Extraosseous Calcification of the Esophagus: Clinicopathologic Correlates of Esophageal Mucosal Calcinosis

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ABSTRACT

Esophageal mucosal calcinosis (EMC) is a rare cause of dysphagia with high morbidity. We present a patient who experienced melena and 3 months of solid and liquid dysphagia along with bilateral lower extremity pain, erythema, and edema later determined to be calcific uremic arteriolopathy (CUA), or calciphylaxis. An esophagogastroduodenoscopy revealed nodularity and linear ulcerations in the upper third of the esophagus. Histology showed active inflammation and ulceration with small foci of subepithelial and intraepithelial calcification consistent with EMC. There is no known treatment for this disorder. Sodium thiosulfate, typically used to treat CUA, did not improve her dysphagia.

INTRODUCTION

Calcific uremic arteriolopathy (CUA), also known as calciphylaxis, and other forms of extraosseous calcification are thought to be the end result of disequilibrium among metabolic substrates leading to oxidative stress, inflammation, and subsequent calcium deposition. Its clinical consequences can be profound depending on the organ involved, with notable examples including painful necrotic skin ulcerations, coronary ischemia, and myriad abdominal symptoms. Esophageal mucosal calcinosis is a rare gastrointestinal (GI) finding and can cause dysphagia and upper GI bleeding.

CASE REPORT

A 76-year-old woman with pertinent past medical history of diabetes mellitus type 2 complicated by end-stage renal disease (on intermittent hemodialysis for 6 years) with secondary hyperparathyroidism presented to our institution for further work-up of melena. She was initially admitted to an outside hospital with shortness of breath that was later determined to be secondary to pneumonia. Review of systems was notable for a 3-month history of progressive solid and liquid food dysphagia without odynophagia and bilateral lower extremity pain, erythema, and edema (later determined by biopsy to be CUA). Review of systems and physical exam were negative for Raynaud’s phenomenon, sclerodactyly, and telangiectasias, suggesting against CREST/systemic sclerosis. An esophagogastroduodenoscopy showed nodularity and linear ulcerations in the upper third of the esophagus 27–32 cm from the incisors (Figure 1). Central and peripheral biopsies of the ulcers were obtained.

Histological examination showed the presence of active inflammation and ulceration without evidence of dysplasia or malignancy. Immunohistochemical stains for cytomegalovirus and herpes simplex virus and a periodic acid-Schiff stain for fungal organisms were negative. However, small foci of subepithelial and intraepithelial calcification
were identified, consistent with a diagnosis of esophageal mucosal calcinosis (Figure 2). Gastric biopsies of a 3-mm ulcer also showed evidence of mucosal calcinosis.

DISCUSSION

Extraosseous calcification is thought to involve a complex interplay between serum calcium and phosphate equilibrium, vitamins K and D, calcification inhibitors, osteogenic transdifferentiation, clearance of calcified debris, and parathyroid function.\(^1\) Calcification of visceral and soft tissue is classified into 4 distinct categories based on causality: dystrophic, iatrogenic, metastatic, and idiopathic.\(^2\) Dystrophic calcification refers to calcium salt deposition in fibrotic or inflamed tissue in the absence of hypercalcemia or hyperphosphatemia. Iatrogenic calcification occurs as a direct result of a pharmacologic or therapeutic intervention (eg, calcium supplementation). Idiopathic calcification occurs in normal tissue in the absence of a serum biochemical antecedent. Finally, metastatic calcification is the end result of hyperphosphatemia or hypercalcemia in normal tissue (typically in patients with end-stage renal disease, sarcoidosis, secondary hyperparathyroidism). Calcification has been rarely reported to occur in the stomach (gastric mucosal calcinosis), a phenomena predominantly attributed to metastatic calcification.\(^3\) However, we found only one abstract and one published case report describing mucosal calcinosis in the esophagus.\(^4,5\) While extraosseous calcification has been noted in multiple organs, vascular calcification is of paramount importance given its correlation with cardiovascular mortality.\(^6\)

Given our patient’s history, we believe her clinicopathologic presentation could be categorized as dystrophic calcification (deposition of calcium salts in ulcerated tissue), iatrogenic calcification (secondary to pill esophagitis from a multivitamin she was prescribed), or metastatic calcification (while the patient did not have hyperphosphatemia/hypercalcemia at the time of diagnosis, she had hyperphosphatemia in the past, which would correlate with her newly diagnosed CUA of her lower extremities), leading to esophageal mucosal calcinosis in the context of end-stage renal disease, secondary hyperparathyroidism, and newly diagnosed CUA. Her labs were notable for normal serum calcium and serum phosphate, although 3 months prior her serum phosphate was above normal (6.1 mg/dL). While the clinical significance of categorization is likely academic, all efforts should be made to reduce the offending agents and inciting events.

The rarity of this diagnosis is made apparent by the paucity of scientific discourse on this topic. A review of the literature identified two cases, both noting a similar case of dysphagia secondary to esophageal calcinosis in a patient with end-stage renal disease.\(^4,5\) Our patient began treatment with sodium thiosulfate (which theoretically increases the solubility of calcium deposits) prior to discharge for CUA.\(^7\) While sodium thiosulfate administered intravenously 3 times/week improved her CUA, her dysphagia did not improve. Further endoscopic evaluation and assessment of motility was deferred as the patient was transitioned to hospice.

Figure 1. Nodularity and ulceration in the upper esophagus.

Figure 2. Immunohistochemical stain showing (A) abundant dystrophic calcification within fibrinopurulent debris at the ulcer site (200x), (B) intact squamous mucosa with focal subepithelial calcification (200x), and (C) a detached fragment of squamous epithelium with intraepithelial calcification (400x).
DISCLOSURES

Author contributions: A. Garber wrote the manuscript. Z. Arora and N. Welch edited the manuscript. J. Lapinski provided the pathology images and edited the manuscript. C. Burke edited the manuscript and is the article guarantor.

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