microgranules within the gastric mucosa. Other authors have also reported that the mucosa appeared white on endoscopic images (7, 9). Thus, whitish lesions are considered to be the essential macroscopic feature of lanthanum deposition in the gastric mucosa (12, 16, 17). However, the other reported features of gastric mucosal lanthanum deposition vary from non-specific gastritis, erosions (9), ulcers (6), and polyps (7, 18). We therefore hypothesize that such variability in the macroscopic morphology reflects the underlying gastric mucosal alterations rather than conditions arising from lanthanum deposition itself.

In addition to the macroscopic features, we propose that the location of the whitish lesions is also influenced by the presence or absence of H. pylori infection. It is well known that H. pylori-associated atrophic gastritis primarily affects the antrum, and then spreads into the angle and body to eventually involve the entire stomach. Thus, the gastric antrum is more likely to be affected by lanthanum deposition in H. pylori-positive patients. The fornix and corpus may show lanthanum deposition in cases involving extensive H. pylori-associated gastritis. Based on the observations in our present case, lanthanum deposition is frequently observed in the gastric body because the gastric body is in contact with ingested lanthanum carbonate for a longer period of time than the gastric antrum. Fig. 6 shows a computed tomography (CT) image from Case 1. Although CT was performed after the patient had abstained from food and medicine for 7 hours, a substantial amount of food debris was retained in the stomach.

It is noteworthy that lanthanum, which is observed as a high-density substance in most cases - likely to be detected in the gastric mucosa in close association with H. pylori infection, we expect that the endoscopic images presented in these cases will facilitate the better understanding of lanthanum-related lesions in the stomach.

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

References

1. Patel L, Bernard LM, Elder GJ. Sevelamer versus calcium-based binders for treatment of Hyperphosphatemia in CKD: a meta-analysis of randomized controlled trials. Clin J Am Soc Nephrol 11: 232-244, 2016.
2. Langote A, Ahearn M, Zimmerman D. Dialysate calcium concentration, mineral metabolism disorders, and cardiovascular disease: deciding the hemodialysis bath. Am J Kidney Dis 66: 348-358, 2015.
3. Byon CH, Chen Y. Molecular mechanisms of vascular calcification in chronic kidney disease: the link between bone and the vasculature. Curr Osteoporos Rep 13: 206-215, 2015.
4. Zhang C, Wen J, Li Z, Fan J. Efficacy and safety of lanthanum carbonate on chronic kidney disease-mineral and bone disorder in dialysis patients: a systematic review. BMC Nephrol 14: 226, 2013.
5. Makino M, Kawaguchi K, Shimojo H, Nakanura H, Nagasawa M, Kodama R. Extensive lanthanum deposition in the gastric mucosa: the first histopathological report. Pathol Int 65: 33-37, 2015.
6. Rothenberg ME, Araya H, Longacre TA, Pasricha PJ. Lanthanum-induced gastrointestinal histiocytosis. ACG Case Rep J 2: 187-189, 2015.
7. Haratake J, Yasunaga C, Ootani A, Shimajiri S, Matsuyama A, Hisaoka M. Peculiar histiocytic lesions with massive lanthanum deposition in dialysis patients treated with lanthanum carbonate. Am J Surg Pathol 39: 767-771, 2015.
8. Goto K, Ogawa K. Lanthanum deposition is frequently observed in the gastric mucosa of dialysis patients with lanthanum carbonate therapy: a clinicopathologic study of 13 cases, including 1 case.
of lanthanum granuloma in the colon and 2 nongranulomatous gastric cases. Int J Surg Pathol 24: 89-92, 2016.
9. Yasunaga C, Haratake J, Ohtani A. Specific accumulation of lanthanum carbonate in the gastric mucosal histiocytes in a dialysis patient. Ther Apher Dial 19: 622-624, 2015.
10. Iwamuro M, Sakae H, Okada H. White gastric mucosa in a dialysis patient. Gastroenterology 150: 322-323, 2016.
11. Yabuki K, Shiba E, Harada H, et al. Lanthanum deposition in the gastrointestinal mucosa and regional lymph nodes in dialysis patients: analysis of surgically excised specimens and review of the literature. Pathol Res Pract 212: 919-926, 2016.
12. Iwamuro M, Urata H, Tanaka T, et al. Lanthanum deposition in the stomach: usefulness of scanning electron microscopy for its detection. Acta Med Okayama 71: 73-78, 2017.
13. Tonooka A, Uda S, Tanaka H, Yao A, Uekusa T. Possibility of lanthanum absorption in the stomach. Clin Kidney J 8: 572-575, 2015.
14. Ban S, Suzuki S, Kubota K, et al. Gastric mucosal status susceptible to lanthanum deposition in patients treated with dialysis and lanthanum carbonate. Ann Diagn Pathol 26: 6-9, 2017.
15. Ji R, Zuo XL, Yu T, et al. Mucosal barrier defects in gastric intestinal metaplasia: in vivo evaluation by confocal endomicroscopy. Gastrointest Endosc 75: 980-987, 2012.
16. Murakami N, Yoshioka M, Iwamuro M, et al. Clinical characteristics of seven patients with lanthanum phosphate deposition in the stomach. Intern Med 56: 2089-2095, 2017.
17. Iwamuro M, Kanzaki H, Kawano S, Kawahara Y, Tanaka T, Okada H. Endoscopic features of lanthanum deposition in the gastroduodenal mucosa. Gastroenterol Endosc 59: 1428-1434, 2017.
18. Hoda RS, Sanyal S, Abraham JL, et al. Lanthanum deposition from oral lanthanum carbonate in the upper gastrointestinal tract. Histopathology 70: 1072-1078, 2017.
19. Miwa H, Watari J, Fukui H, et al. Current understanding of pathogenesis of functional dyspepsia. J Gastroenterol Hepatol 26 (Suppl 3): 53-60, 2011.

The Internal Medicine is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).

© 2018 The Japanese Society of Internal Medicine
Intern Med 57: 801-806, 2018