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Metastatic Calcinosis of Gastric Mucosa

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Abstract

Calcinosis cutis refers to the deposition of calcium salts in the cutaneous and subcutaneous tissue and is frequently associated with inflammation. Gastric calcinosis can be classified into metastatic, dystrophic, and idiopathic; metastatic calcinosis is the most common type. In metastatic calcification, calcium salts are deposited in normal soft tissues in the setting of altered metabolism of serum calcium and phosphorus and is a rare and serious complication of chronic renal failure. The important factors contributing to the development of metastatic calcinosis are hypercalcemia, hyperphosphatemia, and an elevated calcium-phosphate product. The most striking feature of this diagnosis is the calcification around the large joints. While it mostly involves dermis of small and medium-sized vessels, it can rarely affect the mucosal layers of the gastrointestinal (GI) tract. Calcinosis presents as a marker for the presence of calcifications in other organs, such as heart or lung, which can be life-threatening. Patients rarely present with clinical symptoms of GI upset, dyspepsia, or epigastric pain that are attributed to calcinosis. If patients present with GI symptoms, infectious causes remain to be higher on the differential. We present a case of incidental finding of gastric mucosal calcinosis during the workup and treatment of dysphagia.

Keywords

metastatic calcinosis cutis, metastatic gastric calcinosis, chronic kidney disease, hypercalcemia, hyperphosphatemia

Case

A 49-year-old African American male with a history of chronic glomerulonephritis leading to end-stage renal disease followed by an initial renal transplant in 1980 with subsequent graft failure in 1991, requiring re-initiation of dialysis. He had a second transplant in 2016 and had stable graft function. Two years later, he started experiencing persistent worsening dysphagia and weight loss despite normal appetite. The vitals were stable, and the pertinent laboratory data included serum creatinine of 1.8 mg/dL (baseline 1.4-1.8 mg/dL), serum calcium 8.4 mg/dL, phosphorous 4.5 mg/dL, magnesium 1.4 mg/dL, parathyroid hormone 13.1 pg/mL, and vitamin D levels 46.4 ng/mL. Home medications included mycophenolate mofetil 500 mg twice daily, tacrolimus 1 mg twice daily, prednisone 5 mg once daily, aspirin 81 mg daily, carvedilol 3.125 mg twice daily, calcitriol 0.5 µg daily, calcium carbonate 500 mg daily, and magnesium oxide 400 mg daily. He was referred for esophagogastroduodenoscopy for the evaluation of dysphagia. Esophagogastroduodenoscopy showed extensive patchy exudates with underlying friable ulceration of the upper esophagus, erythema of antrum, and few nodular regions in the pre-pyloric area (Figures 1 and 2). Duodenal Villi showed extensive whitish tips. Subsequently, the pathology was consistent with *Candida esophagitis* and *Helicobacter pylori* gastritis that was treated appropriately.

The biopsies also revealed mucosal calcinosis in the gastric antrum and gastric body (Figures 3 and 4). The biopsy findings could be explained by the long-standing history of dialysis and could also be supported by the evidence of extensive calcification of small- and medium-sized arteries, including common iliac and external iliac arteries, heavily calcified bilateral native kidneys along with the calcification of prior transplanted kidney. His symptoms of dysphagia improved with the treatment of *Candida esophagitis* and *Helicobacter pylori* gastritis. During his follow-up visit, the patient did not endorse any symptoms of dysphagia.

Discussion

Calcinosis cutis refers to the deposition of calcium salts in the cutaneous and subcutaneous tissue and is frequently associated with inflammation. Based on the etiology of calcium deposition,

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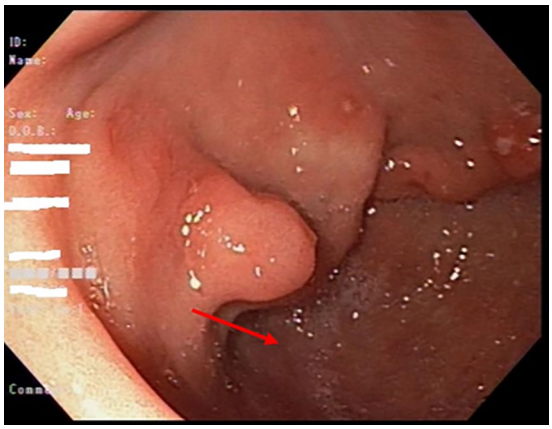

Figure 1. Calcinosis in mucosa of gastric antrum.

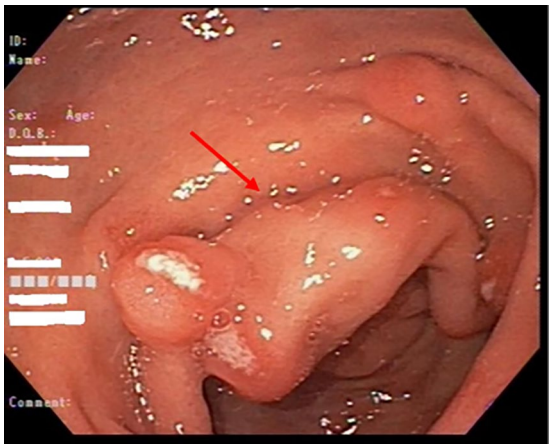

Figure 2. Calcinosis in mucosa of pre-pyloric region.

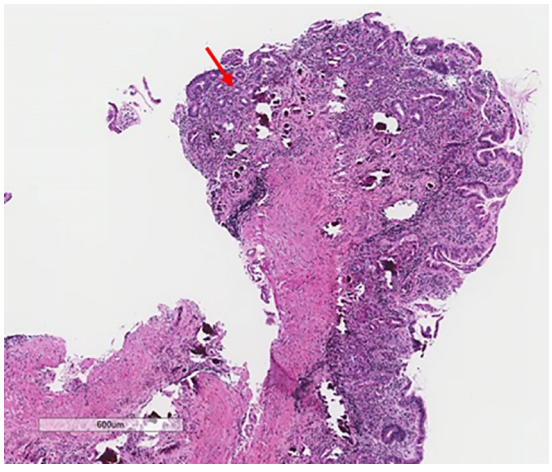

Figure 3. Hematoxylin and eosin stain 100×. Calcium deposits distributed along the lamina propria and under foveolar epithelium.

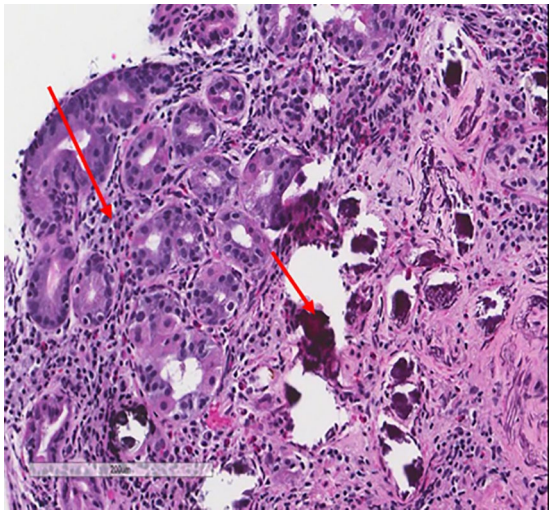

Figure 4. Hematoxylin and eosin stain 200×. Prominent cyanophilic calcium crystals arising from lamina propria vasculature. Concomitant chronic gastritis is present with increased lymphoplasmacytic infiltrates.

calcification is classified into 4 subtypes: dystrophic, metastatic, iatrogenic, and idiopathic.[1] Dystrophic calcification results from local tissue damage and deposition of salts in inflamed, and fibrotic tissue in the setting of normal calcium metabolism. In iatrogenic calcinosis, calcium salts are deposited as a result of therapeutic interventions for other diseases. Idiopathic calcification occurs with no identifiable cause, where calcifications occur in normal tissue with normal serum markers.[1-4] Various causes of calcification and their pathophysiology are described in Table 1. Our patient demonstrated metastatic calcinosis cutis, which is a diagnosis of exclusion and laboratory studies should be analyzed to rule out other diseases. Visceral calcinosis is normally asymptomatic and is usually detected incidentally in procedures performed for other conditions.

Though calcinosis of vascular media is the most common finding, it can rarely involve the mucosal layers of the GI tract causing ulcerations. Gastric calcinosis is classified into metastatic, dystrophic, and idiopathic; metastatic calcinosis is the most common type,[1] constituting about 70% of the reported cases. Given its insidious nature, the incidence of gastric calcifications depends on the patients being studied. In Mulligan's review of 23 chronic kidney disease patients with metastatic calcifications, 13% had gastric calcifications[5]; Stroehlein et al identified 14.6% of 41 renal transplant patients with gastric calcinosis via gastric biopsy.[6] However, in an autopsy study by Kuzela et al, 60% of chronically uremic, dialysis patients had calcification involving the stomach, and the higher incidence of gastric calcinosis in autopsied patients indicates that it does not contribute to the clinical course of the patient.[7]

In metastatic calcification, calcium salts are deposited in normal soft tissues in the setting of altered metabolism of

Table 1. Causes of Calcification.

Causes for calcification	Pathophysiology
Hyperparathyroidism	Hypocalcemia stimulates the secretion of the parathyroid hormone through the feedback mechanism resulting in secondary hyperparathyroidism and resorption of calcium and phosphorus from the bone
Sarcoidosis	Hypercalcemia due to increased 1,25-dihydroxyvitamin D results in soft tissue calcification
Renal failure	Hyperphosphatemia in chronic renal disease, interacts with calcium to form calcium phosphate product
Hemodialysis	Patients with end-stage renal disease are at risk for calcification due to mineral bone disorders
Tumor lysis syndrome (TLS)	TLS results in hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia; increased phosphorous binds with the calcium
Vitamin D intoxication	Vitamin D therapy increases phosphorus level in patients with chronic kidney disease, which also leads to visceral calcifications in the setting of normal calcium levels
Milk alkali syndrome	Milk alkali syndrome can lead to hypercalcemia and calcification
Fibroblast growth factor 23	Regulates the metabolism of vitamin D and phosphorous balance
Diabetes	Insulin resistance is a hallmark of inflammation
Smoking	Increases oxidative stress and inflammation

serum calcium and phosphorus.[7] Calciphylaxis or calcific uremic arteriolopathy is a life-threatening condition and should be considered as a differential diagnosis in patients with advanced kidney disease or end-stage renal disease presenting with such symptoms. It occurs when vascular calcinosis causes ischemia and necrosis of the skin, subcutaneous fat, and other organs.[8,9] Studies have shown that 40% to 80% of adults on maintenance dialysis have soft tissue calcinosis and has an incidence of 0.5% to 3%.[10-12] The calcification of internal visceral organs is clinically more insidious and rarely recognized before death. Autopsy findings from 1969 and 1977 demonstrated soft tissue and vascular calcifications in 50% to 80% of hemodialysis patients.[13] The most frequently involved sites are skin, peripheral blood vessels, cornea, conjunctiva, periarticular tissues, and it rarely involves the heart, lungs, stomach, and kidneys. This vascular and visceral involvement can lead to many complications, such as ischemic necrosis, cardiac arrhythmia, and respiratory failure.[10,14] In patients with advanced kidney disease, fibroblast growth factor 23 levels are elevated which possess phosphaturic property along with suppression of 1α-hydroxylase activity.[15]

The important factors contributing to the development of metastatic calcinosis are hypercalcemia, hyperphosphatemia, and an elevated calcium-phosphate product.[1] In chronic renal disease, the inability to excrete phosphorus lead to hyperphosphatemia. This interacts with calcium to form calcium phosphate product, dropping the serum calcium levels. This drop stimulates the secretion of the parathyroid hormone through the feedback mechanism and subsequently results in secondary hyperparathyroidism and resorption of calcium and phosphorus from the bone.[14,16] The elevated calcium-phosphate product (normal <60) and the supersaturation of calcium and phosphate ions in serum results in deposition of hydroxyapatite in nonvisceral structures, such as arteries, arterioles or skin, and deposition of an amorphous or microcrystalline compound in subcutaneous tissue and dermis of the visceral organs, mostly kidneys, lungs, cardiac, and stomach, due to these organs' relative intracellular alkalinity.[17,18] Hyperphosphatemia plays a significant role in the above mechanism; the size and number of calcifications correlate with the degree of elevated phosphorus level. The vascular lesions regress as the serum levels of calcium and phosphorus normalize; however, visceral calcification may persist.[12,13] Furthermore, vitamin D therapy increases phosphorus level in patients with chronic kidney disease, which also leads to visceral calcifications in the setting of normal calcium levels. The other conditions that cause hypercalcemia and/or hyperphosphatemia related to visceral calcifications include primary hyperparathyroidism, sarcoidosis, multiple myeloma, tumor lysis syndrome associated with non-Hodgkin lymphoma, leukemia, hypervitaminosis D, milk-alkali syndrome, Cope syndrome, and a wide variety of nonmetabolic bone diseases.[6,19-24]

Bone scintigraphy is the most sensitive imaging modality for detecting metastatic calcification as radiographic detection of microscopic calcification is difficult. Computed tomography scan is very sensitive in depicting the lesions as increased densities, and is used to evaluate the disease burden.[11,25,26] Lesion biopsy and histopathological examination remain the definitive diagnosis of calcinosis. Endoscopic evidence of gastric calcifications appears as 1- to 5-mm white flat plaques or nodules in the gastric fundus, body, and/or antrum.[27,28] Histologically, they present as amorphous basophilic deposits in superficial or deeper lamina propria or muscularis mucosa and may also have some other changes, such as mucosal edema, chronic active gastritis, reactive epithelial changes, and ulcerations.[1,5] Our patient presented with few nodular regions in the antrum and pre-pyloric area and biopsies confirmed the cyanophilic calcified deposits on hematoxylin and eosin staining (Figures 1-4).

Calcinosis presents as a marker for the presence of calcifications in other organs, such as heart or lung, which can be

life-threatening.[1,29] Patients rarely present with clinical symptoms of GI upset, dyspepsia, or epigastric pain that are attributed to calcinosis. If patients present with GI symptoms, infectious causes remain to be higher on the differential,[30] which is the case in our patient who was diagnosed with *Candida esophagitis* and *Helicobacter pylori* gastritis and resolution of symptoms of dysphagia with the appropriate treatment.

The appropriate treatment of gastric mucosal calcinosis is unclear and correcting serum calcium and phosphorus levels is imperative to prevent the progression of the disease. The management includes restricting daily calcium and phosphorus intake in the diet and using phosphate binders.[2,11] Sevelamer is a phosphate-binding polymer and helps in reducing the phosphorus load. In one study, sevelamer is shown to significantly prevent renal osteodystrophy and ectopic calcifications in adenine-induced renal failure rats.[13,31] The alternative medical therapies to modify serum calcium and phosphorus levels include bisphosphonates, both intravenous and oral preparations, calcimimetics (cinacalcet), and vitamin D analogues.[2,8] Sodium thiosulfate (STS) is a dialyzable calcium chelator that increases the solubility of calcium deposits; it has variable results in the treatment of calcinosis. While some cases showed moderate improvement in symptoms with STS and cinacalcet, some reports showed that STS did not appear to alter the calcium deposits.[32,33] In the case of calciphylaxis and severe elevation of serum parathyroid hormone with parathyroid hyperplasia, total parathyroidectomy without autotransplantation of gland tissue is the treatment of choice.[12,27]

Conclusion

In summary, metastatic calcinosis is a severe complication of chronic renal disease due to disruption in the metabolism of calcium and phosphorus. Failure of management of hyperphosphatemia in chronic renal failure leads to secondary hyperparathyroidism and precipitation of calcium products in multiple organs. Though calcinosis of vascular media is the most common finding, it can rarely involve the mucosal layers of the GI tract subsequently causing ulcerations and necrosis. Hence, the management of hyperphosphatemia with phosphate binders and a diet low in calcium and phosphorous is of paramount importance to prevent this condition in this patient population.

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Ethics Approval

Our institutions does not require ethical approval for reporting individual cases or case series.

Informed Consent

Verbal informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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