[Review]

Lanthanum Deposition in the Gastroduodenal Mucosa of Dialysis Patients

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Abstract **:** Lanthanum (La) carbonate (LC) is one of the most popular phosphate binders used in dialysis patients with end-stage renal disease. Only a small amount of LC is believed to be absorbed from the gastrointestinal (GI) tract because LC strongly binds to dietary phosphate and forms insoluble complexes. La deposition in the gastroduodenal mucosa has been recently identified. Endoscopically, La deposition is demonstrated as whitish lesions of varying sizes and shapes in the gastroduodenal mucosa. Microscopically, La deposition is characterized by histiocytic reaction or small foreign body granulomas containing gray or brown materials mainly in the lamina propria of the GI mucosa. Some histiocytes containing La can migrate into regional lymph nodes via the lymphatic flow. The amount of La deposition in the gastroduodenal mucosa is correlated with the total dose of LC administration, and La deposition is almost consistently observed in LC-treated dialysis patients. Although the detailed mechanism of La deposition in the GI tract is still unclear, several factors, such as gastric pH and metaplastic change of the mucosal epithelium, may be involved in the La deposition in the gastroduodenal mucosa. Here we present an overview of the feature of La deposition in the GI tract.

Keywords **:** deposition, lanthanum, endoscopy, pathology, stomach.

(Received January 28, 2019, accepted October 16, 2019)

Introduction

Hyperphosphatemia is a major clinical complication in patients with end-stage renal disease (ESRD). Maintaining serum phosphate levels within its physiologic range is important to reduce risks for cardiovascular events and mortality [1, 2]. As dietary restriction of phosphate alone is insufficient to reduce serum phosphate levels, oral phosphate binders are used in many dialysis patients with ESRD [1]. Several phosphate binders, including calcium- or noncalcium-based forms, are currently available. Lanthanum (La) carbonate (LC) is one of the most effective and safe noncalcium-based phosphate binders, and has been available in the United States and Japan since 2005 and 2009, respectively. Dialysis patients have been exposed to LC, and the safety of LC administration has been documented in post-marketing surveillance for 10 years [3]. LC binds to dietary phosphate and forms insoluble complexes excreted in the feces, where LC is poorly absorbed. La deposition in the gastrointestinal (GI) mucosa in LC-treated dialysis patients has been

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reported in Japan in recent years [4−10]. The histopathological findings of La deposition in the GI tract are very unique in that it could be easily recognized even in a routine pathology practice. Here we summarize detailed findings of La deposition in the GI tract in dialysis patients.

Effects of LC administration in the GI tract

Generally, orally administered LC can bind to dietary phosphate in the stomach and form insoluble and undissociated lanthanum phosphate (LaP) complexes that pass through the GI tract. The availability of a single oral dose (i.e., 1,000 mg) of LC is very low (approximately 0.00127%) in healthy humans, and an extremely small amount of absorbed La is eliminated via the hepatobiliary route [11, 12]. No adverse effect in the GI tract caused by LC administration in dialysis patients has been described, except for nonspecific GI symptoms, such as nausea, vomiting, abdominal pain, and diarrhea [3,13]. Thus, LC administration has been believed to be nonharmful, and a little accumulation in the GI tract is considered safe.

Endoscopic findings of La deposition

Some endoscopic features of La deposition in the gastric or duodenal mucosa have been previously described. Whitish lesions of varying sizes and shapes, including white granular spots, white specks, and white plaques, are the most frequently documented or representative findings (Fig. 1) [4, 14, 15]. The distribution of the whitish lesions varies: predominantly in the duodenal or distal gastric mucosa, or diffusely in the gastroduodenal mucosa [4, 15]. Some correlations are described between the whitish area and dose of LC administration in clinical practice. Magnifying endoscopy with narrow-band imaging can detect these findings more clearly [4]. Regardless of LC administration, gastroduodenal abnormalities other than white lesions, such as erosion, peptic ulcer, gastritis, mucosal atrophy, and neoplastic changes, are commonly recognized in dialysis patients [14, 16−18]. Hyperplastic polyps are also likely to be observed in LC-administered dialysis patients [14, 15]. The association between La deposition in the GI tract and *Helicobacter pylori* infection

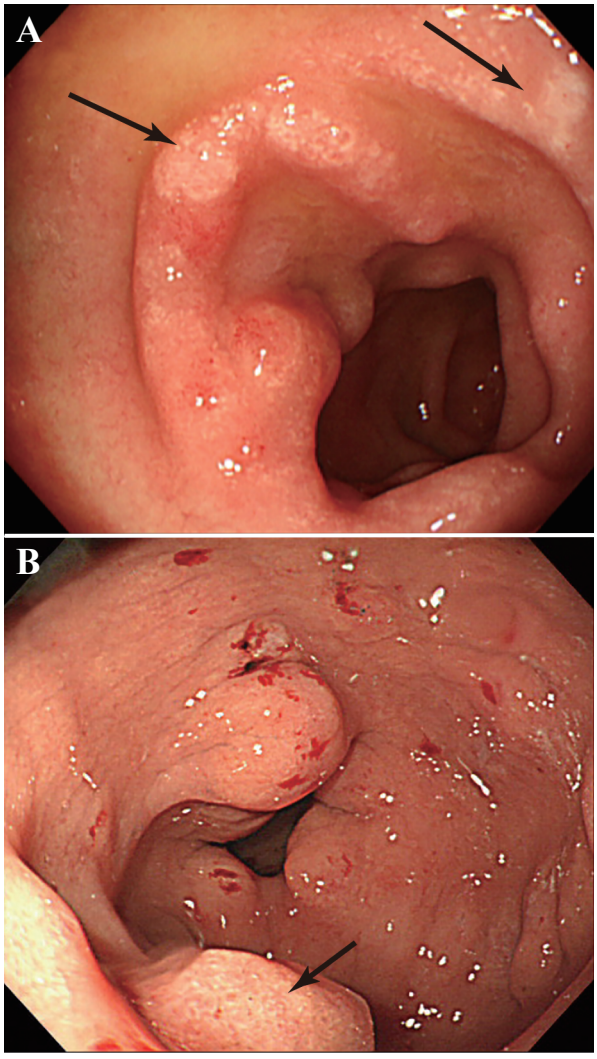

Fig. 1. Endoscopic finding of La deposition. Hyperplastic polyps with white granular spots (arrows) in the duodenum (A) and the antrum (B) are shown.

status is so far unclear, although several researchers have reported La deposition in the GI tract regardless of *H. pylori* infection [4, 14, 15]. In contrast, no La deposition in the colon has been described, except for only one case of colonic mucosa with tubular adenoma [7]. Therefore, information about La deposition in the lower GI tract is limited.

Radiological findings of La deposition

Radiological assessment of La deposition in the GI tract is still inadequate, but Shitomi *et al* showed that 11 of 14 dialysis patients with La deposition had a high-

density linear appearance in the gastric mucosa in plain computed tomography (CT), and this finding might be a helpful diagnostic clue to La deposition [4]. In CT or GI series examinations, many radiocontrast particles in the GI tract, which are suggestive of LC binding to dietary phosphate ($LaPO_4$) within its lumen, differed from the mucosal La deposition mentioned above.

Pathological findings of La deposition

Histologically, La deposition is characterized by subepithelial aggregates of plump eosinophilic histiocytes or small foreign body granulomas containing gray or brown coarse granular, amorphous, or crystal-like structures in the gastroduodenal mucosa (Fig. 2A, B). La deposition is observed predominantly in the lamina propria mucosae than in the submucosa. Immunohistochemically, the histiocytes in the mucosa are easily identified by their positive reaction to CD68 (Fig. 2C). Some foreign bodies are highlighted by metachromasia using toluidine blue staining (Fig. 2D), and they contained iron and calcium [4, 6]. Shitomi *et al* showed that calcium, collagen fiber, and hemosiderin were colocalized with La in some histiocytes [4]. In previously reported cases, La deposition was widely distributed in the surgically resected gastric mucosa associated with intestinal metaplasia [4, 6]. The gastric mucosa obtained by biopsy or surgical resection shows various degrees of histopathological changes, including chronic or active inflammation, glandular atrophy, intestinal metaplasia, regenerative changes, foveolar hyperplasia, and neoplasms. In orally administered LC rat models with a daily dose of 1,000 mg/kg for 5 days a week, the glandular gastric mucosa shows an infiltrate of chronic inflammatory cells including eosinophils in the lamina propria after 2 weeks of LC administration, mucous

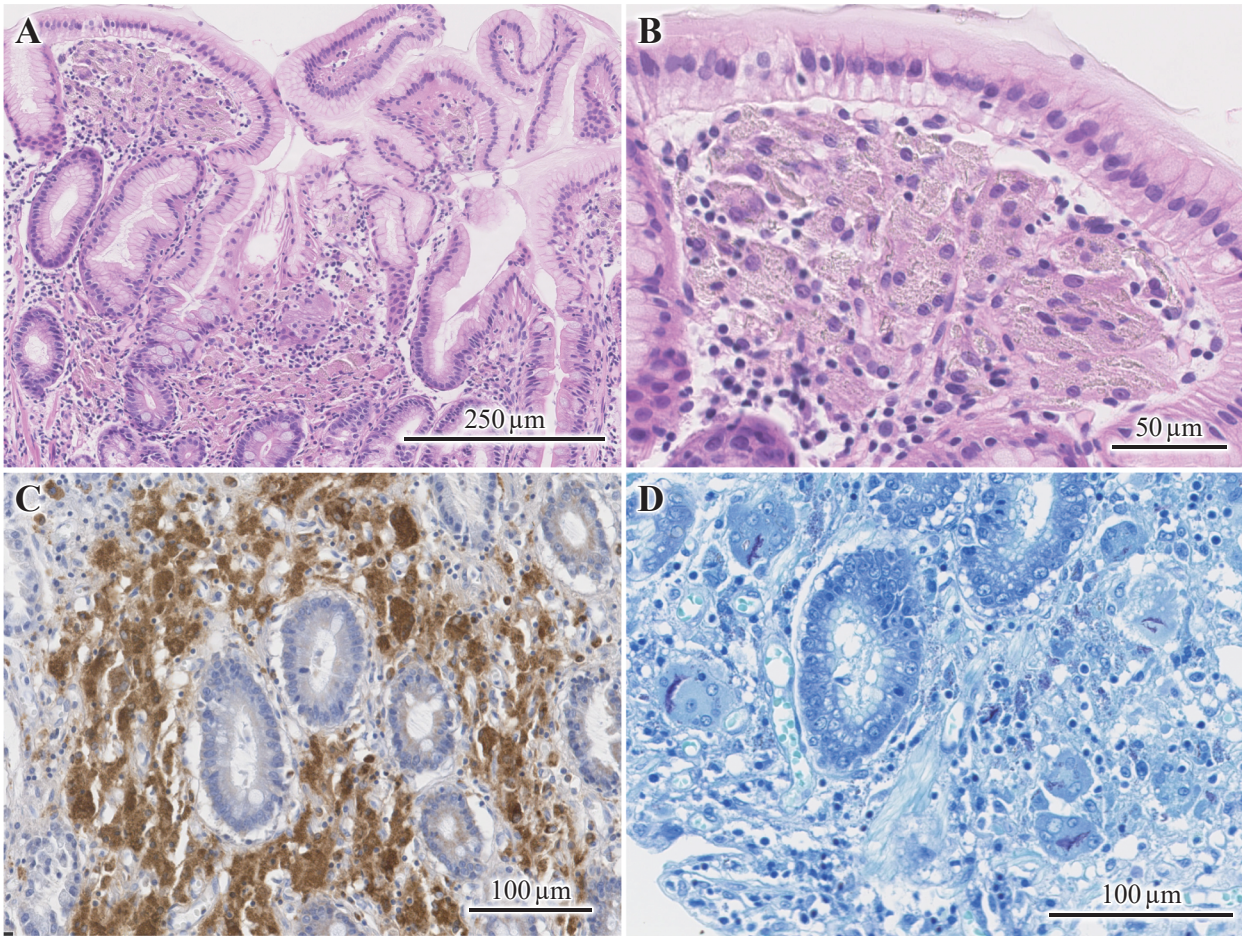

Fig. 2. Histopathological finding of La deposition. Mucosal histiocytic reaction containing foreign bodies (A, B). The histiocytes are immunoreactive to CD68 (C). The foreign bodies are emphasized by metachromasia using toluidine blue staining (D).

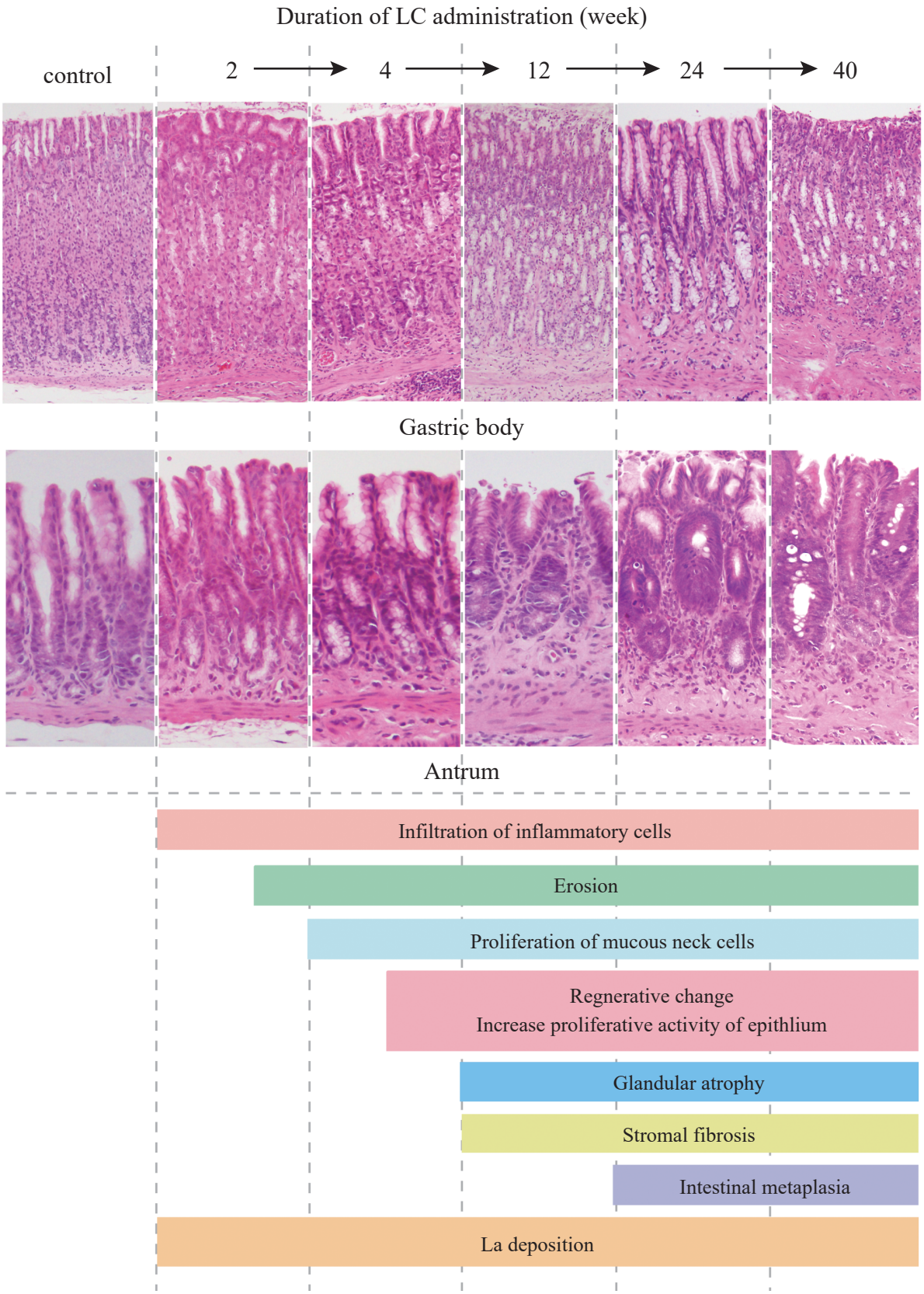

Fig. 3. Schematic representation of summarized histopathological changes in the rat gastric mucosa after LC administration.

neck cell proliferation, regenerative foveolar epithelium and erosion after 4 weeks, atrophic change in fundic and pyloric glands, and stromal fibrosis after 12 weeks, which is more predominant after 40 weeks. Intestinal metaplasia is observed after 24 weeks of LC administration (Fig. 3). Moreover, the mean Ki-67 labeling index of epithelial cells is significantly higher in the experimental group than that in the control group after 12 weeks. In human gastric mucosa, regenerative changes, intestinal metaplasia, and foveolar hyperplasia are likely observed among LC-administered patients [14, 19]. Although oral LC intake and La deposition may enhance the proliferative activity of the gastric mucosal epithelium, it is difficult to consider that GI carcinogenesis is induced in LC-administered patients based only on previously analyzed but limited cases. On the contrary, only a small amount of La deposition in an adenocarcinomatous area has been repeatedly described in the resected stomach [4, 6]. This phenomenon may partially explain the mechanisms of La absorption and subsequent deposition. Thus, careful management of LC-treated patients and further clinical investigation are required.

Ultrastructural findings of La deposition

By scanning electron microscopy, the backscattered electron images of the gastroduodenal mucosa show bright amorphous materials within the histiocytes in subepithelial areas, corresponding to the phagocytized deposits containing lanthanum and phosphorus, which are confirmed using energy dispersive X-ray spectroscopy (Fig. 4A–D). By transmission electron microscopy of the gastroduodenal mucosa, electron-dense

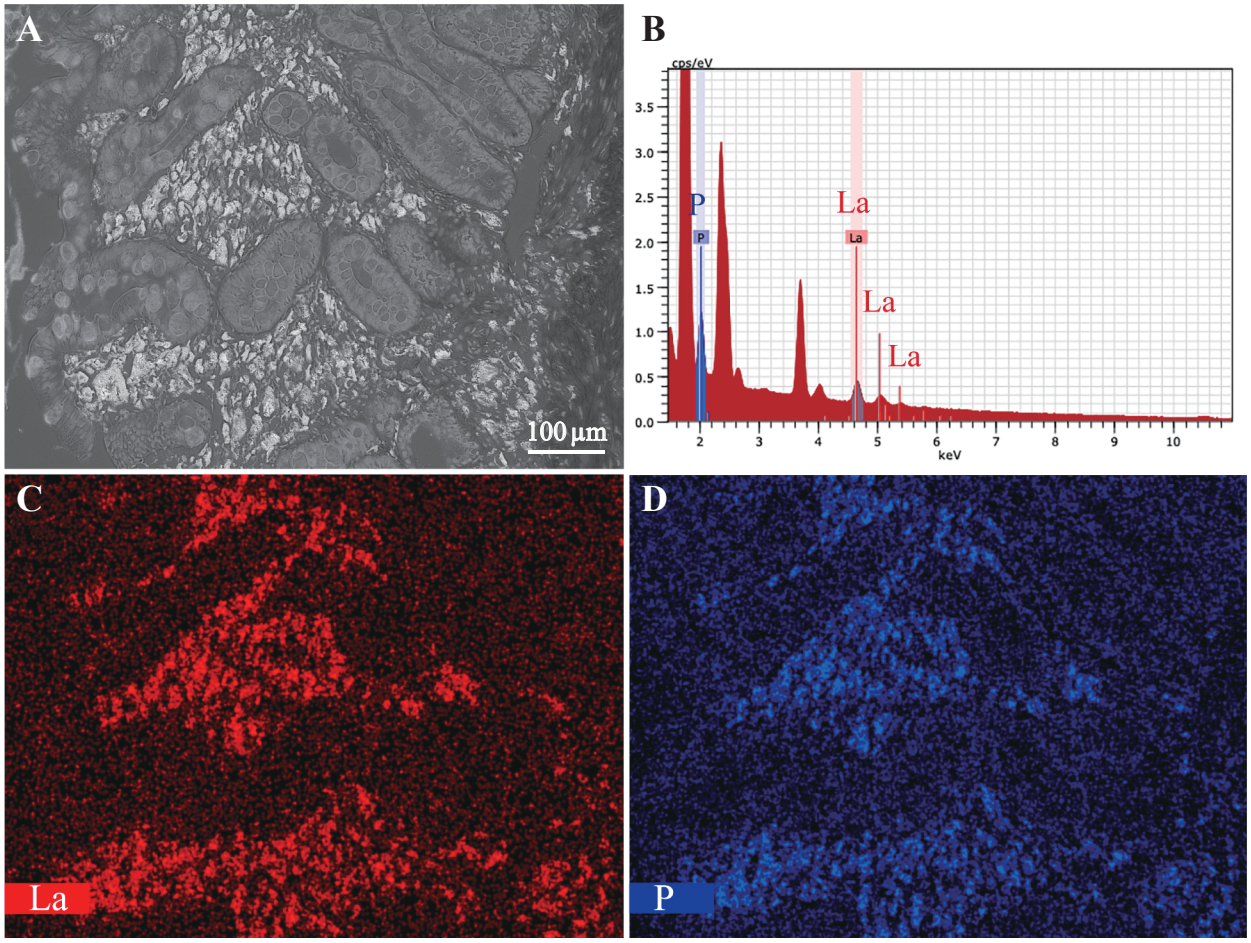

Fig. 4. Scanning electron microscopic findings of La deposition. The histiocytes in the gastric mucosa showing bright materials in backscattered images (A). The spectrum showing peaks of La and P (B). In energy dispersive X-ray electroscopic image, La (C, red) and P (D, blue) are colocalized in the same area of (A).

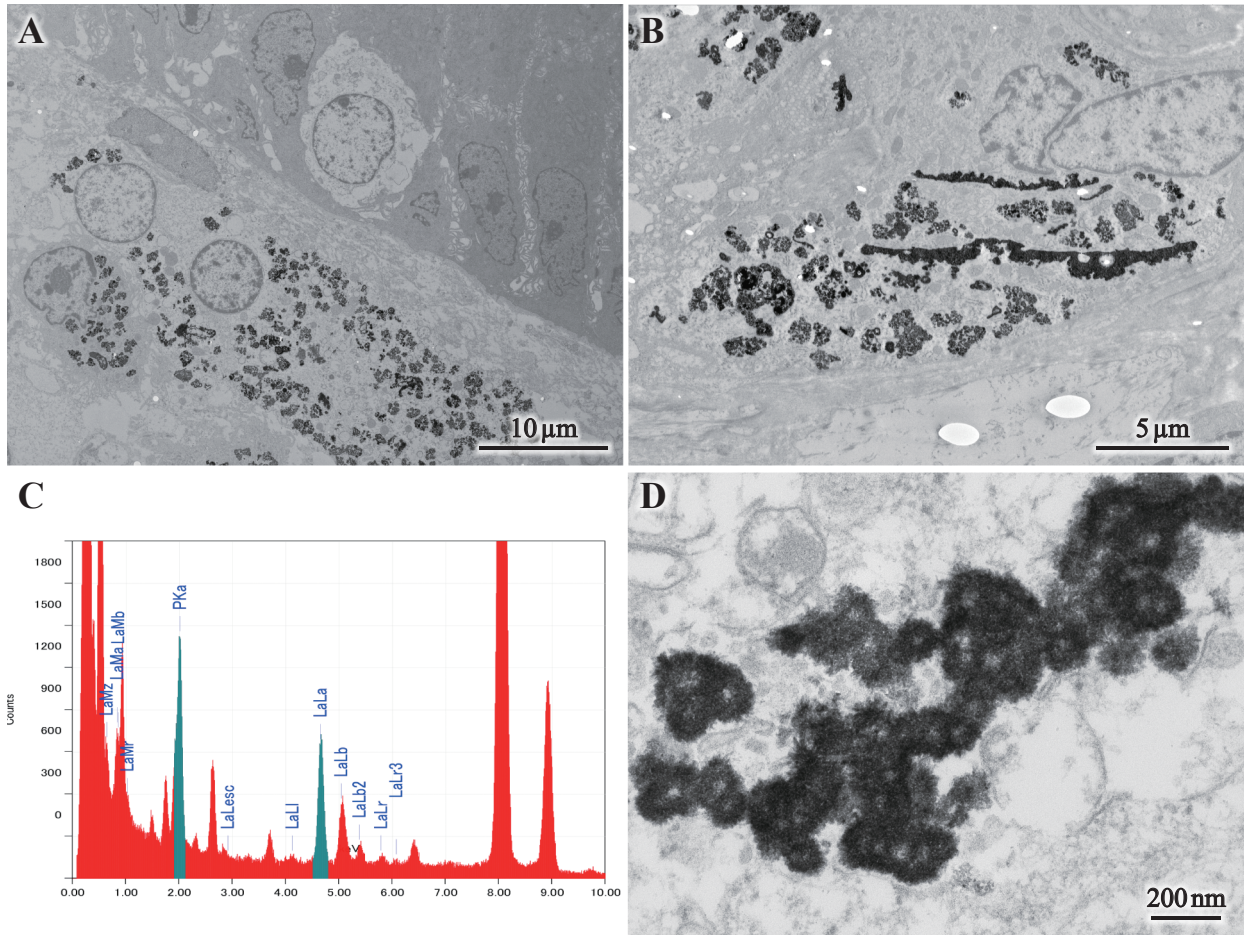

Fig. 5. Transmission electron microscopic findings of La deposition. Many electron dense precipitates are seen within secondary lysosomes in the histiocytes in the gastric mucosa (A, B). The spectrum showing peaks of La and P (C). At high-power magnification, the precipitates are shown as crystalline or granular structures (D).

precipitates are seen within secondary lysosomes in histiocytes beneath the foveolar epithelium or in subepithelial areas (Fig. 5A–C). In rat models, similar deposits are detected in some foveolar epithelial cells. At high-power magnification, the precipitates are composed of crystalloid or granular materials (Fig. 5D).

Incidence of La deposition in the GI tract

Although Goto *et al* reported that La deposition in the GI mucosa was found in 85.7% of dialysis patients treated with LC [7], in previously reported series, almost all LC-administered dialysis patients exhibited La deposition in the gastric mucosa. It was detectable even after 4 weeks and 2 weeks of oral LC administration in patients and rats, respectively [14]. Thus, La deposition in the gastroduodenal mucosa might become apparent soon after LC treatment. In addition, La deposition in the gastric mucosa during a follow-up period with endoscopy and biopsy remains for at least 2 years after withdrawal of LC administration. The amount of La concentration in the gastric mucosa has been shown to correlate with the total exposure dose of LC (daily LC administration dose × period) [5].

Mechanism of La deposition in the gastroduodenal mucosa

The mechanism of La deposition in the gastroduodenal mucosa remains largely unknown. Most orally administered LC are believed to bind to dietary phosphate in the stomach and produce insoluble LaP complexes

that pass through the GI tract. La deposition in the intestinal mucosa is extremely rare, and LaP complexes cannot directly penetrate into the GI mucosa, but LC is dissolved in an acidic environment (pH 1−2) in the presence of gastric juice [4], and a portion of the dissolved or uncoupled La not bound to phosphates may penetrate into the gastroduodenal mucosa. The absorbed La precipitates with phosphates under an alkaline environment in the mucosa. Gastric pH may contribute to LC dissolution in the gastroduodenal lumen. After penetration into the mucosa, La is phagocytosed by tissue histiocytes in a process of foreign body reaction, and some histiocytes can migrate into regional lymph nodes via the lymphatic flow. Although the mechanism of how dissolved or uncoupled LC penetrates into the gastroduodenal mucosa is still vague, passive diffusion by way of paracellular permeability is a plausible mechanism. Indeed, several previously reported cases showed that altered tight junction proteins, including claudin in intestinal metaplasia, increased the epithelial paracellular permeability associated with La deposition [6, 8, 19]. Further, Ji *et al* revealed that the paracellular permeability of the gastric epithelium with intestinal metaplasia was significantly increased using lanthanum nitrate [20]. Incidentally, La deposition in the neoplastic epithelium has not been detected in previous studies [4, 6], suggesting functionally disordered absorption of La in the neoplastic epithelium. Consequently, La deposition in the gastroduodenal mucosa may depend on several factors such as gastric pH and metaplastic or neoplastic epithelium.

Conclusion

La deposition in the gastroduodenal mucosa is observed virtually in all LC-treated dialysis patients with ESRD. La deposition is characterized by endoscopic whitish lesions and histopathological eosinophilic histiocytic reaction. The effect of long-standing mucosal La deposition and its mechanisms remain unclear and need further investigation.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Tonelli M, Pannu N & Manns B (2010): Oral phosphate binders in patients with kidney failure. N Engl J Med 362: 1312−1324
2. Covic A, Kothawala P, Bernal M, Robbins S, Chalian A & Goldsmith D (2009): Systematic review of the evidence underlying the association between mineral metabolism disturbances and risk of all-cause mortality, cardiovascular mortality and cardiovascular events in chronic kidney disease. Nephrol Dial Transplant 24: 1506−1523
3. Hutchison AJ, Wilson RJ, Garafola S & Copley JB (2016): Lanthanum carbonate: Safety data after 10 years. Nephrology (Carlton) 21: 987−994
4. Shitomi Y, Nishida H, Kusaba T *et al* (2017): Gastric lanthanosis (lanthanum deposition) in dialysis patients treated with lanthanum carbonate. Pathol Int 67: 389-397
5. Hattori K, Maeda T, Nishida S, Imanishi M, Sakaguchi M, Amari Y, Moriya T & Hirose Y (2017): Correlation of lanthanum dosage with lanthanum deposition in the gastroduodenal mucosa of dialysis patients. Pathol Int 67: 447−452
6. Yabuki K, Shiba E, Harada H, Uchihashi K, Matsuyama A, Haratake J & Hisaoka M (2016): 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
7. Goto K & Ogawa K (2016): 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
8. Tonooka A, Uda S, Tanaka H, Yao A & Uekusa T (2015): Possibility of lanthanum absorption in the stomach. Clin Kidney J 8: 572−575
9. Makino M, Kawaguchi K, Shimojo H, Nakamura H, Nagasawa M & Kodama R (2015): Extensive lanthanum deposition in the gastric mucosa: The first histopathological report. Pathol Int 65: 33−37
10. Haratake J, Yasunaga C, Ootani A, Shimajiri S, Matsuyama A & Hisaoka M (2015): Peculiar histiocytic lesions with massive lanthanum deposition in dialysis patients treated with lanthanum carbonate. Am J Surg Pathol 39: 767−771

11. Bervoets AR, Behets GJ, Schryvers D *et al* (2009): Hepatocellular transport and gastrointestinal absorption of lanthanum in chronic renal failure. Kidney Int 75: 389–398
12. Pennick M, Dennis K & Damment SJ (2006): Absolute bioavailability and disposition of lanthanum in healthy human subjects administered lanthanum carbonate. J Clin Pharmacol 46: 738–746
13. Zhang C, Wen J, Li Z & Fan J (2013): Efficacy and safety of lanthanum carbonate on chronic kidney disease-mineral and bone disorder in dialysis patients: A systematic review. BMC Nephrol 14: 226
14. Yabuki K, Haratake J, Tsuda Y, Shiba E, Harada H, Yorita K, Uchihashi K, Matsuyama A, Hirata K & Hisaoka M (2018): Lanthanum-induced mucosal alterations in the stomach (lanthanum gastropathy): A comparative study using an animal model. Biol Trace Elem Res 185: 36–47
15. Iwamuro M, Urata H, Tanaka T, Kawano S, Kawahara Y, Kimoto K & Okada H (2018): Lanthanum deposition corresponds to white lesions in the stomach. Pathol Res Pract 214: 934–939
16. Sotoudehmanesh R, Ali Asgari A, Ansari R & Nouraie M (2003): Endoscopic findings in end-stage renal disease. Endoscopy 35: 502–505
17. Abu Farsakh NA, Roweily E, Rababaa M & Butchoun R (1996): Brief report: Evaluation of the upper gastrointestinal tract in uraemic patients undergoing haemodialysis. Nephrol Dial Transplant 11: 847–850
18. Vaziri ND, Dure-Smith B, Miller R & Mirahmadi MK (1985): Pathology of gastrointestinal tract in chronic hemodialysis patients: an autopsy study of 78 cases. Am J Gastroenterol 80: 608–611
19. Ban S, Suzuki S, Kubota K, Ohshima S, Satoh H, Imada H & Ueda Y (2017): Gastric mucosal status susceptible to lanthanum deposition in patients treated with dialysis and lanthanum carbonate. Ann Diagn Pathol 26: 6–9
20. Ji R, Zuo XL, Yu T, Gu XM, Li Z, Zhou CJ & Li YQ (2012): Mucosal barrier defects in gastric intestinal metaplasia: in vivo evaluation by confocal endomicroscopy. Gastrointest Endosc 75: 980–987

炭酸ランタン内服透析患者の胃十二指腸粘膜内ランタン蓄積症

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要　　旨：炭酸ランタンは, 末期腎不全(ESRD)の透析患者に発症する高リン血症治療薬として広く使用されている．炭酸ランタンは, 消化管内で食物中のリン酸と難溶性化合物を形成するため, 消化管粘膜からはほとんど吸収されないとされていた．しかし, 近年炭酸ランタン服用患者の胃十二指腸粘膜にランタンが沈着することが報告されている．ランタン沈着は, 内視鏡的に様々な大きさや形の白色病変として認識できる．病理学的には, 胃十二指腸粘膜内に異物肉芽腫と貪食された沈着物を多数認め, 一部の所属リンパ節にも沈着が及ぶ．また, 炭酸ランタンの内服量や内服期間が長いほど, 胃十二指腸粘膜内のランタン沈着量は多いとされている．詳細なランタン沈着機序は不明な点があるが, 胃内のpH, 腸上皮化生などの様々な要因が関与すると推察される．本総説では, 炭酸ランタン内服患者における胃十二指腸粘膜内のランタン蓄積症について臨床病理学的所見に焦点をあてて解説する．

キーワード：沈着, ランタン, 内視鏡, 病理, 胃．

J UOEH（産業医大誌）41(4)：387 − 395（2019）