CASE REPORT

Acute tumoral calcinosis due to severe hyperphosphatemia in a maintenance hemodialysis patient

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Abstract We report the case of a maintenance hemodialysis patient with severe hyperphosphatemia (26.6 mg/dL) who developed acute tumoral calcinosis. The patient started receiving maintenance hemodialysis after being diagnosed with type 2 diabetes mellitus. The patient's phosphate levels suddenly increased. He had not taken the prescribed phosphate binders for the past 5 years. He noticed swelling of the palmar aspects of his right thumb, which was diagnosed as tumoral calcinosis. His serum phosphate level reached 26.6 mg/dL. He started taking medication to lower his serum phosphate levels. The patient had a long history of eating convenience foods. As food additives in convenience foods could be a major source of phosphate, the patient corrected this habit by replacing convenience foods with special foods for dialysis patients. His symptoms improved along with the decrease in his serum phosphate levels. The main reason for the abrupt decrease in phosphate levels could be the correction of his dietary habits. Therefore, phosphate levels in processed foods should be carefully considered in dialysis patients.

Keywords Acute tumoral calcinosis · Severe hyperphosphatemia · Food additives · Hemodialysis

Introduction

Ectopic calcinosis in patients with chronic kidney disease-mineral and bone disorder (CKD-MBD) is of two types, namely tumoral calcinosis and Mönkeberg's medial calcification. Tumoral calcinosis is induced by $P \times cCa > 60$ (mg/dL)². Mönkeberg's medial calcification is evoked through transformation of vascular medial smooth muscle cells into osteoblasts by persistent hyperphosphatemia.

We experienced an interesting case of a hemodialysis patient with acute tumoral calcinosis due to extremely high phosphate levels (26.6 mg/dL). We report that correction of the patient's dietary habit could be a treatment option. Adding phosphate to food improves its taste [1]. Hence, convenience foods, including cooked chicken (Karaage) and carbonated beverages, contain relatively high levels of phosphate. Estimation of phosphate intake is difficult to determine, as disclosure of the phosphate contents in the additives of processed foods is not required by public health authorities. However, it cannot be overlooked, especially in hemodialysis patients. Here, we discuss the potential impact of dietary phosphate in convenience foods on dialysis patients.

Case report

The patient was a 50-year-old man whose chief complaint was a growing tumor located in his right thumb and middle finger. His height and weight were 161.5 cm and 75.5 kg, respectively. His body mass index was 28.9 (kg/m²) and blood pressure was 160/70 mmHg. He was diagnosed with type 2 diabetes mellitus with retinopathy in 2002. His uncontrolled type 2 diabetes mellitus caused the deterioration of his renal function. He had been receiving

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hemodialysis therapy for 5 years when he first visited our facility in 2011. As for his medical history, he had had bronchial asthma since 1976 and atopic dermatitis since 2003. He underwent an operation for retroperitoneal liposarcoma in 2008 and for bilateral implantation of intraocular lenses due to cataracts. He did not have a remarkable family medical history.

The patient's diet consisted almost entirely of convenience foods, including fried chicken, bread, rice balls, and canned coffee. Dietitians instructed him to consume low phosphate-containing foods. Nutritional instruction was given two times, first in October 13, 2011 and second in November 29, 2011. They recommended him to consume delivery foods for dialysis patients. He modified his dietary habits in December 2011 because of his growing tumor. His serum phosphate concentration was 11.3 mg/dL in October 2011. To treat hyperphosphatemia, the patient was prescribed the maximum dosage of three different phosphate binders as follows: calcium carbonate (3000 mg, absorbs up to 135 mg of phosphate), lanthanum carbonate (2250 mg, absorbs up to 203 mg of phosphate), and sevelamer hydrochloride (5250 mg, absorbs up to 158 mg of phosphate) [2]. Thus, the total absorbing capacity of these phosphate binders was 563 mg. A 25-mg dose of cinacalcet was consistently used. We also prescribed alfacalcidol (0.5–1.0 µg), but not 22-oxacalcitriol.

However, it was disclosed that he did not take the prescribed phosphate binders. Two months later, he noticed swelling of the palmar aspects of his right thumb and middle finger. His serum phosphate level reached 26.6 mg/dL by mid-month in January 2012 (Fig. 1). These tumors did not cause any pain at this point. In February 2012, a mass appeared on the palmar aspect of his right middle finger and another on his right thumb. As the mass was initially considered to be a tumor, the patient was referred to an orthopedist. Radiography revealed a lobulated calcification in his right hand (Fig. 2, left), while no medial calcification was detected in the arterioles. Subsequent magnetic resonance imaging indicated that the mass was likely to be a giant cell tumor. However, a subsequent biopsy confirmed the presence of calcium in the mass. Finally, it was diagnosed as tumoral calcinosis due to acute phosphate loading. His whole parathyroid hormone (w-PTH) level was 127 pg/mL. His int-PTH or w-PTH was not followed up periodically. No imaging data were obtained for the parathyroid.

The growth of the tumors compelled the patient to take the prescribed drugs and change his dietary habits from consuming convenience foods to consuming delivery foods for dialysis patients. Since mid-February 2012, his phosphate levels declined to 10 mg/dL. By the end of April, it reached 5 mg/dL (Fig. 1). By the end of June 2013, the mass in his thumb had disappeared, and only a slight

calcification remained on his middle finger (Fig. 2, right). During the clinical course, the patient was prescribed three types of phosphate binders (Fig. 3).

We determined the patient's potential daily phosphate intake. Before nutritional counseling, he consumed five or six canned coffees daily, corresponding to at least 225 mg of phosphate (45 mg of phosphate per canned coffee, Table 1). He also consumed side dishes, rice balls, and chicken products three times per day (116 mg phosphate/chicken piece $\times$ 5 pieces $\times$ 3 times per day = 1740 mg). Thus, he consumed at least 1965 mg of phosphate per day. The absorption capacity of the prescribed phosphate binders was 496 mg. Thus, the balance of phosphate loading per day was at least 1039 mg. This explains the steep elevation of the phosphate level to 26.6 mg/dL (Table 2). Unfortunately, we could not estimate the total amount of dietary phosphate in the processed foods he consumed because disclosure of phosphate amounts is not required by public health authorities. By contrast, the delivery foods prepared for dialysis patients contain about 700 mg of phosphate per day. Therefore, we assumed that the abrupt decrease in his phosphate levels might have been induced by correcting his dietary habits.

Discussion

In patients with normal renal function, approximately 600 mg of phosphate is absorbed and excreted daily, and does not cause any accumulation of phosphate in the body. In Japan, patients on maintenance dialysis are usually treated three times per week for 4 h per visit. Through this process, patients are able to excrete an average of 430 mg of phosphate, resulting in an accumulation of 170 mg of phosphate in the body per day [3]. Of the inorganic phosphates in food additives, 90 % are absorbed, whereas only 40–60 % of the organic phosphate in protein is absorbed [4]. In the present case, inorganic phosphates from food additives contributed to the acute elevation of phosphate levels as described earlier [5]. We consider that the extremely severe phosphate burden caused the acute tumoral calcinosis. However, nutritional counseling helped the patient to improve his dietary habits after the occurrence of tumoral calcinosis and reduced his phosphate levels to 3–4 mg/dL.

CKD-MBD is associated with two types of ectopic calcification [6]. Alpha-klotho is a co-receptor of fibroblast growth factor 23 (FGF23), which is involved in phosphate and calcium homeostasis [7]. Owing to the decrease in alpha-klotho expression during the early stages of renal injury, FGF23 could not mediate its phosphaturic action. Coincident accumulation of phosphate rather stimulates FGF23 release from osteocytes. The function of FGF23

Fig. 1 Change in P and Ca values during the clinical course. The maximum phosphate level was 26.6 mg/dL on January 26, 2012

Fig. 2 The lobulated calcification in the right hand had disappeared after treatment

that suppresses the activation of vitamin D reduces Ca absorption in the intestine, resulting in hypocalcemia. In its lineage, hyperparathyroidism is accelerated. High PTH evokes high turn-over bone remodeling. Excessive recruitment of P and Ca from bone matrix to blood induces tumoral calcinosis. Acute increase in phosphate levels could cause tumoral calcinosis. In fact, tumoral calcinosis in *Galnt3* knock-out mice could be treated with dietary restriction of phosphates [8]. In general, excess phosphate and calcium are deposited in soft tissue, which can be a potential mechanism for the development of tumoral calcinosis.

By contrast, Mönkeberg's medial calcification is another phenotype caused by hyperphosphatemia. Continued hyperphosphatemia could stimulate transformation of the arteriolar medial vascular smooth muscle cells into osteoblasts, which may be the mechanism underlying Mönkeberg's medial calcification. This process has been demonstrated in vitro using human vascular smooth muscle cells (VSMCs) and in vivo in mice [9]. Similarly, bone mineral deposition also occurs in the media of the peripheral artery in humans, where human VSMCs then develop osteoblast characteristics [10]. Once these cells express increased levels of sodium-dependent phosphate co-transporters in hyperphosphatemic conditions, calcification is induced in VSMCs even under conditions of normal phosphate levels [11].

Unlike Mönkeberg's medial calcification, the condition $P \times cCa > 60 \text{ (mg/dL)}^2$ produces intimal calcification via a passive process, which is characterized by a patchy appearance on radiographs. By contrast, Mönkeberg's medial calcification is associated with the "tram track" phenomenon due to transformed vascular medial osteoblasts. In terms of pathophysiological mechanism, the condition $P \times cCa > 60 \text{ (mg/dL)}^2$ causes not only soft tissue tumoral calcinosis but also vessel stenosis, whereas Mönkeberg's medial calcification causes sclerosis. Physiological examination has shown a reduction in the ankle brachial index in patients with vascular stenosis as compared with the exacerbation of the brachial ankle pulse wave velocity in patients with vascular sclerosis.

Fig. 3 Treatments and change in phosphate levels during the clinical course. The *bar* on the Y axis on the right side of the figures indicates the drug doses

Table 1 Phosphate content of the various foods in Japan

Content of phosphate

(commercial food composition chart by the usual dose. 3rd edn. Ishiyaku Syuppan Co. (in Japanese) 2006)

	Content of (mg/100 g)	Usual dose (g)	P in usual dose (mg)
Polished rice	34	150	51
Soba (buckwheat noodles)	170	130	221
Instant soba	230	75	173
Bread	83	180	149
Raw egg	180	50	90
Milk	93	200	186
Yog(h)urt	100	200	200
Gouda cheese	490	20	98
Processed cheese	730	20	146
Ice cream	110	80	88
Soft ice cream	110	100	110
Coffee (Georgia original)	18	250	45
Coca cola	16	250	40
Original chicken (KFC)	187	62	116
Fish	200–300	100	200–300
Meat	200–300	100	200–300
Dried fish	400		
Food additives	?		?

? means no evaluation

Cardiovascular disease results from both types of calcifications [12]. The mortality rate among patients with CKD-MBD is 10- to 20-fold higher than that among healthy people [13]. In the 1980s, foods containing high phosphate

levels induced secondary hyperparathyroidism, even in people with normal kidney function [14]. Therefore, increased attention should be paid to the presence of food additives to avoid hyperphosphatemia due to the presence

Table 2 The estimated phosphate balance in our case

P management		
Block outside the body		Case P balance (mg) (for a day)
Restriction of P rich products	Food additives	?
	Beverages	225
P binders	Food proteins	1740
	Calcium carbonate; 3000mg (max)	−135
	Sevelamer hydrate; 5250mg (max)	−158
	Lanthanum carbonate; 2250mg (max)	−203
	Bixalomer	
	Ferric citrate hydrate sucroferric oxyhydroxide	
Inhibitor of Na P cotransporter	Niceritrol	
P removal by dialysis		−430
Total burden of phosphate		1039

? means no evaluation

The total phosphate burden was calculated as 1039 mg/dL. About 40–60 % of the value could be absorbed. The amount of phosphate obtained from food additives cannot be estimated

of excessive inorganic phosphates [15, 16]. This is a public health problem, as disclosure of the phosphate content of foods is not currently mandated by public health authorities. Calcium phosphates and potassium phosphates are used in beverages and enhanced meat, poultry, and fish products. The public remain unaware that they are consuming high levels of phosphates from these processed foods [17], especially chicken products [18]. Companies that produce processed foods may explain the addition of inorganic phosphates to their products as flavor enhancers in beverages, leavening agents in baked goods, preservatives in meats, and cleaning agents in toothpaste. Uribarri et al. reported on the lack of information provided about the amount of phosphates in American-style fast foods [19].

Incorrect dietary instructions for reducing phosphates might have also been provided to maintenance dialysis patients. Although food additives are the main source of phosphates in the diet, low protein intake is enforced for maintenance dialysis patients. Thus, traditional dietary instructions have led to aggravated costs, morbidity, and mortality in CKD-MBD patients [20]. Sherman et al. recommended that dietary instructions should be changed to focus on reducing phosphate levels by restricting food additives in the diet. Dietary instructions that recommend protein restrictions may shorten the lifespan of these patients, whereas reducing the consumption of food additives is an easy and effective method for improving hyperphosphatemia [21]. Avoiding phosphate intake is considered to be a means of controlling phosphate levels. Therefore, the most effective treatment of ectopic calcinosis is the restriction of the intake of inorganic phosphates in food additives or beverages. Prescription of phosphate binders and hemodialysis are adjunctive measures.

The utilization of both phosphate and calcium in the body is also important and involves effective recycling of phosphates in the body. A normal, balanced turnover of bone effectively increases hydroxyapatite levels by the suppression of the recruitment of phosphates from the bone matrix. Conversely, a matching of phosphate and calcium moving into the bone matrix leads to a reduction in serum phosphate levels. Thus, controlling a balanced turnover of bone is also important for lowering serum phosphate levels [22].

Overall, acute tumoral calcinosis induced by acute phosphate loading may disappear after appropriate dietary intervention, and administration of phosphate binders and cinacalcet. If the inorganic phosphate supply from foods is curtailed, phosphate and calcium from ectopic calcification are relocated to the bone matrix as hydroxyapatites, reducing the symptoms of tumoral calcinosis.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

References

1. <http://www.prayon.com/en/our-activities/products/food-applications.php>. Accessed 17 June 2016.
2. Daugirdas JT, Finn WF, Emmett M, Chertow GM, Frequent Hemodialysis Network Trial Group. The phosphate binder equivalent dose. *Semin Dial*. 2011;24:41–9.
3. Shigematsu T. Phosphate balance and sevelamer hydrochloride. *JSDT*. 2004;37:2055–6 (in Japanese).
4. Noori N, Sims JJ, Kopple JD, Shah A, Colman S, Shinaberger CS, Bross R, Mehrotra R, Kovesdy CP, Kalantar-Zadeh K. Organic and inorganic dietary phosphorus and its management in chronic kidney disease. *Iran J Kidney Dis*. 2010;4:89–100.

5. Tanaka A, Nakajima Y (eds) (2006) Commercial food composition chart by the usual dose, 3rd edn. Ishiyaku Syuppan Co., Tokyo (**in Japanese**).
6. Amann K. Media calcification and intima calcification are distinct entities in chronic kidney disease. *Clin J Am Soc Nephrol*. 2008;3:1599–605.
7. Nabeshima Y. Discovery of alpha-klotho unveiled new insights into calcium and phosphate homeostasis. *Proc Jpn Acad Ser B Phys Biol Sci*. 2009;85:125–41.
8. Ichikawa S, Austin AM, Gray AK, Allen MR, Econs MJ. Dietary phosphate restriction normalizes biochemical and skeletal abnormalities in a murine model of tumoral calcinosis. *Endocrinology*. 2011;152(12):4504–13.
9. Jono S, McKee MD, Murry CE, Shioi A, Nishizawa Y, Mori K, Morii H, Giachelli CM. Phosphate regulation of vascular smooth muscle cell calcification. *Circ Res*. 2000;87(7):E10–7.
10. Shanahan CM, Cary NR, Salisbury JR, Proudfoot D, Weissberg PL, Edmonds ME. Medial localization of mineralization-regulating proteins in association with Mönkeberg's sclerosis: evidence for smooth muscle cell-mediated vascular calcification. *Circulation*. 1999;100:2168–76.
11. Giachelli CM. The emerging role of phosphate in vascular calcification. *Kidney Int*. 2009;75:890–7.
12. London GM. Cardiovascular calcifications in uremic patients: clinical impact on cardiovascular function. *J Am Soc Nephrol*. 2003;14:S3050–9.
13. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis*. 1998;32:S112–9.
14. Calvo MS, Kumar R, Heath H. Persistently elevated parathyroid hormone secretion and action in young women after 4 weeks of ingesting phosphorus, low calcium diets. *J Clin Endocrinol Metab*. 1990;70:1334–40.
15. Sullivan CM, Leon JB, Sehgal AR. Phosphorus-containing food additives and the accuracy of nutrient databases: implications for renal patients. *J Ren Nutr*. 2007;17:350–4.
16. Sherman RA, Mehta O. Dietary phosphorus restriction in dialysis patients: potential impact of processed meat, poultry, and fish products as protein sources. *Am J Kidney Dis*. 2009;54:18–23.
17. Kemi VE, Rita HJ, Kärkkäinen MU, Viljakainen HT, Laaksonen MM, Outila TA, Lamberg-Allardt CJ. Habitual high phosphorus intakes and foods with phosphate additives negatively affect serum parathyroid hormone concentration: a cross-sectional study on healthy premenopausal women. *Public Health Nutr*. 2009;12:1885–92.
18. Kalantar-Zadeh K, Gutekunst L, Mehrotra R, Kovesdy CP, Bross R, Shinaberger CS, Noori N, Hirschberg R, Benner D, Nissenson AR, Kopple JD. Understanding sources of dietary phosphorus in the treatment of patients with chronic kidney disease. *Clin J Am Soc Nephrol*. 2010;5:519–30.
19. Uribarri J, Calvo MS. Hidden sources of phosphorus in the typical American diet: does it matter in nephrology? *Semin Dial*. 2003;16:186–8.
20. Sherman RA. Dietary phosphate restriction and protein intake in dialysis patients: a misdirected focus. *Semin Dial*. 2007;20:16–8.
21. Shinaberger CS, Greenland S, Kopple JD, Van Wyck D, Mehrotra R, Kovesdy CP, Kalantar-Zadeh K. Is controlling phosphorus by decreasing dietary protein intake beneficial or harmful in persons with chronic kidney disease? *Am J Clin Nutr*. 2008;88:1511–8.
22. Nishime K, Takamine A, Nakamura S, Kinjyo K, Saitou T. A case of calcific uremic arteriolopathy (calciphylaxis) involving a maintenance hemodialysis patients. *JSDT*. 2012;45:591–8 (**in Japanese with English abstract**).