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 calcinosiSication, 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 esophagastroduodenoscopy for the evaluation of dysphagia. 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,
Calcification is classified into 4 subtypes: dystrophic, metastatic, iatrogenic, and idiopathic. 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. 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, 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; Stroehlein et al identified 14.6% of 41 renal transplant patients with gastric calcinosis via gastric biopsy. 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.

In metastatic calcification, calcium salts are deposited in normal soft tissues in the setting of altered metabolism of
serum calcium and phosphorus. Calcium and phosphorus from the bone. The elevated results in secondary hyperparathyroidism and resorption of calcium and phosphorus from the bone.14,16 The elevated hyperphosphatemia. This interacts with calcium to form calcium phosphate product, dropping the serum calcium levels.14,16

Causes for 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 |

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.15 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 ulcersations and necrosis. Hence, the management of hyperphosphatemia with phosphate binders and a diet low in calcium and phosphorus is of paramount importance to prevent this condition in this patient population.

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