Gastrointestinal Bleeding Secondary to Calciphylaxis

Patient: Female, 66
Final Diagnosis: Calciphylaxis
Symptoms: Gastrointestinal haemorrhage
Medication: None
Clinical Procedure: Hemodialysis • blood transfusions
Specialty: Gastroenterology and Hepatology

Objective: Rare disease
Background: Calciphylaxis is associated with a high mortality that approaches 80%. The diagnosis is usually made when obvious skin lesions (painful violaceous mottling of the skin) are present. However, visceral involvement is rare.

We present a case of calciphylaxis leading to lower gastrointestinal (GI) bleeding and rectal ulceration of the GI mucosa.

Case Report: A 66-year-old woman with past medical history of diabetes mellitus, hypertension, end-stage renal disease (ESRD), recently diagnosed ovarian cancer, and on hemodialysis (HD) presented with painful black necrotic eschar on both legs. The radiograph of the legs demonstrated extensive calcification of the lower extremity arteries. The hospital course was complicated with lower GI bleeding. A CT scan of the abdomen revealed severe circumferential calcification of the abdominal aorta, celiac artery, and superior and inferior mesenteric arteries and their branches. Colonoscopy revealed severe rectal necrosis. She was deemed to be a poor surgical candidate due to comorbidities and presence of extensive vascular calcifications. Recurrent episodes of profuse GI bleeding were managed conservatively with blood transfusion as needed.

Following her diagnosis of calciphylaxis, supplementation with vitamin D and calcium containing phosphate binders was stopped. She was started on daily hemodialysis with low calcium dialysate bath as well as intravenous sodium thiosulphate. The clinical condition of the patient deteriorated. The patient died secondary to multiorgan failure.

Conclusions: Calciphylaxis leading to intestinal ischemia/perforation should be considered in the differential diagnosis in ESRD on HD presenting with abdominal pain or GI bleeding.

MeSH Keywords: Calciphylaxis • Gastrointestinal Diseases • Vascular Calcification

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Background

Calciphylaxis was first described in 1961 in rat models by Selye [1]. The first human example of calciphylaxis was described in 1968 [2]. It is characterized by calcification of the intima media of the small arteries and arterioles with subsequent small vessel thrombosis, endovascular fibrosis, and downstream tissue ischemia [2,3].

The most common presentation is the painful violaceous motting of the skin, resembling livedo reticularis [2,4]. However, calciphylaxis rarely manifests with gastrointestinal complications [5]. We present a case of calciphylaxis leading to rare visceral complications: intestinal ischemia, lower gastrointestinal bleeding, and ulceration of the gastro-intestinal mucosa.

Case Report

A 66-year-old woman with past medical history of diabetes mellitus, hypertension, end-stage renal disease on hemodialysis (via tunneled catheter), and recently diagnosed ovarian cancer presented to our hospital with complaints of painful rash on bilateral lower extremities. Her respiratory, cardiovascular, abdominal, and neurological exam results were unremarkable. Skin examination demonstrated black necrotic eschar on bilateral lower extremities (Figure 1A, 1B). The radiograph of the legs demonstrated extensive calcification of the lower-extremity arteries (Figure 1C, 1D).

A skin biopsy was not performed because of the clinically evident disease consistent with calciphylaxis. Our patient was particularly unusual because she had elevated parathyroid hormone (166 pg/ml), low calcium (7.9 mg/dl), normal phosphorus (2.6 mg/dl), and low calcium and phosphorus product. The highest calcium level in our hospital while the patient was on HD was 8.6 mg/dl (reference, 8.6–10.2 mg/dl) and the highest phosphate level was 5.2 mg/dl (reference, 2.3–4.7 mg/dl). The level of 25-hydroxy vitamin D was 8.6 ng/ml. We hemodialyzed her 5-6 times a week for 4 hours per day. We were not able to give her cinacalcet because she had low calcium and low phosphate due to poor oral intake. Supplementation with vitamin D and calcium containing phosphate binders was stopped.

The hospital course was complicated with an episode of lower gastrointestinal (GI) bleed leading to a drop in hemoglobin to 6.3 g/dl. Following the lower GI bleed, she underwent a CT scan of the abdomen/pelvis, which demonstrated severe circumferential calcification of the abdominal aorta and all its branches – celiac artery, superior and inferior mesenteric arteries and their branches – and extensive pneumoperitoneum with no evidence of extravasation of the contrast (Figure 2A, 2B). She also underwent colonoscopy, which revealed severe rectal ulceration extending up to the muscularis mucosa with rectal necrosis (Figure 3). The procedure was terminated because of the risk of perforation. No histologic specimens could be obtained.

We considered colonic resection for the rectal ulceration; however, she was deemed to be a poor candidate for surgery due to comorbidities and presence of extensive vascular calcifications, which would have resulted in poor wound healing. The patient continued to have recurrent episodes of GI bleeding. We continued to manage her conservatively with repeated blood transfusions whenever the hemoglobin dropped below 7 g/dl.

The patient was on broad-spectrum antibiotics (levofloxacin, metronidazole, cefepime, piperacillin-tazobactam, and vancomycin) and antifungals (flucconazole and later micafungin) due to the extensive skin lesions. Hyperbaric oxygen therapy was given. We attempted intravenous sodium thiosulfate along with hemodialysis, as a management strategy for calciphylaxis. There have been recent case reports of intradermal sodium thiosulfate injections that led to improvement of the skin lesions [6]. We combined lidocaine with sodium thiosulfate and injected them intradermally around the areas that were violaceous, after obtaining consent from the patient and the health care proxy. Although it improved the pain, which could have been due to the lidocaine component of the injection, it led to worsening of the skin lesions, leading to abscess formation at the site of the injection.

Clinical condition of the patient deteriorated and the patient subsequently died secondary to multiorgan failure, likely secondary to calciphylaxis and cardiopulmonary arrest.

Discussion

Calciphylaxis is a rare disease, also known as metastatic calcification [7]. Cutaneous purpura and necrosis are the cardinal features of calciphylaxis [8]. Hence, dermatologists can play a key role in making an early diagnosis. There has been a case report where a patient with calciphylaxis presented with herpes simplex viral lesions [9]. Thus, presence of concomitant conditions incidentally is unfortunate and can lead to missing the correct diagnosis of calciphylaxis [9]. In such cases, the actual diagnosis is often not made until skin biopsy is performed. Biopsy reveals extensive deposits of calcium within the walls of blood vessels [9,10]. Differential diagnosis includes other vasculitides, such as polyarteritis nodosa, Churg-Strauss syndrome, Henoch-Schönlein purpura, Wegener’s granulomatosis, Takayasu arteritis, giant cell arteritis, disseminated intravascular coagulation, warfarin-induced skin necrosis, anti-phospholipid antibody syndrome, panniculitides, deep fungal infections, necrotizing fasciitis, and cholesterol embolization with superadded infection [11].
Figure 1. (A, B) Black necrotic eschar on bilateral lower extremities. (C, D) Radiograph of legs showed extensive calcification of the lower extremity arteries.
The pathogenesis of calciphylaxis is unclear. However, the proposed mechanism is that the presence of hyperparathyroidism, hyperphosphatemia, and high calcium-phosphate product in the uremic milieu down-regulates the inhibitors of vascular calcification. The ensuing vascular calcification leads to vasocostriction, which ultimately leads to decreased distal perfusion and ischemic manifestations [12]. Secondary hyperparathyroidism and disturbances in the metabolism of calcium and phosphate are thought to be the risk factors for calciphylaxis; therefore, it is more prevalent in patients with chronic renal failure on hemodialysis [1]. There is often marked elevation in the serum calcium, phosphate, and intact parathormone levels; however, absence of these findings does not preclude the diagnosis [9]. Radiographically, “pipe stem” calcification of the arteries and arterioles can be seen, as was seen in our patient (Figure 1C, 1D). Initially, patients with end-stage renal disease on hemodialysis present with violaceous skin lesions, but further manifestations depend upon the area of compromised blood supply. It ranges from central nervous system manifestations due to compromised blood supply to the brain parenchyma, to involvement of the visceral organs, which is rare. There have been very few reported cases of patients with gastrointestinal complications of calciphylaxis [13]. Coates et al. described 16 patients with calciphylaxis; the cause of death in 2 of these patients was gastrointestinal hemorrhage [14]. Gastrointestinal manifestations can include mucosal edema, diffuse ulcer formation, and bowel perforation arising from bowel infarction. Intestinal ischemia leading to gastrointestinal bleeding is a common presentation in these patients. Rarely, there can be an elevation of the liver function tests from involvement of the portal vein and hepatic arteries, leading to hepatic ischemia [15]. Although the exact etiology of gastrointestinal bleeding in our patient could not be determined, the presence of extensive vascular calcification, multiple stenotic areas in the artery and its tributaries, and other overt manifestations of calciphylaxis led us to believe calciphylaxis was the cause of bleeding.

Figure 2. (A, B) CT scan of the abdomen demonstrating severe circumferential calcification of the abdominal aorta, celiac artery, superior and inferior mesenteric arteries and their branches (stars highlight areas of extensive calcification along the visceral organs, arrow heads and arrows indicate extensive calcification of all the arteries within the abdomen).

Figure 3. Colonoscopy demonstrating severe rectal ulceration extending up to the muscularis mucosa with rectal necrosis.
We considered surgical resection of the ulcerated colon in our patient; however, it was not pursued further. The chances of healing of the resected margins were remote because of widespread calciphylaxis. Nieves et al. reported a case in which the colon was resected but the incisions did not heal and the patient eventually died of sepsis [15].

Management of gastrointestinal bleeding in patients with calciphylaxis can thus be done with the resection of the intestinal segment if the disease is not widespread and the long-term prognosis is good. Proton pump inhibitors can be used to manage the stress ulceration. Ablative therapies can be used if the area of bleeding is accessible and ablable. Conservative management with blood transfusion as needed is usually pursued after exhaustion of definitive measures to stop the cause of bleeding.

Supportive treatment is the mainstay of management of systemic calciphylaxis [12]. Sodium thiosulphate has emerged as a novel treatment modality for the management of calciphylaxis. It binds to calcium and forms calcium thiosulphate, which can later be dialyzed. Some studies have shown that it increases the calcium solubility and inhibits the precipitation of calcium in tissues [2,6]. Although intravenous sodium thiosulphate has been the preferred route of treatment, a literature review revealed intravascular injections of sodium thiosulphate as an emerging new experimental treatment modality for cutaneous lesions [6]. Patients who received sodium thiosulphate has been reported to produce a good response within a few weeks [2,6], but it did not help in our case. Pamidronate has also been used for managing calciphylaxis [16–18]. Hyperbaric treatment has been tried in patients to assist with wound healing [19], and parathyroidectomy has also been attempted [9,12]. Normalization of the abnormal calcium and phosphorus levels can also be helped by diet, binding agents, and low-calcium bath dialysate [9].

Conclusions

Calciphylaxis is associated with a very high mortality that approaches 80% [6,20]. The diagnosis is usually made when the obvious skin lesions are present. However, visceral involvement is rare. It should be considered in the differential diagnosis in end-stage renal disease patients (on hemodialysis) presenting with abdominal pain or gastrointestinal bleeding.

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