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Case Report

Lanthanum Deposition in the Stomach: Usefulness of Scanning Electron Microscopy for Its Detection

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After having been treated with lanthanum carbonate administration for 4 years for hyperphosphatemia, a 75-year-old Japanese woman undergoing hemodialysis was diagnosed with lanthanum phosphate deposition in the stomach. The deposition, seen as white microgranules, was observed using esophagogastroduodenoscopy with magnifying observation. To the best of our knowledge, these are the minutest endoscopy images of lanthanum phosphate deposition in the gastric mucosa. Scanning electron microscopy (SEM) observation enabled easier identification of the deposited material, which was visible as bright areas. The present case suggests the usefulness of SEM observation in the detection of lanthanum phosphate deposition in the gastrointestinal tract.

Key words: hyperphosphatemia, lanthanum carbonate, scanning electron microscopy analysis, xanthoma

In the majority of end-stage renal disease (ESRD) patients, phosphate binders are required to trap dietary phosphate and reduce its absorption, which is important because hyperphosphatemia leads to various disorders, including secondary hyperparathyroidism, soft tissue calcification, and renal osteodystrophy [1]. Lanthanum carbonate, an orally administered phosphate binder, is widely used for treating ESRD patients [2-5]. After its ingestion, lanthanum carbonate binds with the phosphate in foods to form highly insoluble complexes. It was reported that the insoluble complexes of lanthanum phosphate are minimally absorbed in the gastrointestinal tract and are excreted with the feces [6,7], but more recently, several research groups have reported cases of patients with lanthanum deposition in the gastrointestinal mucosa [8-14].

Here we describe the case of a hemodialysis patient who was diagnosed with lanthanum phosphate deposition in the stomach. The lesion was endoscopically observed as white microgranules, and the diagnosis of lanthanum phosphate deposition was confirmed by energy dispersive x-ray spectroscopy. Notably, a scanning electron microscopy observation (SEM) enabled easier identification of the deposited areas, which were visible as brighter areas. This case demonstrated the potential utility of SEM for the detection of lanthanum phosphate deposition in the gastrointestinal tract.

Case Report

A 75-year-old Japanese woman was referred to Okayama University Hospital for further investigation of bilateral hilar lymphadenopathy. She had been

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undergoing hemodialysis for 7 years for nephrosclerosis and had been taking oral lanthanum carbonate for 4 years as treatment for hyperphosphatemia, in addition to beraprost, lafutidine, mosapride, cinacalcet, azilsartan, bisoprolol, nifedipine, olmesartan, doxazosin, and brotizolam. A physical examination revealed no abnormalities, and no evidence of peripheral lymphadenopathy was detected.

Laboratory findings demonstrated elevated levels of soluble interleukin-2 receptor (sIL-2R) (5,489 U/mL, normal range: 122-496 U/mL), angiotensin-converting enzyme (29.7 U/L, normal range: 8.3-21.4 U/L), and lysozyme (73.3 μg/mL, normal range: 5.0-10.2 μg/mL). The patient's serum phosphate (6.0 mg/dL), creatinine (9.41 mg/dL), and blood urea nitrogen (42.9 mg/dL) levels were also elevated.

Subsequent ^{18}F-fluorodeoxyglucose-positron emission tomography detected tracer uptake in the mediastinal, hilar, and porta hepatis lymphadenopathies, and a transbronchial needle aspiration biopsy by bronchoscopy demonstrated noncaseating epithelioid granuloma; we therefore diagnosed the patient with sarcoidosis [15, 16].

An esophagogastroduodenoscopy was performed, which demonstrated atrophic mucosa and two small, elevated lesions in the lesser curvature of the gastric body which were white in color (Fig. 1A, arrows). Magnifying observation with narrow-band imaging revealed white depositions within the elevated lesions (Fig. 1B), and sparse white microgranules were detected in the lesser curvature of the gastric body (Fig. 1A, arrowheads). Magnifying observation with white light (Fig. 1C) and narrow-band imaging (Fig. 1D) facilitated a clearer view of these white microgranules. There were no other mucosal alterations or evidence of sarcoidosis-related lesions in the stomach.

A biopsy specimen from the gastric mucosa with white microgranules (Fig. 1C, D) contained deposition of fine, amorphous, eosinophilic material (Fig. 2A). Staining for CD68 was positive in these areas, indicating the presence of histiocytes (Fig. 2B). For the SEM analysis, a paraffin-embedded section was deparaffinized with xylene (10 min, twice) and subsequently washed with a serial dilution ethanol series (100% for 5 min, 3 times; 80% for 5 min and 50% for 5 min). The surface of the sample was coated with osmium for 10 sec (HPC-1S-type osmium coater; Shinku Device Co., Ibaraki, Japan) and examined closely an S4800 scanning electron microscope (Hitachi, Tokyo, Japan).

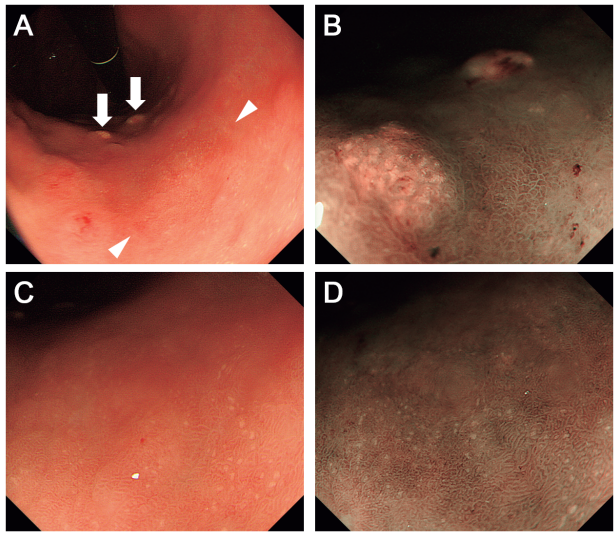

Fig. 1 Representative esophagogastroduodenoscopy images. Two small, whitish, elevated lesions are detected (A, arrows). Magnifying observation with narrow-band imaging revealed white depositions (B). White microgranules were also detected (A, arrowheads), which were more clearly demonstrated by magnifying observation with white light (C) and narrow-band imaging (D).

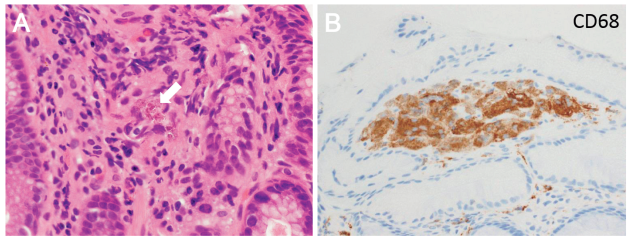

Fig. 2 Pathological images of the gastric lanthanum deposition, as detected by hematoxylin and eosin staining. The deposition of fine, amorphous, eosinophilic material was detected (A), and these areas of deposition were positive for CD68 (B).

For the analysis of the elemental composition, we used the S4800 scanning electron microscope to perform energy dispersive X-ray spectroscopy (EDAX Genesis APEX2 system, Ametek, Paoli, PA, USA). The deposited material appeared bright in the SEM observation (Fig. 3A). The deposition was seen as aggregates of particles, measuring 1-3 μm in diameter (Fig. 3B). Elemental mapping by energy dispersive X-ray spectroscopy confirmed that the distribution of lanthanum (Fig. 3C) and phosphate (Fig. 3D) was iden-

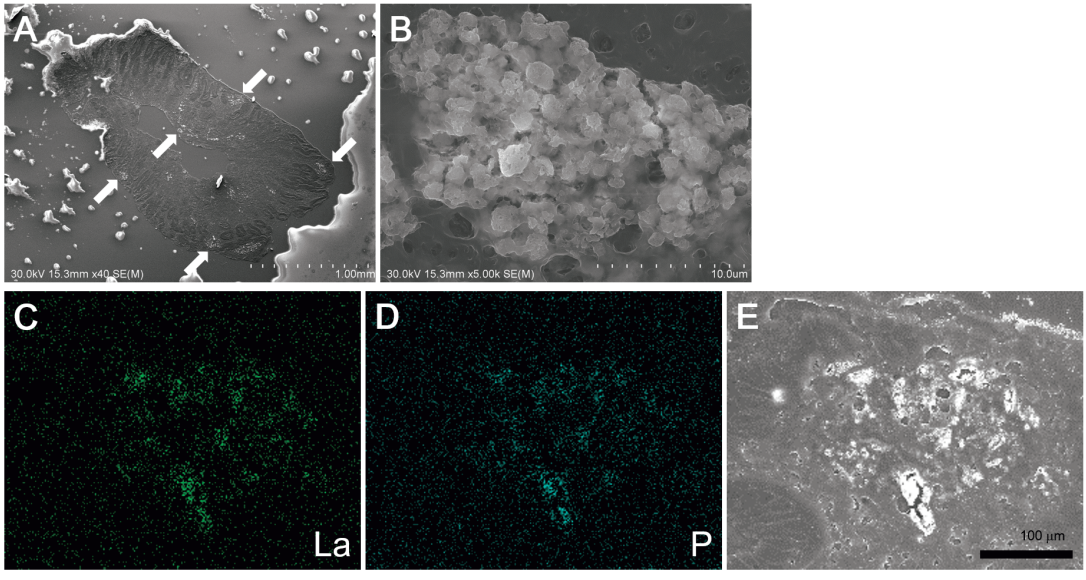

Fig. 3 SEM demonstrated that the deposited material appeared bright (**A**) and consisted of microparticles (**B**). Elemental mapping by energy dispersive X-ray spectroscopy confirmed that the distribution of lanthanum (**C**) and phosphate (**D**) was identical to that of the bright areas (**E**).

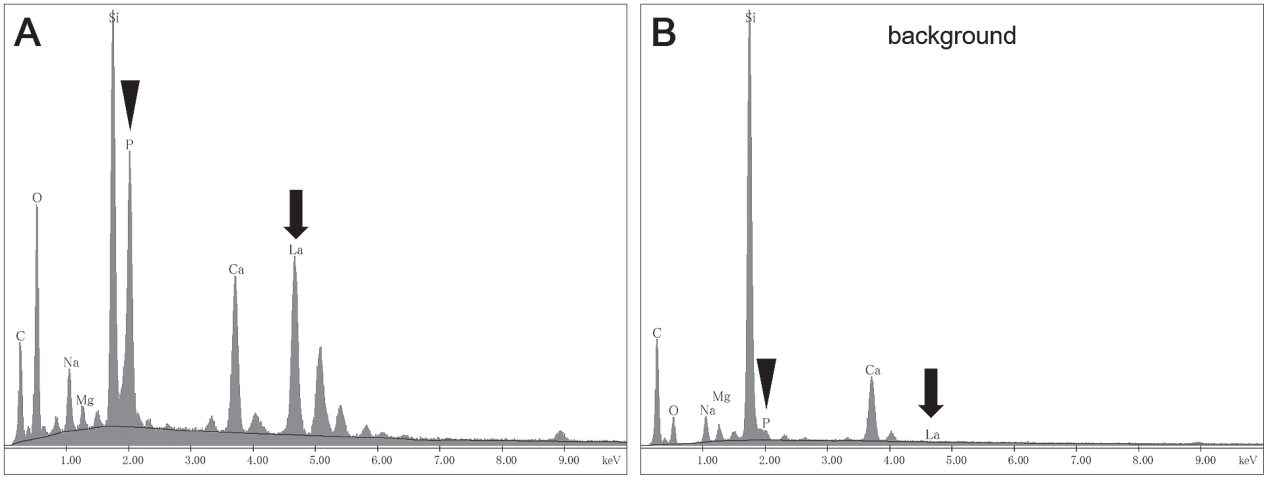

Fig. 4 Spectra obtained by energy dispersive x-ray spectroscopy. Lanthanum (arrow) and phosphate (arrowheads) were detected in the bright areas (**A**), whereas these elements were almost or completely absent in the background mucosa (**B**).

tical to that of the bright areas (Fig. 3E). Our comparative analysis of the spectra between the bright areas and the background also demonstrated that lanthanum and phosphate were present in the bright areas, whereas these elements were almost completely absent in the background mucosa (Fig. 4). Consequently, we diagnosed the gastric lesion as lanthanum phosphate deposition.

The histological examination of the small elevated white lesions (Fig. 1A, arrows) demonstrated foamy cells in the gastric mucosa (Fig. 5A, B) that were positive for CD68 (Fig. 5C), which indicated that they were histiocytes; thus, a diagnosis of gastric xanthoma was made. Deposition of lanthanum phosphate was not noted by pathologists at the initial inspection of this hematoxylin and eosin (H&E)-stained biopsied speci-

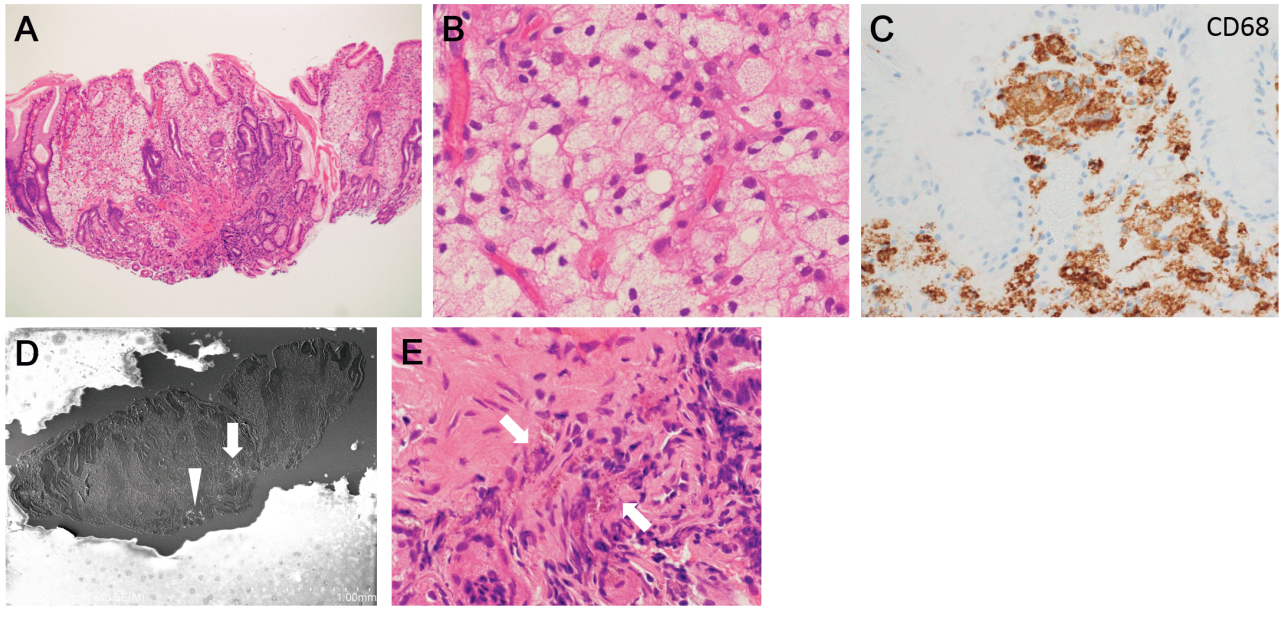

Fig. 5 Representative pathological images of the gastric xanthoma. Foamy cells were observed in the gastric mucosa (A, B), which were positive for CD68 (C). The SEM revealed bright areas (D, arrow and arrowhead), and the re-evaluation of the H&E-stained specimen by energy dispersive x-ray spectroscopy demonstrated the deposition of fine, amorphous, eosinophilic material (E), which was confirmed to be the deposition of lanthanum and phosphate.

men. However, SEM revealed the bright areas (Fig. 5D, arrow and arrowhead), and energy dispersive x-ray spectroscopy confirmed the deposition of lanthanum and phosphate. Re-evaluation of the H&E-stained specimen confirmed the deposition of fine, amorphous, eosinophilic material (Fig. 5E).

Discussion

Historically, aluminum-containing compounds such as aluminum hydroxide were used as phosphate binders for dialysis patients from the 1970s. However, the use of aluminum is now contraindicated as it has been demonstrated that prolonged aluminum intake may induce encephalopathy and osteomalacia [17]. Precipitated calcium carbonate, polymers such as sevelamer hydrochloride, and lanthanum carbonate were developed as phosphate binders and have been widely used in clinical practice [18, 19].

In Japan, a chewable tablet form of lanthanum carbonate was approved and has been marketed since March 2009, and lanthanum carbonate granules were released to the market in May 2012. As described above, orally administered lanthanum produces insoluble complexes following ionic binding to phosphate and prevents the absorption of dietary phosphate. The majority of the insoluble complexes is thought to be excreted in the feces. A phase I study was conducted to determine the absolute bioavailability of orally administered lanthanum in healthy subjects, the results of which demonstrated that the absolute bioavailability of lanthanum was extremely low, ranging from 0.00015% to 0.00224% [6].

The minimal fraction of lanthanum that is absorbed from the intestinal tract into the systemic circulation is predominantly excreted in bile, with < 2% eliminated by the kidneys [20]. This drug clearance by non-renal mechanisms allows for the safe use of lanthanum carbonate in patients with chronic kidney disease.

Despite the documented safety profile and tolerability of orally administered lanthanum in humans, several reports have described lanthanum deposition in the gastrointestinal tract, particularly in the stomach [8-14]. A recent retrospective study by Goto *et al.* revealed that among 14 patients who were administered lanthanum carbonate and underwent an endoscopic biopsy of the gastric mucosa, lanthanum deposition was detected in 12 patients (85.7%) [12]. This result

indicates that deposition of lanthanum in the stomach may occur frequently in patients who are being treated with lanthanum carbonate.

The reported features of gastric lesions vary from erosions, ulcers, and polyps to white mucosa. For example, Yasunaga *et al.* described the gastric lesion of a 64-year-old man with lanthanum deposition as "multiple erosions and small ulcers in the antral mucosa" [13]; however, white mucosa is detectable around the erosions in the endoscopic images presented by those authors. Similarly, Haratake *et al.* reported a gastric lesion as "multiple irregular erosions," whereas white granules are also observable in the endoscopic image [11].

We therefore hypothesize that white granules are essential features of lanthanum phosphate deposition in the gastric mucosa. The white color may be imparted by the aggregated particles of lanthanum phosphate itself, as detected by SEM in the present case. Another possible explanation is that the white color is a result of histiocytes entrapping lanthanum phosphate. The similarity of color we observed between the lanthanum deposition and xanthoma, which consists of clusters of foamy histiocytes, supports the latter hypothesis.

Regardless of the mechanism that contributes to the white color, to the best of our knowledge, the endoscopic features demonstrated in the present case are the minutest lesions of lanthanum phosphate deposition in the gastric mucosa reported to date. Endoscopists and gastroenterologists should therefore suspect this disease pathology when they observe white granules in the stomach of patients who are being treated with lanthanum carbonate.

It is also noteworthy that our scanning electron microscopy observation enabled easier identification of deposited lanthanum in the biopsy specimen harvested from the xanthoma, compared to the conventional histopathological evaluation of the H&E-stained section. As demonstrated herein, lanthanum deposition can be detected histologically as fine, amorphous, eosinophilic material. Although a diagnosis of lanthanum deposition was made in our patient based on microscopic assessment of the gastric mucosa, which contained white granules, we suggest that SEM observation may be useful for the detection of lanthanum phosphate deposition in the gastrointestinal tract, as these deposits can be clearly observed as bright areas.

It has been reported that the intake of several medications such as antihypertensive agents and oral iron supplementation results in color changes of the gastric and duodenal mucosa [20-22]. In this condition, there is deposition of pigment within macrophages in the gastroduodenal mucosa. Endoscopically, the stomach and/or duodenum show dark pigmentation, which is called pseudomelanosis. Although in the present case we observed whitish deposition in the gastric mucosa (which is a different macroscopic feature than that occurring in pseudomelanosis), the SEM analysis was useful for confirming that the deposited material was lanthanum phosphate rather than other chemical substances.

Conversely, differential diagnoses of whitish lesions in the stomach include xanthoma, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) [23], plasmacytoma [24], and crystal-storing histiocytosis [25]. These disorders are distinguishable from lanthanum phosphate deposition by a pathological analysis with appropriate immunostainings.

In the present case, a concomitant diagnosis of sarcoidosis was made. We believe that the co-occurrence of lanthanum phosphate deposition in the stomach and sarcoidosis detected in the lymph nodes is coincidental, because no sarcoidosis-related lesions were macroscopically or microscopically identified in the stomach. Moreover, in the previous reports of lanthanum deposition in the gastrointestinal tract, no cases had sarcoidosis [8-14].

To date, it is unknown whether lanthanum phosphate deposition in the gastrointestinal tract causes health problems. Although there were no mucosal alterations caused by lanthanum phosphate deposition in the present case, several groups have reported cases with erosions and/or ulcers and lanthanum deposition in the same gastric mucosa [11-13]. One possible explanation is that lanthanum deposition results in mucosal friability and finally leads to mucosal damage.

Yasunaga *et al.* reported a case in which the patient presented with epigastric discomfort and gastric erosions and ulcers [13]. After termination of the lanthanum carbonate administration, the patient's symptoms were relieved and the gastric mucosal injury healed. This case suggests that mucosal damage is secondarily caused by lanthanum deposition. Another hypothesis is that mucosal damage may enhance the entry of lanthanum phosphate into the gastrointestinal mucosa [12].

Further studies are required to understand the pathogenicity of lanthanum phosphate deposition in the gastrointestinal tract.

In conclusion, we have described a case of lanthanum phosphate deposition in the stomach, and we observed the potential value of SEM for the detection of these deposits. Although a histopathological examination is essential, we suggest that the application of SEM may enhance the detection sensitivity of deposited material in patients who are receiving oral lanthanum phosphate.

References

1. Delmez JA and Slatopolsky E: Hyperphosphatemia: its consequences and treatment in patients with chronic renal disease. Am J Kidney Dis (1992) 19: 303–317.
2. Shigematsu T; Lanthanum Carbonate Research Group: One year efficacy and safety of lanthanum carbonate for hyperphosphatemia in Japanese chronic kidney disease patients undergoing hemodialysis. Ther Apher Dial (2010) 14: 12–19.
3. Tsuchida K, Nagai K, Yokota N, Minakuchi J and Kawashima S: Impact of Lanthanum Carbonate on Prognosis of Chronic Hemodialysis Patients: A Retrospective Cohort Study (Kawashima Study). Ther Apher Dial (2016) 20: 142–148.
4. Cernaro V, Santoro D, Lacquaniti A, Costantino G, Visconti L, Buemi A and Buemi M: Phosphate binders for the treatment of chronic kidney disease: role of iron oxyhydroxide. Int J Nephrol Renovasc Dis (2016) 9: 11–19.
5. Giotta N and Marino AM: Pharmacoeconomic Analysis: Analysis Of Cost-Effectiveness Of Lanthanum-Carbonate (Lc) In Uncontrolled Hyperphosphatemia In Dialysis. Value Health (2015) 18: A511.
6. Pennick M, Dennis K and Damment SJ: Absolute bioavailability and disposition of lanthanum in healthy human subjects administered lanthanum carbonate. J Clin Pharmacol (2006) 46: 738–746.
7. Zhang C, Wen J, Li Z and Fan J: 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.
8. Tonooka A, Uda S, Tanaka H, Yao A and Uekusa T: Possibility of lanthanum absorption in the stomach. Clin Kidney J (2015) 8: 572–575.
9. Makino M, Kawaguchi K, Shimojo H, Nakamura H, Nagasawa M and Kodama R: Extensive lanthanum deposition in the gastric mucosa: the first histopathological report. Pathol Int (2015) 65: 33–37.
10. Rothenberg ME, Araya H, Longacre TA and Pasricha PJ: Lanthanum-Induced Gastrointestinal Histiocytosis. ACG Case Rep J (2015) 2: 187–189.
11. Haratake J, Yasunaga C, Ootani A, Shimajiri S, Matsuyama A and Hisaoka M: Peculiar histiocytic lesions with massive lanthanum deposition in dialysis patients treated with lanthanum carbonate. Am J Surg Pathol (2015) 39: 767–771.
12. Goto K and 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 (2016) 24: 89–92.
13. Yasunaga C, Haratake J and Ohtani A: Specific Accumulation of Lanthanum Carbonate in the Gastric Mucosal Histiocytes in a Dialysis Patient. Ther Apher Dial (2015) 19: 622–624.
14. Iwamuro M, Sakae H and Okada H: White Gastric Mucosa in a Dialysis Patient. Gastroenterology (2016) 150: 322–323.
15. Valeyre D, Bernaudin JF, Jeny F, Duchemann B, Freynet O, Planes C, Kambouchner M and Nunes H: Pulmonary Sarcoidosis. Clin Chest Med (2015) 36: 631–641.
16. Govender P and Berman JS: The Diagnosis of Sarcoidosis. Clin Chest Med (2015) 36: 585–602.
17. Locatelli F, Del Vecchio L, Violo L and Pontoriero G: Phosphate binders for the treatment of hyperphosphatemia in chronic kidney disease patients on dialysis: a comparison of safety profiles. Expert Opin Drug Saf (2014) 13: 551–561.
18. Goldsmith DR, Scott LJ, Cvetkovi RS and Plosker GL: Sevelamer hydrochloride: a review of its use for hyperphosphataemia in patients with end-stage renal disease on haemodialysis. Drugs (2008) 68: 85–104.
19. Raaijmakers R, Houkes LM, Schroder CH, Willems JL and Monnens LA: Pre-treatment of dairy and breast milk with sevelamer hydrochloride and sevelamer carbonate to reduce phosphate. Perit Dial Int (2013) 33: 565–572.
20. Damment SJ and Pennick M: Clinical pharmacokinetics of the phosphate binder lanthanum carbonate. Clin Pharmacokinet (2008) 47: 553–563.
21. Bisordi WM and Kleinman MS: Melanosis duodeni. Gastrointest Endosc (1976) 23: 37–38.
22. Qureshi NU, Younus MF, Alavi K and Sheikh MY: Gastric and Duodenal Pseudomelanosis: An Extended Unusual Finding in a Patient with End Stage Kidney Disease. Case Rep Gastrointest Med (2016) 2016: 2861086.
23. Kodama Y, Kawabata K, Yoshida S, Notohara K, Fujimori T and Chiba T: Malt lymphoma simulating an extramedullary plasmacytoma of the stomach. Am J Med (1999) 107: 530–532.
24. Park CH, Lee SM, Kim TO, Kim DU, Jung WJ, Kim GH and Song GA: Treatment of solitary extramedullary plasmacytoma of the stomach with endoscopic submucosal dissection. Gut Liver (2009) 3: 334–337.
25. Iwamuro M, Kanzaki H and Okada H: A White Lesion in the Stomach. Gastroenterology (2016) 150: 44–45.