

# Gastric Mucosal Calcinosis

## *Clinicopathologic Considerations*

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**Abstract:** Generally, gastric mucosal calcinosis (GMC) is only rarely encountered in routine biopsies. GMC may be classified as dystrophic, metastatic, or idiopathic. Metastatic calcification represents the most frequently encountered subtype, and refers to the deposition of calcium salts on largely normal tissues in the setting of an abnormal serum biochemical environment (hypercalcemia, hyperphosphatemia, and/or an elevated  $\text{Ca} \times \text{PO}_4$  product). In contrast, dystrophic calcification implies calcification in inflamed, fibrotic, or otherwise altered tissue in the setting of a normal biochemical environment. The gastric mucosa, along with the kidneys and lungs, are preferential sites for metastatic calcification, a finding that has been attributed to the relative intracellular alkalinity at these sites. In addition to the wide variety of hypercalcemia and/or hyperphosphatemia-causing clinical conditions, GMC has also been associated with atrophic gastritis, hypervitaminosis A, organ transplantation, gastric neoplasia, uremia with eucalcemia/euphosphatemia, and the use of aluminum-containing antacids, citrate-containing blood products, isotretinoin, and sucralfate. Although GMC has rarely been associated with epigastric pain and/or dyspepsia, most come to clinical attention owing to their accumulation of bone-seeking radiopharmaceuticals or represent a postmortem finding. The precise significance or mechanistic basis for GMC remains to be elucidated. However, their presence in gastric biopsies should be reported, as they may serve as an indicator for generalized metastatic calcification, especially in organs where they may be fatal, such as the heart. Furthermore, some examples of systemic calcification are reversible with normalization of biochemical parameters, which highlights the need for pathologists to report this finding when encountered in a premortem gastric biopsy.

**Key Words:** stomach, gastric, calcification, calcinosis, calcium, calciphylaxis

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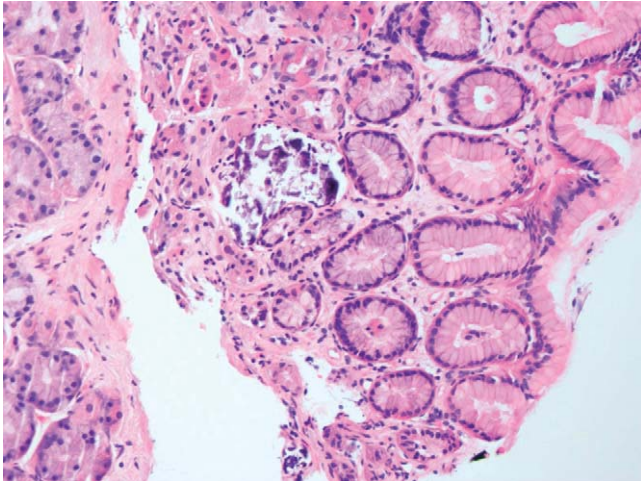
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Calcifications of soft tissue are frequently associated with inflammation and lack broad clinical significance. Gastric mucosal calcinosis (GMC),<sup>1–27</sup> although a distinctly rare finding, has been recognized for more than 150 years.<sup>1</sup> Most examples are associated with a specific set of clinical syndromes related to hyperphosphatemia and hypercalcemia. GMC are frequently unassociated with inflammation and may thus be overlooked. Herein, the most salient clinicopathologic parameters of GMC are reviewed. An argument is advanced for the routine reporting of GMC when encountered.

### MACROSCOPIC AND MICROSCOPIC FEATURES

Endoscopically, GMC are seen as varying numbers of 1 to 5-mm white flat plaques or nodules in the gastric fundus, body, and/or antrum.<sup>2–4,8</sup> The histologic features of GMC have been described primarily in biopsy specimens. The most significant finding includes amorphous basophilic deposits predominantly localized to the subepithelial compartment in the superficial lamina propria or just below the foveolar tips (Fig. 1).<sup>2,5–8</sup> These deposits may also be found in the deeper lamina propria or muscularis mucosa of the gastric fundus, antrum, and/or body.<sup>3,5,6,8–10</sup> A previously suggested predilection for the acid-producing corpus<sup>11</sup> was not confirmed in a more recent analysis.<sup>9</sup> In severe cases, granular and linear calcifications may be seen along the basement membrane and in the submucosal vessels, which may also display luminal stenosis.<sup>6</sup> These 40 to 500  $\mu\text{m}$  deposits are tinctorially similar to cytomegalovirus (CMV) inclusions, may be rimmed by histiocytes, and do not exhibit birefringence when exposed to polarized light.<sup>5,8,9</sup> Because metastatic calcification is the most common type of GMC, the background mucosa was essentially normal in the majority of the reported cases. However, approximately 30% of the reported cases had some background changes that included one or more of the following features: sparse inactive chronic inflammation,<sup>8</sup> foveolar hyperplasia,<sup>5,9</sup> mucosal edema,<sup>5</sup> reactive epithelial changes,<sup>5</sup> ulceration,<sup>5,9</sup> chronic active gastritis,<sup>9</sup> and atrophic gastritis.<sup>3</sup> Changes indicative of “chemical gastritis” were present in 82% of cases in one series.<sup>5</sup> *Helicobacter pylori* is not significantly associated with GMC, and where present, seems to be fortuitous association. Stroehlein et al<sup>9</sup> and Greenson et al<sup>5</sup> identified *H. pylori* in 1 (16.6%) of 6 and 0 (0%) of 28 gastric biopsies with organ transplant-associated GMC,



**FIGURE 1.** An example of metastatic gastric mucosal calcification in a patient with chronic renal failure.

respectively. The role of CMV is unclear. This virus was an associated finding in 50% of GMC biopsies in one study.<sup>5</sup> However, another study did not find any evidence of CMV in the 6 reported patients.<sup>9</sup>

### CLASSIFICATION

Soft tissue and visceral calcifications may be classified into 4 broad categories: metastatic, iatrogenic, dystrophic, and idiopathic.<sup>12,13</sup> In dystrophic calcification, calcium salts are deposited in inflamed, fibrotic, or otherwise altered tissue in the setting of a normal serum biochemical environment. In iatrogenic calcifications, calcifications develop in normal or abnormal tissues owing to an altered serum biochemical milieu that can be directly attributed to therapeutic measures, typically intravenous calcium chloride or calcium gluconate therapy.<sup>13</sup> As its name suggests, idiopathic calcification implies an absence of a readily identifiable basis for the calcification, that is, calcifications developing in normal tissues in the setting of a normal serum biochemical environment. In metastatic calcification, calcium salts are deposited in normal tissues owing to an altered serum biochemical milieu, typically hyperphosphatemia, and/or hypercalcemia.<sup>11,14–16</sup> Some authors have included cutaneous-type calciphylaxis (in which there is prior tissue sensitization at or remote from the site of calcification and calciphylaxis-type vascular changes are present) in this classification.<sup>10</sup> However, to the authors' knowledge, gastric calciphylaxis, and iatrogenic calcifications, as described above, have not been reported. Thus, GMC can broadly be classified into metastatic, dystrophic, and idiopathic. The precise role of each of the many potentially confounding factors in patients with GMC is not easily deciphered. GMC in the setting of gastric ulcers<sup>5</sup> and atrophic gastritis<sup>3</sup> are likely of the dystrophic type. However, some cases are not easily classified, an example of which is the GMC seen in the setting of concurrent renal transplantation and gastric ulceration.<sup>9</sup>

Our review of the literature revealed that metastatic calcification is the most commonly encountered subtype of GMC, constituting approximately 70% of the approximately 100 reported cases.

### PATIENT PRESENTATION

In general, most examples of GMC are detected postmortem<sup>6</sup> or premortem owing to the use of bone-seeking radiopharmaceuticals such as technetium-99 m methylene diphosphonate.<sup>17–22</sup> As such, GMC generally does not contribute to the clinical course<sup>15</sup> outside of potentially serving as a marker for the presence of metastatic calcifications in organs such as the heart, where they may be fatal.<sup>6</sup> However, there have been rare reports of clinical symptoms such as dyspepsia and epigastric pain that were not readily attributable to factors other than the GMC.<sup>2,8</sup> In one series of 28 organ transplant-related cases, many of the patients presented with nausea, vomiting, or gastrointestinal (GI) bleeding.<sup>5</sup> However, CMV infection was a clinical suspicion in almost all the cases, and indeed 50% turned out to be infected.<sup>5</sup> In another series of 6 renal transplant-related cases, 5 patients underwent the biopsy-generating endoscopy owing to symptoms such as diarrhea, fever, GI bleeding, nausea, and vomiting. The role, if any, of sex in influencing the probability of systemic calcification is unclear. Milliner et al<sup>24</sup> reviewed their experience with 43 pediatric patients with end-stage renal disease who developed systemic calcifications. In a multivariate logistic regression model, the authors found that males were significantly more likely to develop systemic calcifications. In contrast, Stroehlein et al<sup>9</sup> found that all 6 patients who developed GMC in their series were females. These 6 patients were from the larger group of 41 patients (male and female in approximately equal proportions) who had a GI biopsy after a renal transplant.<sup>9</sup>

### INCIDENCE

The incidence of GMC is largely dependent on the population being studied. In Mulligan's<sup>14</sup> 1911 review of 35 patients with bone disease and metastatic calcification, 10 (29%) had gastric calcifications. Of 23 patients with chronic renal disease and metastatic calcifications, 3 (13%) had gastric calcifications.<sup>14</sup> In the aforementioned study of Stroehlein et al,<sup>9</sup> GMC was identified in 6 (14.6%) of 41 renal transplant patients who underwent a gastric biopsy. As one may anticipate, autopsy studies tend to yield significantly higher rates and dialysis seems to be contributory. Kuzela et al<sup>6</sup> found GMC in 25 (60%) of 42 chronically uremic, dialyzed patients, as opposed to 4 (29%) of 14 chronically uremic, nondialyzed patients. Greenson et al<sup>5</sup> found GMC in 18 (32.7%) of 55 transplant patients in contrast to 3 (5%) of 59 non-transplant patients with gastric ulcers. As is evident from the above studies, these are highly selected patient groups. The true incidence of GMC among an unselected group of patients without any of the risk factors in Table 1 is

**TABLE 1.** Summary of Clinical Conditions That Have Been Associated With Gastric Mucosal Calcifications

Primary Factor	Potential Contributing, Complicating, Associated or Underlying Factor(s)	Selected and/or Representative Reference(s)*
Hypercalcemia and/or hyperphosphatemia associated with	End stage renal disease, uremia, dialysis, and/or secondary hyperparathyroidism Primary hyperparathyroidism Sarcoidosis Multiple myeloma Hypervitaminosis D Tumor lysis syndrome complicating non-Hodgkin lymphoma Multiple nonmetabolic bone diseases, including metastatic malignancies Milk-Alkali syndrome Cope syndrome Hypervitaminosis A Hodgkin lymphoma	Kuzela et al, <sup>6</sup> Parfitt, <sup>15</sup> Milliner et al <sup>24</sup> Hwang et al, <sup>22</sup> Mulligan <sup>14</sup> Gezici et al <sup>17</sup> Reitz et al, <sup>23</sup> Esser et al <sup>21</sup> Corstens et al, <sup>18</sup> Mulligan <sup>14</sup> Avci et al <sup>2</sup> Mulligan <sup>14</sup> Castaigne et al <sup>13</sup> Delcourt et al <sup>19</sup> Bush and Dahms <sup>26</sup> Jayabalan and De Witt <sup>10</sup>
Elevated BUN (92 mg/dL) in the setting of eucalcemia/euposphatemia	Aluminum-containing antacids, sucralfate, CMV (biochemical parameters unstated)	Greenson et al <sup>5</sup>
Organ transplant (liver, kidney, pancreas, bone marrow, heart)	Renal failure and secondary hyperparathyroidism	Munoz et al <sup>7</sup>
Organ transplant (liver)	None (biochemical parameters unstated)	Strohlein et al <sup>9</sup>
Organ transplant (kidney)	Renal transplantation, aluminum-containing antacid therapy (biochemical parameters unstated)	Greenson et al, <sup>5</sup> Strohlein et al <sup>9</sup>
Gastric ulcers	Liver transplantation for hepatocellular carcinoma	Munoz et al <sup>7</sup>
Citrate-containing blood products	None	Rodina et al, <sup>16</sup> Inchiisi et al, <sup>28</sup> Niwa et al <sup>27</sup>
Gastric neoplasms	None	Tim et al <sup>3</sup>
Chronic atrophic gastritis and pernicious anemia	None	
Isotretinoin	None	Franco et al <sup>20</sup>

\*References are nonexhaustive.

An unspecified subset of these patients may have had renal failure and secondary hyperparathyroidism.

unclear. Furthermore, at least a subset of GMC seem to be reversible with normalization of biochemical parameters, rendering this determination in the general population an even more difficult proposition.<sup>13,15,19</sup> In the authors' experience with a large upper GI pathology service, gastric calcifications are seen in less than 0.1% of routine gastric biopsies obtained for a variety of indications.

## ETIOLOGY AND PATHOGENESIS

### Hypercalcemia and/or Hyperphosphatemia Attributable to Chronic Renal Disease, Uremia, Dialysis, Secondary Hyperparathyroidism

One or more of the above interrelated conditions can be identified in many patients with GMC. In most instances, these are examples of metastatic calcification. Metastatic calcification, the most common type of GMC, was originally described by Virchow<sup>1</sup> in 1855. In his index case, a young girl with malignant nodules involving the skeletal system was found to have renal calculi as well as calcific deposits in the stomach and lungs. The author postulated that the calcium deposits were attributable to an oversaturation of blood by calcium salts consequent to their removal from normal osseous depots, followed by their hematogenous transfer to susceptible peripheral sites. In Mulligan's<sup>14</sup> 1911 review of 88 previously reported cases of metastatic calcification, the underlying diseases were hypervitaminosis D (n = 9), primary

hyperparathyroidism (n = 21), uremia and chronic renal disease (n = 23), and bone diseases of varying types (n = 35). Virchow<sup>1</sup> noted the striking propensity for certain organs to develop metastatic calcification, most notably the kidneys, lungs, left cardiac chamber, and stomach. Several subsequent reports have confirmed this observation.<sup>6,14,24</sup> This has been attributed to the relative intracellular alkalinity at these sites,<sup>11,14,15</sup> given that the solubility of secondary calcium phosphate varies inversely with pH.<sup>15</sup> Hypercalcemia, hyperphosphatemia, and an elevated Ca × PO<sub>4</sub> product have been suggested as the most important factors in the development of metastatic calcifications. In most examples of soft tissue calcifications in chronic renal disease, the Ca × PO<sub>4</sub> product is > 70 (normal < 60).<sup>15</sup> Mulligan<sup>14</sup> outlined the well-known sequence for this mechanism: chronic renal disease results in an inability to excrete phosphate and hence hyperphosphatemia. A drop in calcium occurs as a compensatory mechanism to maintain the Ca × PO<sub>4</sub> product. The drop results in secondary hyperparathyroidism, which results in hypercalcemia, hyperphosphatemia, serum supersaturation, and the precipitation of calcium salts in the aforementioned susceptible tissues. Hyperphosphatemia seems to be the most significant factor,<sup>14,15</sup> as metastatic calcification have been observed even when calcium levels are depressed or normal.<sup>14</sup> Furthermore, vitamin D is well-known to potentially increase phosphate levels in patients with chronic renal disease, and may thus lead to visceral calcifications even

in the setting of eucalcemia.<sup>25</sup> Additionally, some studies have NOT found the probability of soft tissue calcification in chronically uremic patients to be related the  $\text{Ca} \times \text{PO}_4$  product.<sup>6</sup>

### Hypercalcemia and/or Hyperphosphatemia Associated With Other Conditions

Hypercalcemia and/or hyperphosphatemia that were not associated with the above conditions, and which have been related to GMC are also well documented in the literature. These diverse other conditions include primary hyperparathyroidism,<sup>14,22</sup> sarcoidosis,<sup>17</sup> multiple myeloma, and a wide variety of nonmetabolic bone diseases,<sup>14,21,23</sup> Tumor lysis syndrome associated with Non-Hodgkin lymphoma,<sup>2</sup> hypervitaminosis D,<sup>14,18</sup> Milk-alkali syndrome,<sup>13</sup> and Cope syndrome.<sup>19</sup> Bush and Dahms<sup>26</sup> reported a patient who developed metastatic calcification attributable to hypervitaminosis A. Hypervitaminosis A is well-known to cause bone disease<sup>29</sup> (Table 1). Variations of the previously outlined sequence, for example, the generation of phosphate and calcium from bone disease, are probably operational in cases of metastatic calcification that are not associated with chronic renal disease. Furthermore, experimental models suggest that severe hypercalcemia, hypervitaminosis D, and excess parathyroid hormone can, in of themselves, cause tissue damage and calcification.<sup>15</sup>

### Antacids, Sucralfate, and Organ Transplantation

Generalized calcification are occasionally encountered in the posttransplant setting, and the dominant etiologic factor is often unclear. The calcification in most of metastatic calcifications is calcium phosphate (although differences may exist between renal disease-related calcifications and hypercalcemia-related calcifications regarding the levels of inorganic constituents such as pyrophosphate and magnesium).<sup>30</sup> Greenson et al<sup>5</sup> performed an elemental analysis using x-ray dispersion on 2 samples from a single patient in a series of 28 transplant patients with GMC. Aluminum, phosphorus, calcium, and chlorine were present in the calcific deposits. Because antacids and sucralfate were the only aluminum-containing medications common to all their 28 patients, the authors concluded that the GMC was attributable to these medications. In the series of Stroehlein et al,<sup>9</sup> however, none of 6 renal transplant patients that developed GMC were taking sucralfate and only 1 of 6 was taking an aluminum-containing antacid (at low doses).

### Blood Products

Munoz et al<sup>7</sup> proposed a pathogenetic basis for metastatic calcification that was related to large use of blood products.<sup>7</sup> In their study of patients with soft tissue calcification after liver transplantation, the authors found that these patients were more likely to have received fresh frozen plasma, red blood cells, and elemental calcium. However, patients who developed calcification did not differ significantly from those that did not regarding

serum levels of calcium, magnesium, vitamin D, or phosphate levels. The authors proposed that the citrate in these blood products, in this particular clinical setting, causes hypocalcemia and the resultant sequence of secondary hyperparathyroidism, hypercalcemia, etc.<sup>9</sup> In this model, calcium is deposited in certain tissues if tissue injury or other unknown factors are concurrently present.<sup>9</sup>

### Others

GMC has also been associated with a wide variety of gastric epithelial and mesenchymal neoplasms<sup>16,27,28</sup> as well as medications such as isotretinoin.<sup>20</sup>

### MORPHOGENESIS

Electron microscopic analysis of GMC has shown them to consist of both small intracellular deposits and larger extracellular deposits.<sup>5</sup> The underlying mechanism by which a given cell or group of cells accumulate calcium is unclear. It has been suggested that calcium enters the cell by passive diffusion attributable to the concentration gradient across the gastric cell membrane, and that accumulation occurs when the ability to extrude these salts is exceeded.<sup>13</sup> In his unifying hypothesis, Parfitt<sup>15</sup> suggested that an initial calcifiable matrix is formed, on which calcium and phosphate ions bind, and that factors such as hyperphosphatemia, hypercalcemia, vitamin D, or parathyroid hormone excess, simply "facilitate this (binding) process."

These hypotheses notwithstanding, the precise mechanistic basis for GMC remains to be elucidated and will require future research.

### SUMMARY AND CONCLUSIONS

Calcific deposits in the gastric mucosa (GMC) are only rarely encountered in routine biopsies. They have been associated with a wide spectrum of clinical conditions, as summarized in Table 1. Metastatic calcification represents the most frequently encountered subtype, and refers to the deposition of calcium salts on largely normal tissues in the setting of an abnormal serum biochemical environment (hypercalcemia, hyperphosphatemia, and/or an elevated  $\text{Ca} \times \text{PO}_4$  product). The precise significance or mechanistic basis for GMC remains to be elucidated. However, in our opinion, their presence in gastric biopsies should be reported, as they may serve as an indicator for generalized metastatic calcification, especially in organs where they may be fatal, such as the heart.<sup>6</sup> Furthermore, some examples of systemic calcification are reversible with normalization of biochemical parameters, which highlights the need for pathologists to highlight this finding when encountered in a premortem gastric biopsy.

### REFERENCES

1. Virchow R. Kalk metastaten. *Virchows Arch Path Anat.* 1855;8:103–113.
2. Avci Z, Alioglu B, Canan O, et al. Calcification of the gastric mucosa associated with tumor lysis syndrome in a child with non-Hodgkin lymphoma. *J Pediatr Hematol Oncol.* 2006;28:307–310.

3. Tim LO, Hurwitz S, Tuch P. The endoscopic diagnosis of gastric calcification. *J Clin Gastroenterol.* 1982;4:213–215.
4. Hiba MR, Eaker EY. The white plaque represents gastric mucosal metastatic calcification, which stains as dark deposits in the submucosa. *Gastroenterology.* 2000;119:894, 1179.
5. Greenson JK, Trinidad SB, Pfeil SA, et al. Gastric mucosal calcinosis. Calcified aluminum phosphate deposits secondary to aluminum-containing antacids or sucralfate therapy in organ transplant patients. *Am J Surg Pathol.* 1993;17:45–50.
6. Kuzela DC, Huffer WE, Conger JD, et al. Soft tissue calcification in chronic dialysis patients. *Am J Pathol.* 1977;86:403–424.
7. Munoz SJ, Nagelberg SB, Green PJ, et al. Ectopic soft tissue calcium deposition following liver transplantation. *Hepatology.* 1988;8:476–483.
8. Saab S, Venkataramani A, Behling CA, et al. Gastric mucosal calcinosis in a patient with dyspepsia. *J Clin Gastroenterol.* 1996;22:156–164.
9. Stroehlein KB, Stroehlein JR, Kahan BD, et al. Gastric mucosal calcinosis in renal transplant patients. *Transplant Proc.* 1999;31:2124–2126.
10. Jayabalan V, De Witt B. Gastric calcification detected in vivo by 99mTc-pyrophosphate imaging. *Clin Nucl Med.* 1978;3:27–29.
11. Wells HG. Metastatic calcification. *Arch Intern Med.* 1915;15:574–580.
12. Walsh JS, Fairley JA. Calcifying disorders of the skin. *J Am Acad Dermatol.* 1995;33:693–706; quiz 707–710.
13. Castaigne C, Martin P, Blocklet D. Lung, gastric, and soft tissue uptake of Tc-99m MDP and Ga-67 citrate associated with hypercalcemia. *Clin Nucl Med.* 2003;28:467–471.
14. Mulligan RM. Metastatic calcification. *Arch Pathol.* 1947;43:177–230.
15. Parfitt AM. Soft tissue calcification in uremia. *Arch Intern Med.* 1969;124:544–556.
16. Rodina I, Zhdanova MM, Vorotilkin AI. Cancer of the gastric mucosa with calcification. *Med Annu.* 1961;39:128–129.
17. Gezici A, van Duijnhoven EM, Bakker SJ, et al. Lung and gastric uptake in bone scintigraphy of sarcoidosis. *J Nucl Med.* 1996;37:1530–1532.
18. Corstens F, Kerremans A, Claessens R. Resolution of massive technetium-99m methylene diphosphonate uptake in the stomach in vitamin D intoxication. *J Nucl Med.* 1986;27:219–222.
19. Delcourt E, Baudoux M, Neve P. Tc-99m-MDP bone scanning detection of gastric calcification. *Clin Nucl Med.* 1980;5:546–547.
20. Franco A, Hampton WR, Greenspan BS, et al. Gastric uptake of Tc-99m MDP in a child treated with isotretinoin. *Clin Nucl Med.* 1993;18:510–511.
21. Esser JP, Oei HY, Kwekkeboom DJ, et al. Diffuse lung and stomach uptake of Tc-99m oxidronate (HDP). *Clin Nucl Med.* 2003;28:845–846.
22. Hwang GJ, Lee JD, Park CY, et al. Reversible extraskeletal uptake of bone scanning in primary hyperparathyroidism. *J Nucl Med.* 1996;37:469–471.
23. Reitz MD, Vasinrapee P, Mishkin FS. Myocardial, pulmonary and gastric uptake of technetium-99m MDP in a patient with multiple myeloma and hypercalcemia. *Clin Nucl Med.* 1986;11:730.
24. Milliner DS, Zinsmeister AR, Lieberman E, et al. Soft tissue calcification in pediatric patients with end-stage renal disease. *Kidney Int.* 1990;38:931–936.
25. Mallick NP, Berlyne GM. Arterial calcification after vitamin D therapy in hyperphosphatemic renal failure. *Lancet.* 1968;2:1316–1318.
26. Bush ME, Dahms BB. Fatal hypervitaminosis A in a neonate. *Arch Pathol Lab Med.* 1984;108:838–842.
27. Niwa Y, Goto H, Hayakawa T, et al. Early gastric cancer with psammomatous calcification. *Hepatogastroenterology.* 1998;45:1527–1530.
28. Ichiishi E, Kogawa T, Takeda S, et al. Eight cases of gastric tumors with calcification. *Intern Med.* 1995;34:1038–1042.
29. Penniston KL, Tanumihardjo SA. The acute and chronic toxic effects of vitamin A. *Am J Clin Nutr.* 2006;83:191–201.
30. Alfrey AC, Solomons CC, Ciricillo J, et al. Extrasosseous calcification. Evidence for abnormal pyrophosphate metabolism in uremia. *J Clin Invest.* 1976;57:692–699.