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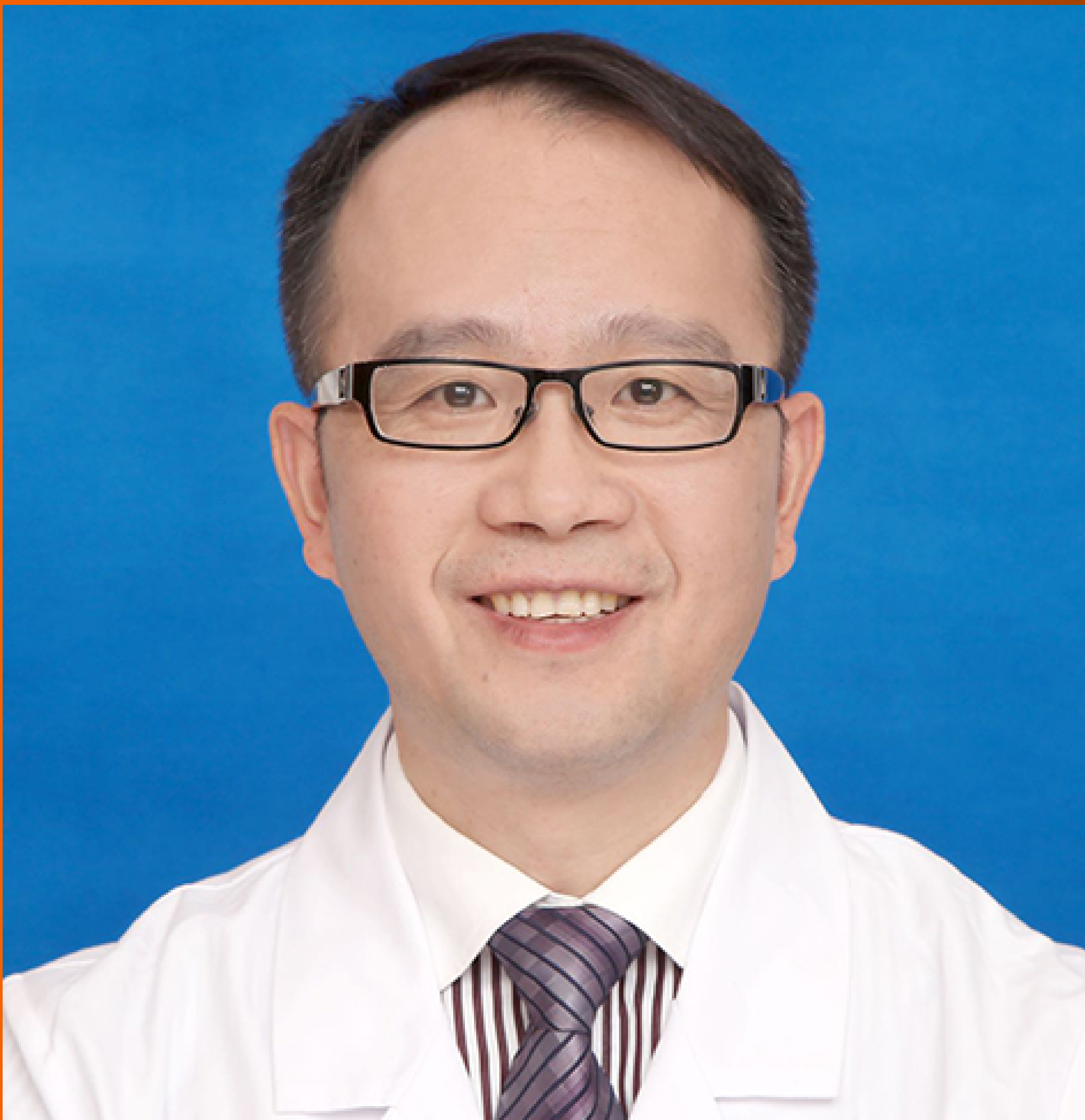

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ABOUT COVER

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CASE REPORT

New method of local adjuvant therapy with bicarbonate Ringer's solution for tumoral calcinosis: A case report

Takashi Noguchi, Akio Sakamoto, Kensaku Kakehi, Shuichi Matsuda

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Abstract

BACKGROUND

Tumoral calcinosis is a condition characterized by deposits of calcium phosphate crystals in extra-articular soft tissues, occurring in hemodialysis patients. Calcium phosphate crystals are mainly composed of hydroxyapatite, which is highly infiltrative to tissues, thus making complete resection difficult. An adjuvant method to remove or resolve the residual crystals during the operation is necessary.

CASE SUMMARY

A bicarbonate Ringer's solution with bicarbonate ions (28 mEq/L) was used as the adjuvant. After resecting calcium phosphate deposits of tumoral calcinosis as much as possible, while filling with the solution, residual calcium phosphate deposits at the pseudocyst wall can be gently scraped by fingers or gauze in the operative field. A 49-year-old female undergoing hemodialysis for 15 years had swelling with calcium deposition for 2 years in the shoulders, bilateral hip joints, and the right foot. A shoulder lesion was resected, but the calcification remained and early re-deposition was observed. Considering the difficulty of a complete rection, we devised a bicarbonate dissolution method and excised the foot lesion. After resection of the calcified material, the residual calcified material was washed away with bicarbonate Ringer's solution.

CONCLUSION

The bicarbonate dissolution method is a new, simple, and effective treatment for tumoral calcinosis in hemodialysis patients.

Key Words: Tumoral calcinosis; Adjuvant therapy; Bicarbonate; Ringer's solution; Surgery; Case report

Core Tip: Tumoral calcinosis, which occurs in 2%-3% of hemodialysis patients, involves calcium phosphate deposits, thus making surgical resection challenging. Hydroxyapatite, the main component of tumoral calcinosis, infiltrates tissues extensively. A bicarbonate Ringer's solution is used post-resection. A 49-year-old hemodialysis patient with calcified shoulder, hip, and foot lesions underwent the bicarbonate dissolution method. After resection, the operative field was washed with the solution. This simple and effective treatment offers a novel approach for managing tumoral calcinosis in hemodialysis patients.

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INTRODUCTION

Tumoral calcinosis is a condition characterized by solitary or multifocal calcium phosphate deposits in extra-articular soft tissues. The joints of the hips, shoulders, and elbows are most often involved; the hands, feet, and knees are less often involved. Tumoral calcinosis often presents as painful tumor-like masses that limit joint range of motion; cosmetic problems also occur[1-5].

Tumoral calcinosis has a primary type with no associated disease, which is due to a genetic abnormality, and a secondary type that is associated with other disorders, especially chronic renal failure[1,6]. The prevalence of tumoral calcinosis has been reported to range from 0.5%-3% among dialysis patients[7-9]. The exact mechanisms underlying tumoral calcinosis are unclear. The role of repeated joint microtrauma has been suggested to cause tumoral calcinosis[10]. Previous studies have reported that elevated calcium phosphate production is closely associated with soft tissue calcification[11,12]. Regardless of the etiology, hyperphosphatemia is associated with tumoral calcinosis. Medical treatment for tumoral calcinosis in hemodialysis patients includes dietary phosphorus restriction, calcium-free phosphate binders, and frequent dialysis with low-calcium dialysis solutions; however, these treatments are usually ineffective[7,13,14].

Surgical resection is only used when these treatments are insufficient[15]. Surgical resection of tumoral calcinosis lesions has been the primary treatment[13] but surgical resection is not curative. In contrast, it has been reported that tumoral calcinosis is reduced or resolved with improved systemic symptoms following parathyroidectomy[16-18]. Parathyroidectomy is effective for tumoral calcinosis patients, especially patients with secondary hyperparathyroidism [5]. Following a parathyroidectomy, calcified tissue is significantly resorbed; however, bone renewal is reduced following parathyroidectomy because of lower parathyroid hormone (PTH) levels, resulting in increased circulating calcium and promotion of vessel and soft tissue calcification[19,20].

Calcium phosphate deposits in tumoral calcinosis have been shown to be comprised of hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$][21]. Experimentally, hydroxyapatite is known to be insoluble; however, hydroxyapatite is easily dissolved by blowing carbon dioxide (CO_2) into a hydroxyapatite suspension, in which the dissolution amount is 200 times that found without CO_2. Calcium carbonate ($CaCO_3$) is an insoluble calcium salt. Hydroxyapatite co-exists with CO_2; $CaCO_3$ changes into the highly-soluble calcium hydrogen carbonate [$Ca(HCO_3)_2$][22,23]. We therefore assumed that hydroxyapatite in tumoral calcinosis could be soluble with co-existing CO_2 or HCO_3^-.

A bicarbonate Ringer's solution was used. The solution had a pH of 7.0 and an osmotic pressure of approximately 1.0. The solution contained HCO_3^- (28 mEq/L) (Tables 1-3). After resecting calcium phosphate deposits of tumoral calcinosis as much as possible, while filling with bicarbonate Ringer's solution, residual calcium phosphate deposits at the pseudocyst wall are gently scraped with fingers or gauze in the operative field. Because the concentration of HCO_3^- (28 mEq/L) is normal *in vivo*, the amount to be used is not restricted, but we use approximately 1000 mL of the solution for 1 operation. The use of the solution as a washing solution is explained to the patients and consent is obtained.

Herein we report the successful treatment of a patient with tumoral calcinosis by local adjuvant therapy with bicarbonate Ringer's solution. The procedure, chemical background, and safety are discussed.

CASE PRESENTATION

Chief complaints

The patient is a 49-year-old woman with a diagnosis of tumoral calcinosis.

History of present illness

She had noticed swelling in her right shoulder 2 years before the initial assessment. Nine months later, there was bilateral hip and right foot swelling. The size of the right shoulder swelling had increased to be from the supraclavicular fossa to the maxilla, and the size of the swelling was > 20 cm in diameter.

Table 1 Composition bicarbonate solution

Ion	mEq/L
Na^+	130
K^+	4
Mg^{2+}	2
Ca^{2+}	3
Cl^-	109
HCO_3^-	28
Citrate^{3-}	4

Table 2 Property of bicarbonate solution

Bicarbonate solution	
Appearance	Colorless and transparent
pH	6.8-7.8
Osmotic pressure	Apraxia 1

Table 3 Component of bicarbonate solution

Component		500 mL	1000 mL
Sodium chloride	NaCl	2.92 g	5.84 g
Potassium chloride	KCl	0.15 g	0.30 g
Calcium chloride hydrate	$CaCl_2 \cdot 2H_2O$	0.11 g	0.22 g
Magnesium chloride	$MgCl_2$	0.10 g	0.20 g
Sodium bicarbonate	$NaHCO_3$	1.175 g	2.35 g
Sodium citrate hydrate	$C_6H_9Na_3O_9$	0.10 g	0.20 g
Citric acid hydrate moderation	$HOC(COOH)(CH_2COOH)_2 \cdot H_2O$	Moderate	Moderate

History of past illness

She has a history of hemodialysis for 15 years.

Personal and family history

There was no specific personal or family history.

Physical examination

The size of the bilateral hip swelling was > 20 cm in diameter and that of the sole of the foot was 3 cm. Each mass was elastic and soft with fluid palpitation.

Laboratory examinations

The leukocyte count was normal [7140/mm^3 (normal range, 3300-8600/mm^3)]. The differential was as follows: neutrophils, 68.8% (normal range, 46%-62%); lymphocytes, 22.4% (normal range, 30%-40%); monocytes, 6.7% (normal range, 4%-7%); eosinophils, 1.7% (normal range, 3%-5%); and basophils, 0.4% (normal range, < 1%). Laboratory data showed the following: corrected Ca^{2+}, 9.7 mg/dL (normal range, 8.8-10.1 mg/dL); inorganic phosphorus, 5.5 mg/dL (normal range, 2.7-4.6 mg/dL); creatinine, 5.16 mg/dL (normal range, 0.16-0.79 mg/dL); estimated glomerular filtration rate, 7.8 mL/min/1.73 m^2 (normal range, < 90 mL/min/1.73 m^2), and PTH-intact, 1110 pg/mL (reference value, 10-65 pg/mL). The serum phosphorus level was elevated, even after medical treatment. The serum PTH level was also elevated, suggesting secondary hyperparathyroidism.

Imaging examinations

Plain radiographs and computed tomography (CT) showed that the lesions were multilocular, opaque, and homogeneous. Axial CT showed various densities of calcium crystals and a liquid level within an elementary formation related to the sedimentation of calcium crystals with a serous supernatant (sedimentation sign)[4,10] (Figure 1). In the right shoulder lesion, erosions of the bone cortex of the clavicle were noted. Magnetic resonance imaging showed that the cystic lesions had a homogenous low-signal intensity on T1-weighted images and high-signal intensity at the top of the cyst and low-signal intensity at the bottom of the cyst on T2-weighted images. Brachial plexus and vessels were located between the cyst and chest wall (Figure 2).

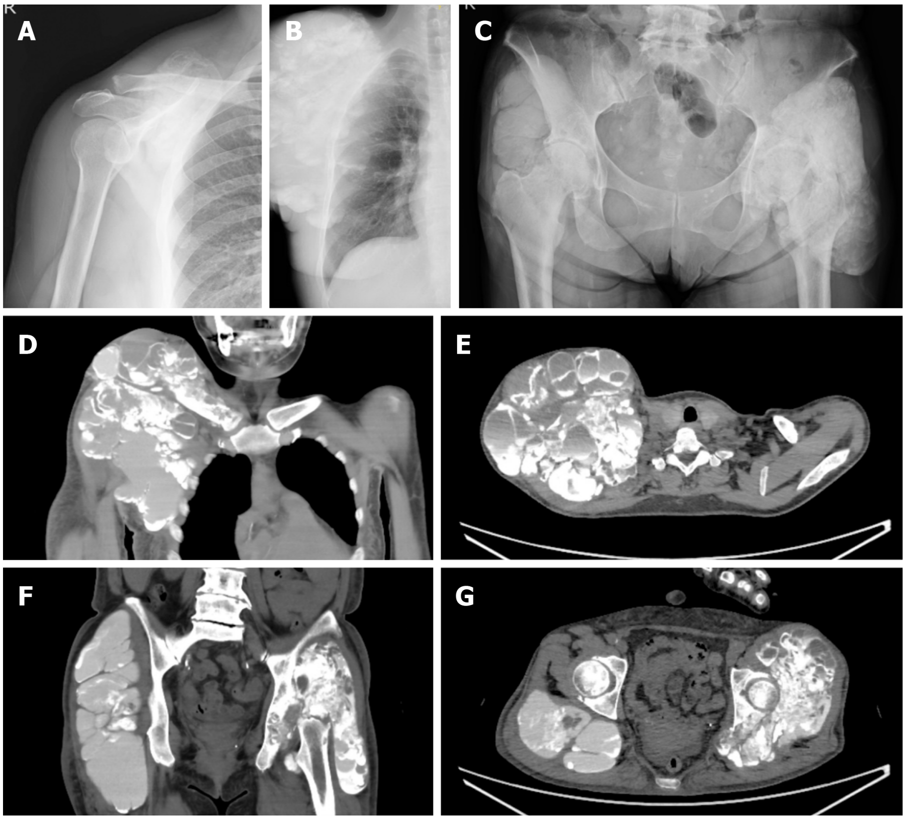

Figure 1 Plain radiograph and computed tomography of tumoral calcinosis. A-C: The images have an opaque and nodular appearance in the right shoulder 12 months (A) and 3 months before the operation (B) and the bilateral hips (C); D-G: Computed tomography (CT) shows calcified multi-cystic lesions in the right shoulder (D and E) and the bilateral hips (F and G); E and G: Axial CT shows each cyst has fluid-fluid level with a dense CT value at the bottom.

FINAL DIAGNOSIS

The diagnosis was based on the clinical course and the imaging findings were tumoral calcinosis associated with hemodialysis.

TREATMENT

Because growth of the lesion after medical treatment with low-calcium dialysis failed, surgical intervention was considered. The right shoulder lesion was not acceptable esthetically and the foot lesion caused discomfort when walking. Although a parathyroidectomy was an option, given the side effects, surgical resection was selected.

Under general anesthesia, an incision was made from the supraclavicular region to the axilla. A pseudofibrous capsule was noted and white fluid and muddy material extended to the subcutaneous tissue. The fluid material was removed. A solid white material was entrapped in the fibrous wall and the fibrous wall was removed as much as possible. The fibrous wall was continuous with the surrounding tissue without a clear border. Because the brachial plexus and vessels were located between the cyst and chest wall, complete resection was not possible. A curettage was performed for the calcified tissue in the fibrous wall and a massive, calcified lesion was removed. The operative field was routinely washed with normal saline to reduce the possibility of infection. A postoperative plain radiograph showed a diffuse, calcified intensity in the operative field (Figure 2). The fluid collection at the right shoulder gradually increased, and the swelling returned to the preoperative size within 2 months.

Because of the unsatisfactory results of the resected shoulder lesion, adjuvant therapy was added to the foot lesion resection. Under general anesthesia, a tourniquet was used. The calcified lesion was located on the sole and an incision

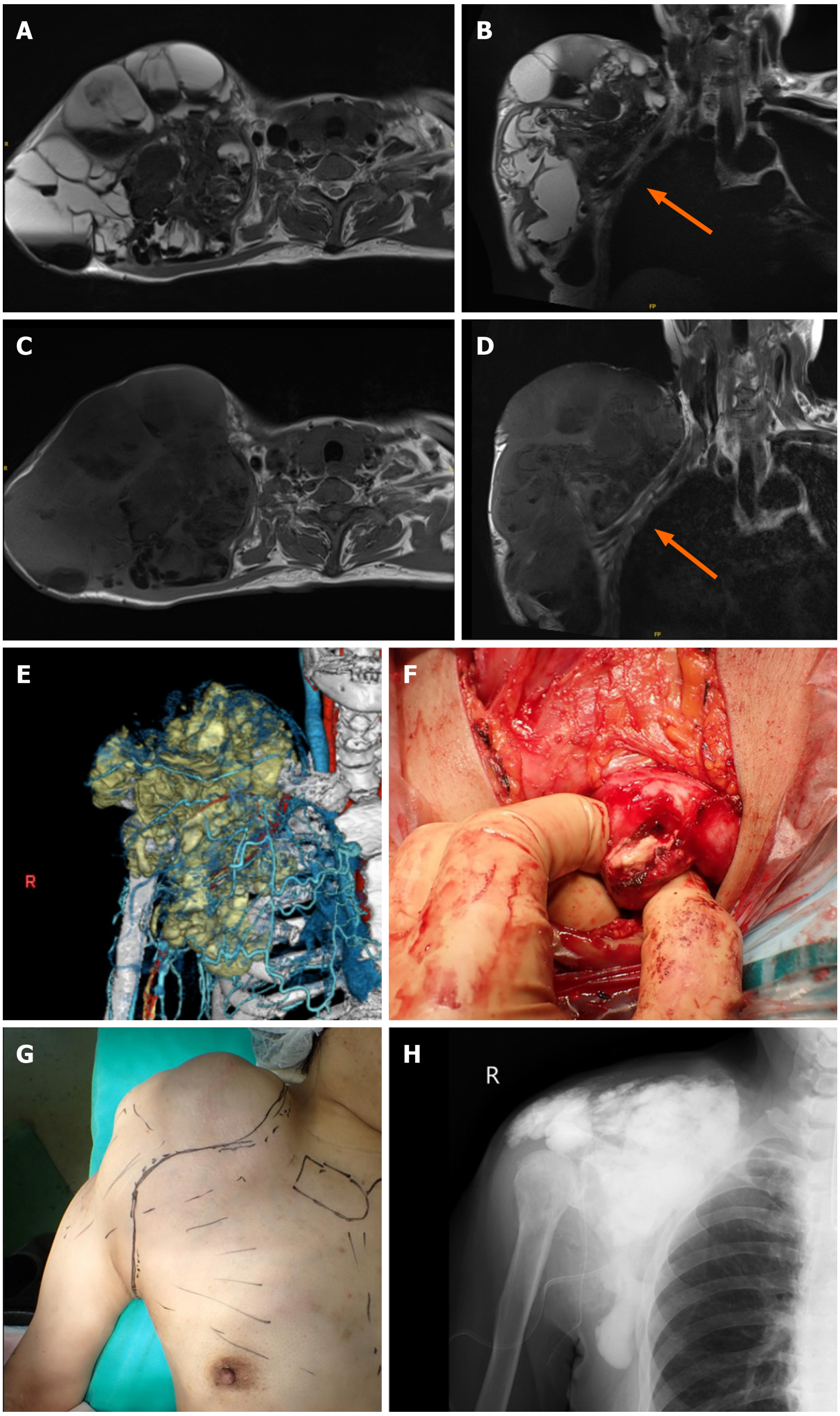

Figure 2 Magnetic resonance imaging and perioperative images. A-D: The magnetic resonance (MR) images reveal multi-cystic lesions with low-to-high signal intensity on T2- (A and B) and T1-weighted images (C and D); A: Axial T2-weighted image shows a fluid-fluid level with a high signal at the top and a low signal at the bottom; B and D: Coronal MR images show brachial plexus and subclavian vessels between the lesion and the chest wall (orange arrows); E: Three-dimension computed tomography shows the extension of the calcified lesion; F: The operation field shows solid calcified lesion trapped in the fibrous wall; G: A photograph shows swelling and planned incision line; H: After the resection, the plain radiograph shows residual calcified fluid and the materials over the operative field.

was made at the lateral side of the sole. Muddy material with the same appearance as the shoulder lesion was removed. A cystic fibrous wall had formed, but was smaller than the shoulder lesion. The fibrous cystic wall was preserved, but calcified materials embedded in the cystic wall were removed as much as possible. Particles of calcified tissue at the fibrous wall were observed, even after resection of the calcified material (Figure 3). After filling with a total of 1000 mL of bicarbonate Ringer's solution, a significant decrease in calcareous deposits was observed by the naked eye and fluoroscopy during the operation (Figure 3). Intra- and post-operative examinations showed no abnormalities in pH or

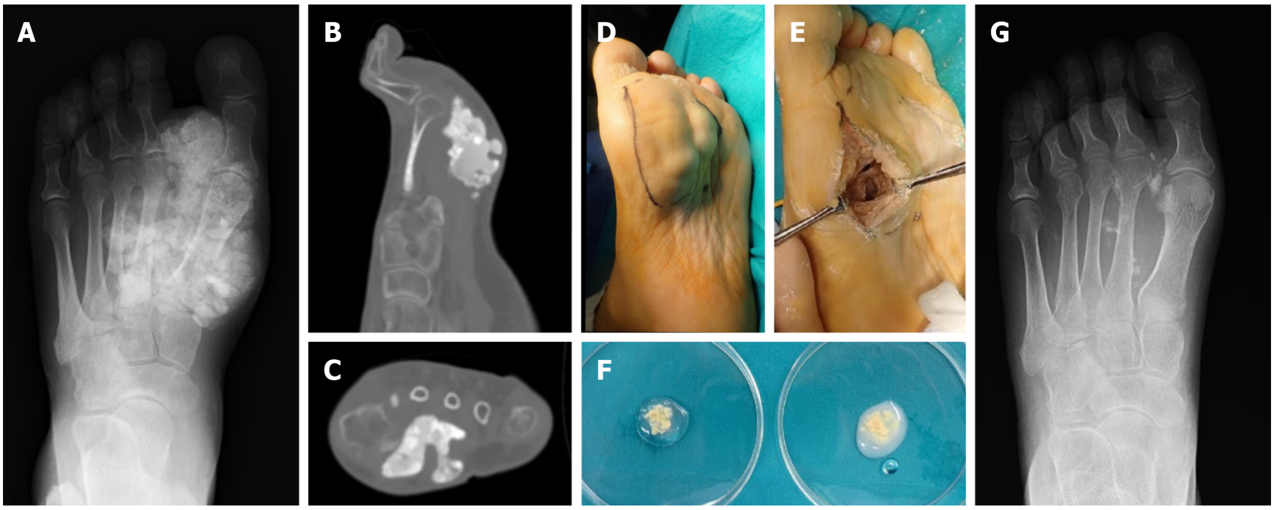

Figure 3 Tumoral calcinosis in the foot. A-C: A plain radiograph (A) and computed tomography (B and C) shows a calcified lesion of the foot; D: A photograph shows swelling and the planned incision line; E: Calcified lesion deposits at the wall after the calcified lesion were removed with suction and curettage; F: The resected calcified material had no reaction in saline (left), but became turbid and dissolved in bicarbonate Ringer's solution (right); G: The calcified lesion was almost removed and no additional deposition was noted 6 months postoperatively.

base excess values. The postoperative course was uneventful. No fluid collection was observed 6 months postoperatively.

OUTCOME AND FOLLOW-UP

The resected materials of tumoral calcinosis were soaked with saline or bicarbonate at the side of the operation theatre. The calcified materials soaked with saline did not change, while the calcified materials soaked with bicarbonate Ringer solution became turbid immediately.

DISCUSSION

The current case was a typical presentation of tumoral calcinosis associated with hemodialysis. According to the literature, the average time of appearance of the mass after the start of dialysis ranges from a few months to several years [10]. Clinically, the lesions present as masses of slow evolution, up to 20 or 30 cm in diameter[10]. The location of the tumoral calcinosis was also typical, and is most often located in the vicinity of the large joints (hips, shoulders, and elbows)[10].

Histologically, tumoral calcinosis has a nodular architecture with fibrous septa coursing between nodules. The fibrous wall shows calcification surrounded by macrophages, osteoclast-like multinucleated giant cells, fibroblasts, and chronic inflammatory cells. Calcified materials are entrapped into the fibrous wall[24,25]. Surgical resection of the lesions is not considered in accordance with the recommendations in the literature. The unsatisfactory results of surgical resection are due to these trapped calcified lesions in the fibrous wall. Calcium phosphate deposits in tumoral calcinosis have been shown to be $Ca_{10}(PO_4)_6(OH)_2$[21]. We have developed a method to dissolve hydroxyapatite as an adjuvant therapy in surgical resection.

Hydroxyapatite has very low solubility. Hydroxyapatite is easily dissolved by blowing CO_2 into the hydroxyapatite suspension. The dissolution amount was 200 times that found without CO_2 blowing[22,23]. $Ca_{10}(PO_4)_6(OH)_2$ reacts with CO_2 as soluble $Ca(HCO_3)_2$ and liquid phosphoric acid (H_3PO_4) [$Ca_{10}(PO_4)_6(OH)_2 + 20CO_2 + 18H_2O \rightarrow 10Ca(HCO_3)_2 + 6H_3PO_4$][26]. CO_2 reacts with H_2O to form carbonic acid (H_2CO_3). Then, H_2CO_3 further dissociates into HCO_3^- and a H^+. Therefore, CO_2 and HCO_3^- have the same chemical reaction in solution. $CaCO_3$ is a calcium salt with the same insolubility, but dissolves easily in solutions containing CO_2. Hydroxyapatite co-existing with CO_2 or $CaCO_3$ changes into the highly soluble $Ca(HCO_3)_2$[22,23]. The bicarbonate Ringer's solution had HCO_3- 28 mEq/L. The bicarbonate Ringer's solution was used in emergency cases as well as in liver transplantation for compensation of extracellular fluid and correct metabolic acidosis. A bicarbonate Ringer's solution is used in the current new method to dissolve hydroxyapatite in tumoral calcinosis.

Use of bicarbonate of Ringer's solution was shown to be safe. The value of HCO_3- (28 mEq/L) was within normal limits *in vivo*, the solution had a pH of 7.0, and the osmotic pressure was approximately 1.0. In a previous report, critical alkalosis occurred in a patient who was irrigated with 1000 mL of 7% sodium bicarbonate solution intraperitoneally as adjuvant therapy for pseudomyxoma peritonei. The peritoneal capillary vessels easily absorb sodium bicarbonate in the abdominal cavity by diffusion, such as in peritoneal dialysis, and the peritoneal surface area is equal to the body surface area. The predicted amount of absorbed sodium bicarbonate was estimated to be approximately 30% of the entire irrigation volume[27]. The 7% sodium bicarbonate solution was 833 mEq/L, which is much greater than the 28 mEq/L in the solution used in our case. Alkalosis was not reported in a patient who was twice-irrigated with 200 mL of 7% sodium bicarbonate solution for 2 min (total volume = 400 mL; estimated absorbed volume = 85 mL), even for intraperitoneal irrigation for adjuvant therapy for pseudomyxoma peritonei[27].

CONCLUSION

In conclusion, bicarbonate Ringer's solution was used as an adjuvant therapy for tumoral calcinosis, which is a common complication in hemodialysis patients. Bicarbonate Ringer's solution has a role in dissolving $Ca_{10}(PO_4)_6(OH)_2$. The bicarbonate dissolution method is a new, simple, and effective treatment for tumoral calcinosis in hemodialysis patients. The dissolution mechanism needs to be chemically verified in a corollary study.

FOOTNOTES

Co-corresponding authors: Takashi Noguchi and Akio Sakamoto.

Author contributions: Noguchi T, Sakamoto A, Kakehi K and Matsuda S were participated in the treatment; Sakamoto A drafted the manuscript; All authors reviewed the manuscript and approved the final version of the manuscript. Noguchi T and Sakamoto A contributed equally to this work as co-corresponding authors. This invention was achieved through the cooperation of Noguchi T and Sakamoto A, they contributed efforts of equal substance throughout the research process, the designation of co-corresponding authorship accurately reflects our team's collaborative spirit and equal contributions.

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