Clinical Kidney Journal

ckj

OXFORD

Leading European Nephrology

Clinical Kidney Journal, 2015, vol. 8, no. 5, 572–575

doi: 10.1093/ckj/sfv062
Advance Access Publication Date: 16 July 2015
Exceptional Case

EXCEPTIONAL CASE

Possibility of lanthanum absorption in the stomach

Akiko Tonooka[1], Susumu Uda[2], Hiroki Tanaka[1], Atsushi Yao[2], and Toshimasa Uekusa[1]

[1]Department of Diagnostic Pathology, Kanto Rosai Hospital, Kanagawa, Japan, and [2]Department of Nephrology, Kanto Rosai Hospital, Kanagawa, Japan

Correspondence to: Akiko Tonooka; E-mail: akitono@gmail.com

Abstract

Lanthanum carbonate (LC) is an orally administered phosphate binder. Its absorption is generally thought to be minimal. We report here the case of an 81-year-old woman who underwent subtotal gastrectomy for gastric cancer after receiving hemodialysis for 1 year and taking LC for 7 months. Lanthanum phosphate compounds were found histologically in the gastric mucosa and a regional lymph node and confirmed by scanning and transmission electron microscopy–energy-dispersive X-ray spectroscopy. These findings suggest that lanthanum is absorbed in the stomach and transported via lymph flow. This observation could prove helpful in future investigation of lanthanum disposition.

Key words: absorption, dialysis, lanthanum, lymph node, stomach

Background

Lanthanum carbonate (LC) is a non-calcium, non-aluminum phosphate binder used to treat hyperphosphatemia in end-stage renal disease. LC is taken orally and dissolves in the gastrointestinal tract, releasing La^{3+}. There, this cation binds with phosphate to produce lanthanum phosphate, which is excreted with the feces. It has been reported that lanthanum is absorbed and deposited in many organs in a rat model [1]. In humans, however, LC is considered safe because its absorption in the gastrointestinal tract is reported to be minimal [2, 3]. Recently, two Japanese groups reported lanthanum deposits in the gastric or duodenal mucosa of the patients treated with LC [4, 5]. The patients exhibited no adverse effects from the deposits, but it is necessary to clarify whether lanthanum phosphate compounds are just deposited in the stomach or whether they are absorbed there and transported throughout the body.

Case report

An 81-year-old woman with a history of partial gastrectomy for early gastric cancer 7 years earlier was admitted to our hospital for treatment of gastric cancer. Because of diabetic nephropathy, she had received hemodialysis three times a week for 1 year and had taken LC (one 250 mg chewable tablet after each meal) for 7 months. She complained of gastric discomfort and underwent endoscopic examination of the stomach, which revealed three tumors. Early gastric cancer was diagnosed, and she underwent subtotal gastrectomy.

Histological examination of the resected specimens showed that all three tumors (diameter, 2–15 mm) were well-differentiated tubular adenocarcinomas located in intestinal metaplastic mucosa with no submucosal invasion. No lymphovascular invasion or lymph node metastasis was observed. All the tumors were resected completely. In the lamina propria of the mucosa, however, we noticed many macrophages with abundant cytoplasm containing some basophilic material (Figure 1A and B). The macrophages were found grouped just beneath the epithelium and were widespread in the intestinal metaplastic mucosa, including in the neoplastic lesion (Figure 1C). Then, we analyzed the resected specimen by scanning electron microscopy–energy-dispersive X-ray spectroscopy (SEM-EDS) and transmission

Received: March 24, 2015. **Accepted:** June 29, 2015

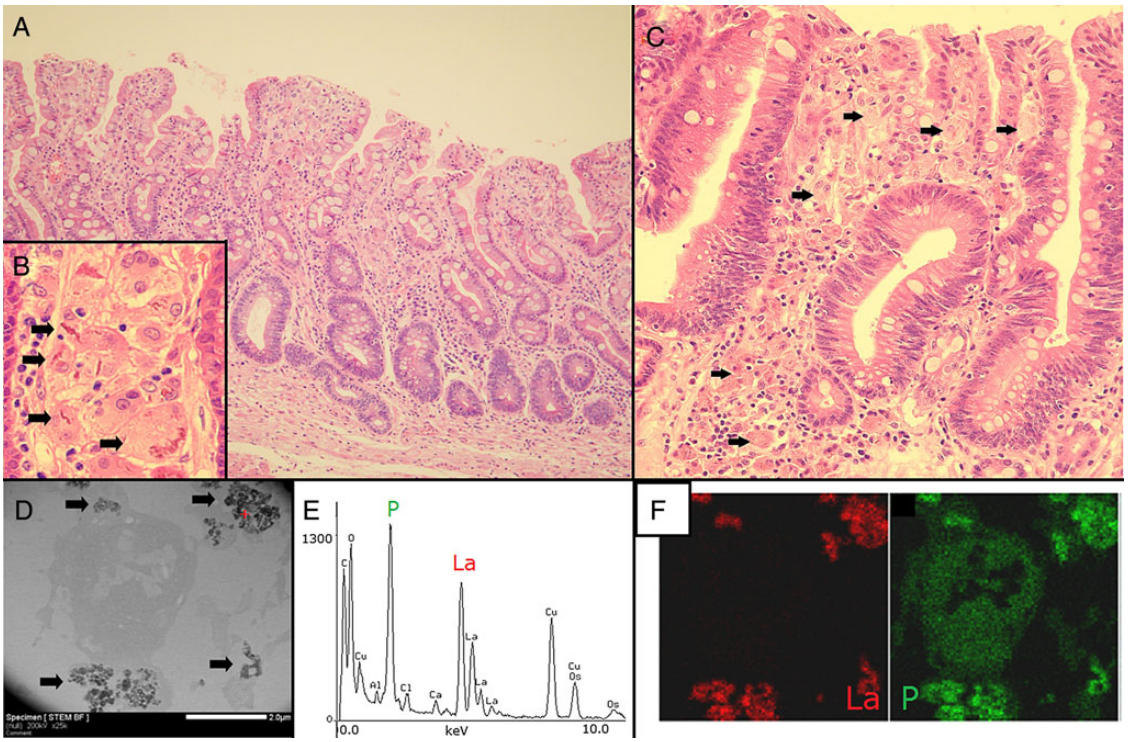

Fig. 1. Light micrograph and transmission electron microscope–energy-dispersive X-ray spectroscopy (TEM-EDS) results of the gastric mucosa. (**A**) Gastric mucosa of non-neoplastic area showing accumulation of macrophages in the lamina propria. The foveolar epithelium is fully replaced with intestinal metaplasia and pyloric glands are atrophic. (**B**) High-power magnification of (A), showing macrophages with abundant granular cytoplasm with some eosinophilic materials (indicated by arrows). (**C**) Macrophages in the neoplastic area (indicated by arrows). (**D**) TEM bright-field image of a macrophage showing deposits around the nucleus (indicated by arrows). (**E**) EDS spectrum showing the presence of lanthanum (La) and phosphorus (P) in the area analyzed (indicated by the '+' in D). (**F**) Deposits indicated by the '+' in (D) correspond to La and P.

electron microscopy-EDS. In the macrophages, we found lanthanum deposits with a spectrum similar to that of LC (Figure 1D). Furthermore, similar macrophages were found histologically in a regional lymph node. Also, SEM-EDS showed that the lymph node contained lanthanum (Figure 2A–D). An elemental map of phosphorus and lanthanum indicates that they were deposited together (Figure 1E and F). Because the patient continued to take lanthanum after gastrectomy, we measured the plasma lanthanum concentration, which was 0.47 ng/mL (within the range of values in a control group of patients on dialysis who took lanthanum as a phosphate binder [6]). Three years after the surgery, the patient has shown no signs of recurrence and had no notable illness.

Discussion

There have been few reports of lanthanum being detected in patients who took LC orally [4, 5, 7–9]. Lymph nodes had been the only tissue with histologically confirmed lanthanum deposition in humans [7], but the pathway to the lymph nodes remains unclear [6]. However, lanthanum deposits were recently found and histologically confirmed in the gastric or duodenal mucosa of patients who took LC orally [4, 5]. Lanthanum is generally thought to be minimally absorbed, so these findings were remarkable. The authors of those reports [4, 5] observed no apparent clinical problems arising from the lanthanum deposits but did not report long-term patient outcomes. Here, we report the case of a patient with lanthanum deposits in the stomach and a regional lymph node. The histological findings of the stomach are similar to those in the previous two reports. In those studies, the findings were from gastroduodenal biopsies or endoscopic submucosal dissection specimens, so regional lymph nodes were not examined. In our case, the stomach had many macrophages in the lamina propria, whereas the lymph node did not have many; therefore, these findings suggest that lanthanum is not just deposited in the stomach, but also absorbed there and possibly transported via lymph flow. In general, the plasma lanthanum concentration of dialysis patients who took lanthanum as a phosphate binder is higher than healthy individuals because of little absorption of lanthanum from the intestine [6] and the plasma lanthanum concentration of our patient is the same as that of dialysis patients that were reported in the literature [6]. Therefore, we cannot rule out the possibility that absorbed lanthanum is transported from the intestine to the stomach. However, blood flow from the intestine usually reaches the liver via the portal vein, not the stomach, unless the patient suffers from liver cirrhosis. Our patient did not suffer from liver disease, so it is unlikely that blood flow goes from the intestine to the stomach. Furthermore, lanthanum absorbed in the intestine is transported by blood flow, so the possibility that lanthanum is carried from the intestine to the lymph nodes seems to be low. This is why we considered that lanthanum was absorbed in the stomach and transported via lymph flow. As of this writing, our patient has shown no adverse reaction associated with continuous use of LC for 3 years, but it remains unclear whether deposits of lanthanum compounds throughout the body are harmful; therefore, further investigation of similar cases is needed.

In the past reports of histologically confirmed lanthanum deposits in human gastric mucosa [4, 5], the duration of LC treatment was at least 1 year 9 months, far longer than our patient's

Clinical Kidney Journal
ckj

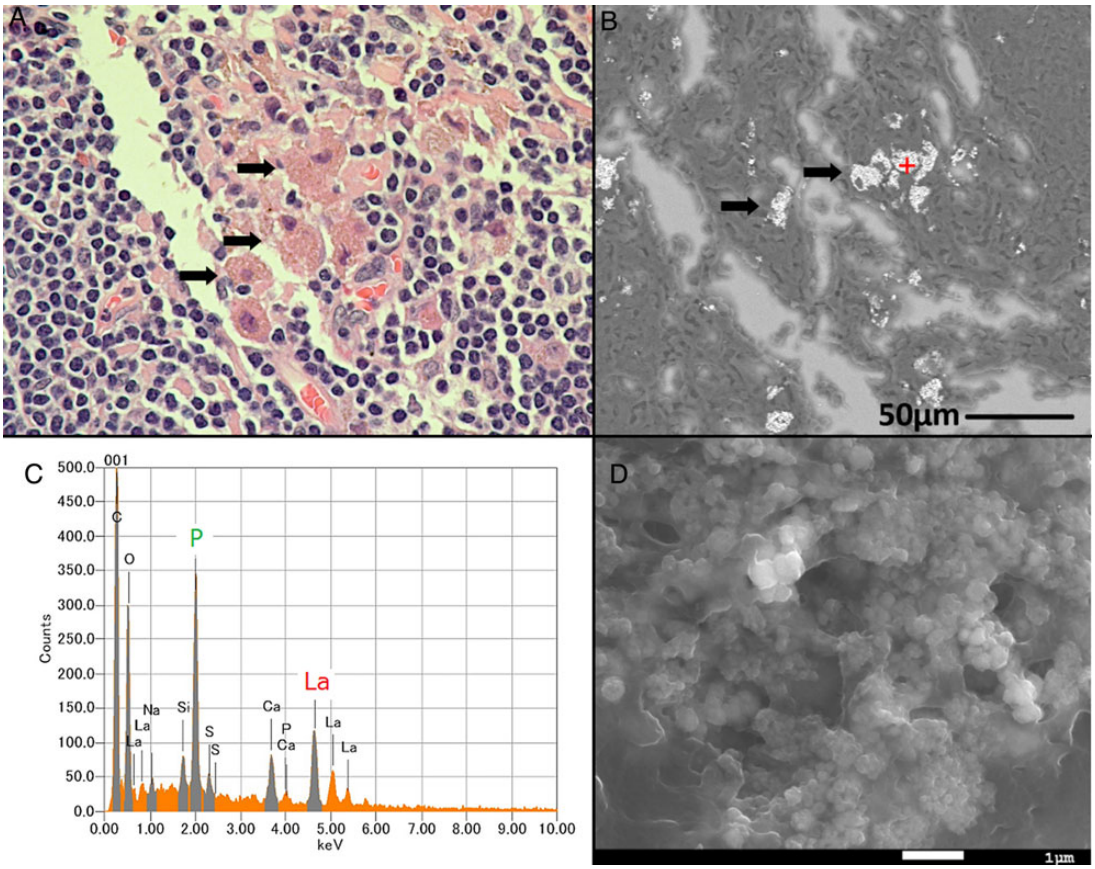

Fig. 2. Light micrograph and SEM-EDS results of a regional lymph node. (**A**) Macrophages with granular cytoplasm in the lymph node (indicated by arrows). (**B**) SEM image of the lymph node showing bright elements (indicated by arrows). (**C**) EDS spectrum showing the presence of La and P at the area analyzed (indicated by the '+' in B). (**D**) Magnified image of the analysis point showing granular substances.

LC treatment (7 months at the time of surgery). We speculate that one mechanism regulating lanthanum deposition may be gastric epithelial permeability. Our patient had a history of partial gastrectomy for early gastric cancer 7 years earlier; therefore, this second occurrence of gastric cancer suggests susceptibility to gastric cancer. Also, the macrophages were found mainly in the atrophic mucosa with metaplastic epithelia, which is considered to be an initial step toward carcinogenesis. In gastric epithelia with intestinal metaplasia, the expression of claudin, which is a core protein of tight junctions, is reported to differ from that in normal gastric epithelia [9]. This difference could also cause the increased permeability possibly leading to lanthanum deposition or absorption in the gastric mucosa. In fact, we encountered another patient who had taken LC for years and died from malignant lymphoma without gastric involvement, and we found no such macrophages. This patient's gastric mucosa showed no atrophy or intestinal metaplasia, suggesting that these metaplastic changes are associated with lanthanum deposition.

In summary, we have reported the case of a patient who had lanthanum phosphate deposits in the gastric mucosa and a regional lymph node, suggesting that lanthanum was absorbed in the stomach and carried via lymph flow.

Acknowledgements

The authors thank Dr Shigeru Kawagoe for providing the clinical information and the Bayer Corporation for helping to measure the concentration of lanthanum.

Conflict of interest statement

None declared.

References

1. Lacour B, Lucas A, Auchère D *et al*. Chronic renal failure is associated with increased tissue deposition of lanthanum after 28-day oral administration. *Kidney Int* 2005; 67: 1062–1069
2. Pennick M, Dennis K, Damment SJ. Absolute bioavailability and disposition of lanthanum in healthy human subjects administered lanthanum carbonate. *J Clin Pharmacol* 2006; 46: 738–746
3. Zhang C, Wen J, Li Z *et al*. Efficacy and safety of lanthanum carbonate on chronic kidney disease-mineral and bone disorder in dialysis patients: a systematic review. *BMC Nephrol* 2013; 14: 226
4. Makino M, Kawaguchi K, Shimojo H *et al*. Extensive lanthanum deposition in the gastric mucosa: the first histopathological report. *Pathol Int* 2015; 65: 33–37
5. Haratake J, Yasunaga C, Ootani A *et al*. Peculiar histiocytic lesions with massive lanthanum deposition in dialysis patients treated with lanthanum carbonate. *Am J Surg Pathol* 2015; 39: 767–771
6. Shigematsu T, The Lanthanum Carbonate Research Group. Three-year extension study of lanthanum carbonate therapy in Japanese hemodialysis patients. *Clin Exp Nephrol* 2010; 14: 589–597
7. Davis RL, Abraham JL. Lanthanum deposition in a dialysis patient. *Nephrol Dial Transplant* 2009; 24: 3247–3250

8. Spasovski GB, Sikole A, Gelev S *et al*. Evolution of bone and plasma concentration of lanthanum in dialysis patients before, during 1 year of treatment with lanthanum carbonate and after 2 years of follow-up. *Nephrol Dial Transplant* 2006; 21: 2217–2224
9. Damment SJ, Pennick M. Clinical pharmacokinetics of the phosphate binder lanthanum carbonate. *Clin Pharmacokinet* 2008; 47: 553–563
10. Iravani O, Tay BW, Chua PJ *et al*. Claudins and gastric carcinogenesis. *Exp Biol Med* 2013; 238: 344–349

Clinical Kidney Journal
ckj