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CASE REPORT

Early gastric cancer with lanthanum deposition mucosa by endoscopic submucosal dissection: a case report and literature review

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Abstract

Lanthanum carbonate is used to prevent hyperphosphatemia in dialysis patients with chronic renal failure and generally recognized as poorly absorbed by the gastrointestinal tract. However, some clinical cases of lanthanum deposition in the stomach have been shown. In addition, few endoscopic images of lanthanum deposition have been reported, particularly with respect to early-stage gastric cancer. A 64-year-old man with 22 years history of dialysis was treated with lanthanum carbonate for 3 years. With screening esophagogastroduodenoscopy, he was diagnosed with intramucosal gastric cancer, surrounded by the specific endoscopic images of the lanthanum deposition, and underwent endoscopic submucosal dissection. Histopathologically, massive accumulations of macrophages containing fine, granular, eosinophilic materials were observed in the lamina propria. These eosinophilic depositions were present in the lamina propria of the non-tumor region, but not in that of the tumor region. The histological features were further identified as lanthanum phosphate deposition by scanning electron microscopy. This case indicates the clinical significance of lanthanum deposition associated with gastric cancer. It is further required to evaluate more endoscopic images of the gastric mucosa, especially intramucosal cancer, with lanthanum deposition.

Keywords Lanthanum deposition · Gastric cancer · Endoscopic submucosal dissection · Scanning electron microscopy · Chronic renal failure

Introduction

Lanthanum carbonate is a phosphate-binding chemical agent to treat patients with end-stage kidney disease and reduce the absorption of phosphate due to their hyperphosphatemia. After oral ingestion, it binds phosphate to form an insoluble complex substance, and the oral bioavailability is extremely low to be approximately 0.001% [1]. Lanthanum carbonate was introduced as an alternative, non-aluminum, non-calcium phosphate binder in 2005 in the United States and in 2009 in Japan [2], and have become widely used as a safe chemical compound over the past decade.

The initial description of lanthanum deposition in the gastric mucosa was in 2015 [3]. Since then, there have been reports of lanthanum deposition in the stomach. In small cases, their endoscopic images of lanthanum deposition were described as irregular white spots and annular white thickening in the gastric mucosa [4, 5], but the precious endoscopic images still remain unclear. In addition, there were limited clinical cases of early-stage gastric cancer with lanthanum deposition indicating endoscopic treatment [3, 6, 7].

Here, we reported a patient receiving oral administration of lanthanum carbonate due to dialysis and diagnosed with early-stage gastric cancer who underwent endoscopic submucosal dissection (ESD). Furthermore, the lanthanum deposition in the gastric mucosa was analyzed using scanning electron microscopy (SEM) in detail.

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Case report

A 64-year-old man with *Helicobacter pylori* (*H. pylori*) infection was undergoing hemodialysis for 22 years due to nephrosclerosis and received lanthanum carbonate preparations for 3 years (1500 mg/day). Blood tests revealed severe renal impairment during the dialysis treatment. After the eradication of *H. pylori*, the patient underwent esophagogastroduodenoscopy (EGD) with a regular health check-up. The recent endoscopic images revealed the thickness of mucosal folds in the greater curvature of the gastric corpus and were associated with fine, white, granular deposition on its mucosal surface (Fig. 1a). Similar to the findings of corpus, we observed the same mucosal changes in the gastric antrum (Fig. 1b). Magnified narrow-band imaging (NBI) showed numerous small, irregular white spots in the mucosal surface of the gastric corpus and antrum (Fig. 1c, d). In parallel, a depressed small red lesion (10 mm) surrounded by annular whitish mucosa was found in the gastric angle, suggesting intramucosal gastric cancer (Fig. 2a, b). Magnified NBI detected the depressed lesion surrounded by numerous small, irregular white spots (Fig. 2c), and the surface pattern of the depressed lesion was mostly absent (Fig. 2d). With biopsies from this lesion, tubular adenocarcinoma was confirmed.

Then, we diagnosed intramucosal gastric cancer and performed an endoscopic submucosal dissection (ESD). Histopathologically, the well-differentiated tubular adenocarcinoma was confined to the mucosa of the depressed lesion (Fig. 3a, b). With hematoxylin–eosin (HE) staining, extensive accumulation of macrophages containing eosinophilic materials were found in the lamina propria of the non-tumor region (Fig. 3c, d), but not in that of the tumor region (Fig. 3a, b). Multi-nucleated giant cells were also present in the non-tumor region (Fig. 3d). During ESD, the other biopsy specimen was taken from the surface of whitish, rough granular mucosa on the gastric corpus. Similar to the finding of ESD tissue, massive macrophages with granular eosinophilic deposits were observed in the lamina propria, consistent with the presence of inflammation (Fig. 3e). With immunohistochemical staining, macrophages were strongly positive for CD68, indicating the presence of phagocytosis of a foreign substance, with the possibility of lanthanum (Fig. 3f).

Next, we analyzed the element detection of the deposited substance by scanning electron microscopy (SEM) (JSM-6510A, Hitachi, Japan). A thin section obtained from a paraffin-embedded gastric tissue block was used for this analysis. This study was approved by the Naruto Hospital Ethical Committee (March 27, 2020; protocol #1378). Informed, written consent was obtained. Spectral analysis

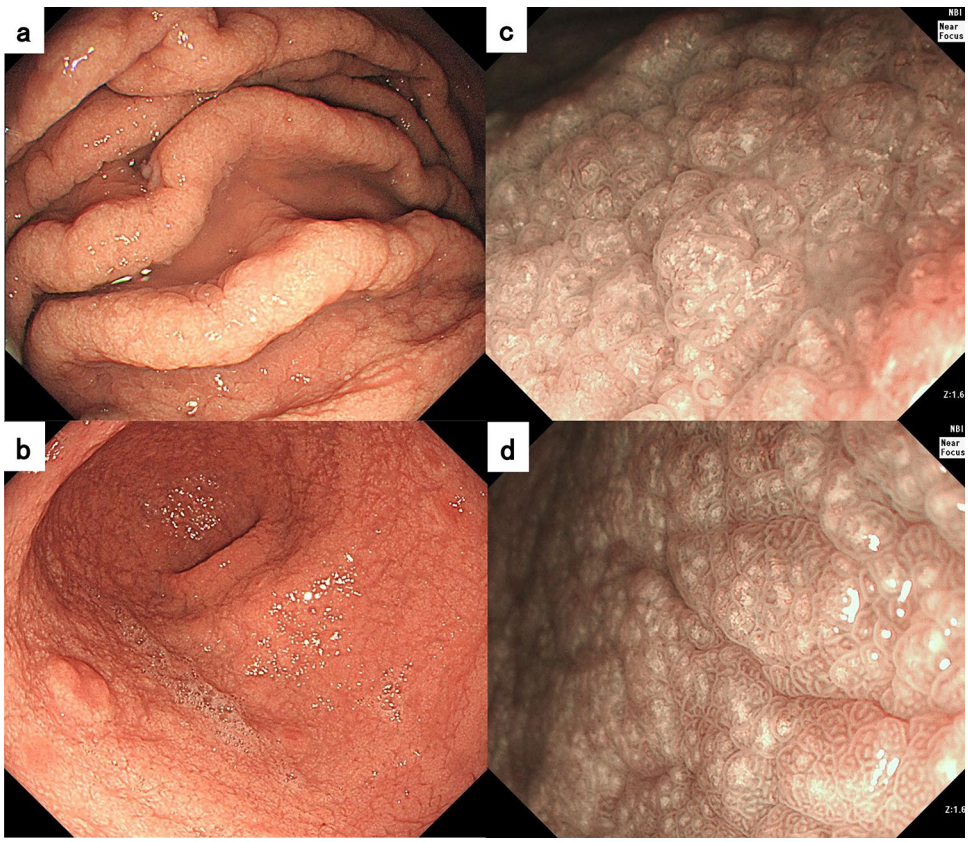

Fig. 1 **a** Endoscopic images of the gastric corpus as background. Whitish, rough mucosa was present. **b** Endoscopic images of the antrum. **c** Magnified narrow-band imaging showed fine, granular, whitish deposition in the gastric corpus. **d** Magnified NBI imaging in the antrum. For **c**, **d**, the magnified scope (GIF-H290Z, Olympus) was used

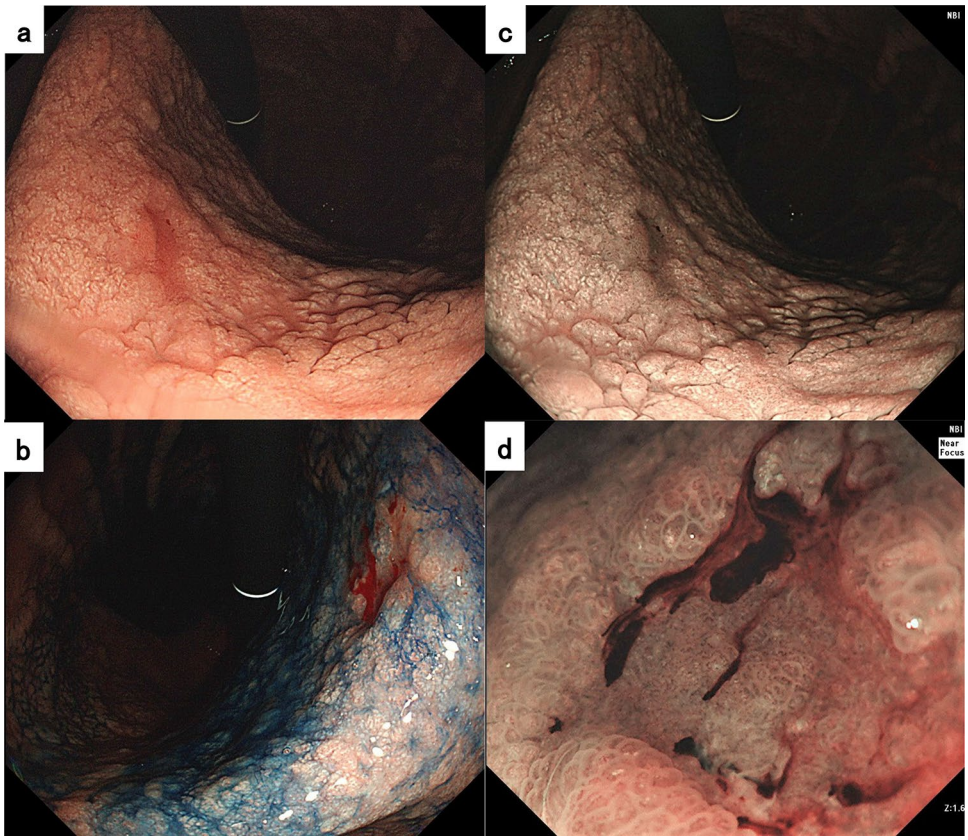

Fig. 2 **a** Endoscopic images of intramucosal gastric cancer. Depressed red lesion was surrounded by annular whitish mucosa in the lesser curvature of the gastric angle. **b** Endoscopic images with an indigocarmine-sprayed. **c** Magnified narrow-band imaging. Numerous small, irregular white spots were observed in the non-tumor region. **d** These white spots were not on the surface of tumor. For **c**, **d**, the magnified scope (GIF-H290Z, Olympus) was used

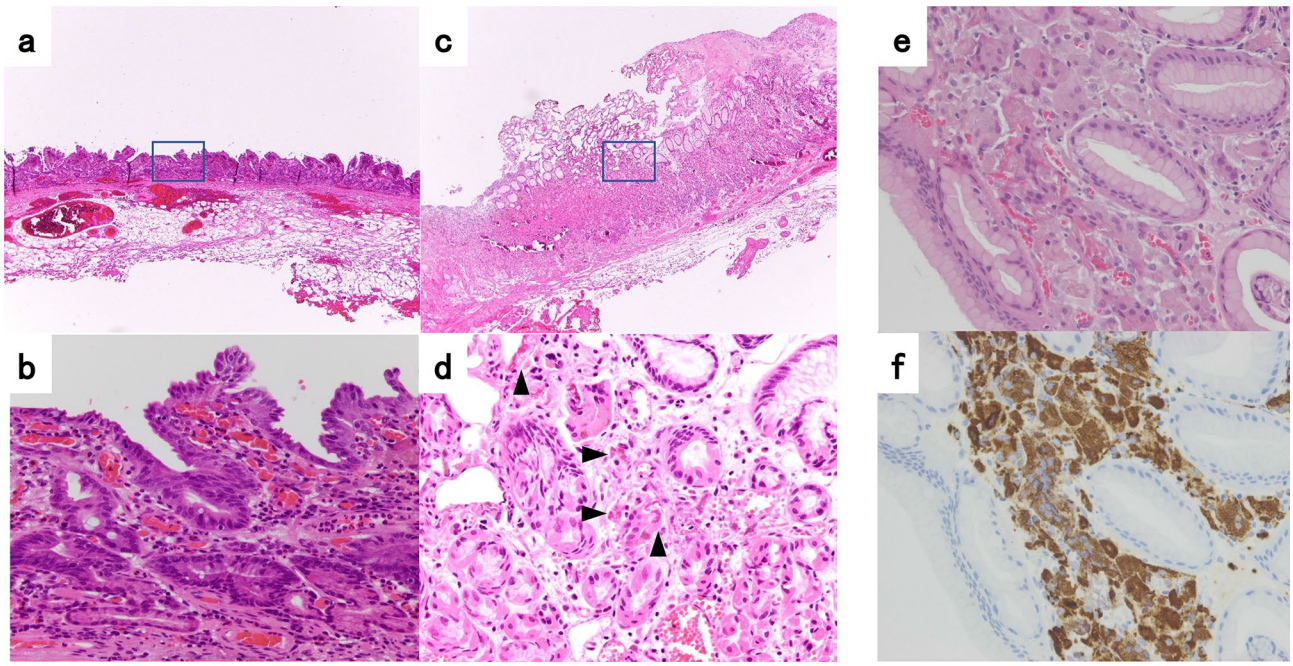

Fig. 3 **a** Histopathological views of the endoscopic submucosal dissection. Lower-power view of the tumor region. The well-differentiated tubular adenocarcinoma was confined to the mucosa. **b** High-power view of the blue square in a. The eosinophilic material was absent under the intramucosal cancer. **c** Lower-power view of the non-tumor region. **d** High-power view of the blue square in c. The mucosa had fine, granular, eosinophilic materials as shown in black triangles. **e** Biopsy tissues from the gastric corpus. The deposition of fine, amorphous, eosinophilic materials, and massive macrophages were shown in the lamina propria. **f** These macrophages were immunoreactive to CD68 in the same tissue sample

of SEM characterized the constituent elements of the gastric mucosa (Fig. 4a, b), and detected deposits of lanthanum and phosphorus as a bright element within macrophages in the lamina propria. Digital mapping via SEM indicated a change in element concentration of gastric mucosa (Fig. 4c–f). Red and blue indicated the presence of lanthanum and phosphorus, respectively, and purple spots formed with the presence of lanthanum and phosphorus. The distribution of lanthanum and phosphorus correlated with a bright area on the SEM image (Fig. 4f), which showed lanthanum to exist in the form of lanthanum phosphate in the gastric mucosa.

Discussion

Lanthanum carbonate was approved in 2004 and has been reported to be effective with fewer adverse effects and a potential decreased risk of mortality compared to calcium-based phosphate binders [1]. Despite the safety of lanthanum use, recent reports are beginning to describe the patients showing the signs of local gastrointestinal (GI) complications with long-term lanthanum treatment [8]. In the present case, we could endoscopically diagnose intramucosal gastric cancer with lanthanum deposition and indicate endoscopic treatment.

Few studies have been addressed the endoscopic images of lanthanum deposition in the gastric mucosa [4, 5], and the idea on endoscopic images of its deposition has been gradually established. We observed specific whitish mucosa of granular deposition, supported by the summarized case that whitish mucosa was evident in 70.6% cases [4]. NBI and its magnified picture were also helpful to reveal the lanthanum deposition and detect the whitish substance in the lamina propria similar to the previous findings [4, 5]. However, it is unclear whether the endoscopic image of lanthanum deposition would facilitate or make difficult the detection of intramucosal gastric cancer usually described as the depressed red lesion. To date, four cases, including our report, have described early-stage gastric cancer with lanthanum deposition indicating an endoscopic treatment [3, 6, 7] (Table 1). Although the gastric mucosa with lanthanum deposition has been gradually reported, there were potential factors for underestimation and forgotten lanthanum deposition. In addition, we could find no common clinical features in the reported cases. It will be necessary to examine more endoscopic images of early-stage gastric cancer with lanthanum deposition and analyze the specific clinical characteristics of these patients.

These deposits have been well characterized by a detailed SEM analysis and identified the presence of

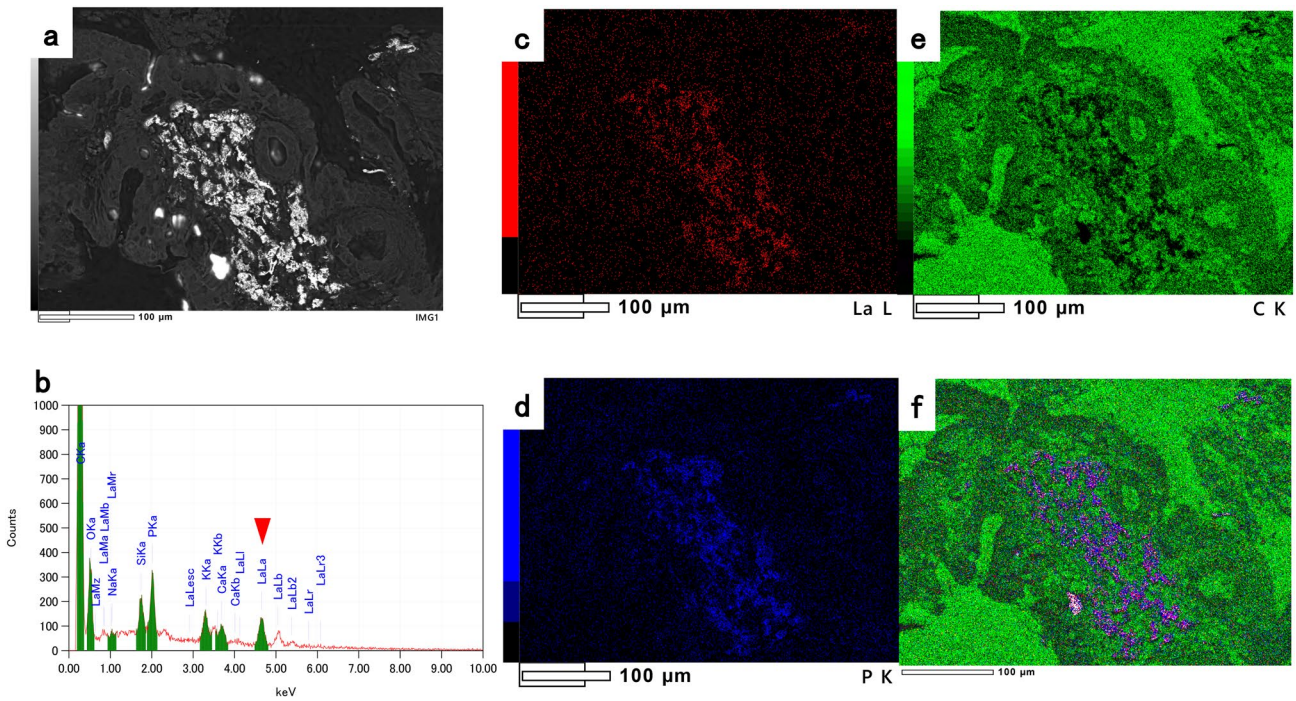

Fig. 4 **a** Scanning electron microscopy (SEM) images. Deposition in macrophages was observed as bright elements in the lamina propria. **b** Spectral analysis of SEM confirmed the peak of lanthanum (La) and phosphorus (P) observed in the bright area. Red arrow indicated peak of La. **c** Digital mapping via SEM indicated a change in element concentration of gastric mucosa. Element mapping on the SEM images of lanthanum (red). **d** Element mapping of phosphorus (blue). **e** Background SEM images of carbon (green). **f** Purple spots formed by the presence of lanthanum and phosphorus

Table 1 Summary of early gastric cancer cases with lanthanum deposition mucosa

Author	Year	Age (years)	Sex	Duration of LC administration (months)	Dose of LC (mg/day)	Deposition area	Site of cancer	Depth	Size (mm)	Treatment	*H. pylori*
Makino et al. [3]	2015	63	M	41	750	Body, antrum	Lower	m	20×10	ESD	Uninfected
Takatsuna et al. [6]	2019	78	M	36	NA	Body, antrum	Lower	m	10	ESD	Infected
Tabuchi et al. [7]	2019	50	M	NA	NA	Body, antrum	Lower	m	NA	ESD	Uninfected
Tonooka et al. [10]	2015	81	F	7	750	NA	Remnant stomach	m	15–2 (three tumors)	Surgical resection	NA
Yabuki et al. [11]	2016	77	F	36	1500	Body, antrum, duodenum	Lower	sm	20	Surgical resection	Uninfected
Yabuki et al. [11]	2016	68	F	3	750	Body, antrum, duodenum	Middle	sm	50	Surgical resection	Uninfected
Yabuki et al. [11]	2016	77	M	12	750	Body	Lower	sm	60	Surgical resection	Uninfected
Present case	2021	64	M	36	1500	Body, antrum	Lower	m	10	ESD	Uninfected

LC lanthanum carbonate, *ESD* endoscopic submucosal dissection, *NA* not available

lanthanum and phosphorus in the gastric mucosa. However, the pathological role of lanthanum deposition has not been fully identified. In humans, low levels of lanthanum have been shown to absorb from the gut into the systemic circulation following oral intake [1]. As a result, its deposition in the gastric mucosa appeared to occur directly through the gastric epithelium [8]. This was attributed in part to the gastric epithelium disturbance, which resulted in increased permeability in patients with chronic kidney disease [9]. The present case may have a condition, such as increased permeability caused by chronic kidney disease. In addition, the pathological role of gastritis has been shown in increased permeability of gastric mucosa [8, 10]. In our case, *H. pylori* infection was recognized, and induced chronic gastritis with intestinal metaplasia. Furthermore, this lanthanum deposition will be investigated as another factor in chronic gastritis.

We could find lanthanum deposition in the lamina propria of the non-tumor region, but not in that of the tumor region. The reason for this absence of lanthanum deposition was unclear. This finding suggests the potential differential permeability between tumor and non-tumor epithelia. Its deposition tended to be shown in the region of regenerative change and/or intestinal metaplasia, suggesting that the relationship between the favored sites of lanthanum deposition and the underlying mucosal pathogenicity [8]. This is also supported by the other case, in which the disruption of the tight junction was different between normal gastric epithelia and gastric epithelia with intestinal metaplasia [11]. The gastric mucosal changes seemed to be caused by lanthanum deposition, but the exact pathological roles associated with its deposition should be addressed in future investigations.

In conclusion, we described the change of gastric mucosa caused by lanthanum deposition and analyzed the detailed histological features of its deposition using SEM method. Currently, there is little recognition of co-existence of early cancer and lanthanum deposition in the gastric mucosa. We could suggest to accumulate more endoscopic images of lanthanum deposition in the gastric mucosa, particularly with respect to cancer. This case is helpful to the progression of endoscopic diagnosis in the *H. pylori* negative era.

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Declarations

Conflict of interest All authors declare that they have no conflict of interest.

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

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

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