Kidney Medicine

Isolated Mesenteric Calciphylaxis With Ischemic Colitis in a Hemodialysis Patient Without Active Cutaneous Calciphylaxis: A Case Report of Calcific Uremic Arteriolopathy

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Calciphylaxis, also known as calcific uremic arteriolopathy, is a devastating systemic disease most commonly associated with chronic kidney failure. Its hallmark histopathologic features of small-vessel calcification, intimal hyperplasia, and microthrombi lead to microvascular occlusion and tissue necrosis. Clinically, it typically presents with painful cutaneous lesions that may be distal or proximal, with proximal lesions associated with higher mortality. Visceral involvement in this disease process is rare and in such case reports, all patients have coincident active cutaneous lesions. We present a case of a man in his 40s receiving hemodialysis presenting with mesenteric calciphylaxis complicated by ischemic colitis without active cutaneous lesions. Treatment consisted of sodium thiosulfate, vitamin K, and surgical resection. He previously had penile calciphylaxis treated with 3 months of sodium thiosulfate therapy and optimization of his serum calcium, phosphate, and parathyroid hormone levels. His penile calciphylaxis healed 12 months before his presentation with mesenteric calciphylaxis. This is the first known case report of isolated mesenteric calciphylaxis. It raises a number of clinical dilemmas, including duration of sodium thiosulfate use, monitoring for disease activity, and suitability for future kidney transplantation.

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INTRODUCTION

Calciphylaxis, also known as calcific uremic arteriolopathy (CUA), is a systemic disease most commonly associated with chronic kidney failure. It has also been described in patients with chronic kidney disease and kidney transplant recipients, with diabetes, rapid weight loss, and elevated calcium, phosphate, and parathyroid hormone (PTH) levels being risk factors.[1,2] In North America, the estimated incidence of CUA is 3.5 new cases per 1,000 patient-years among patients with kidney failure receiving hemodialysis. The outcomes remain poor, with mortality of 27% at 6 months and 45% at 12 months, and sepsis being the leading cause of death.[2]

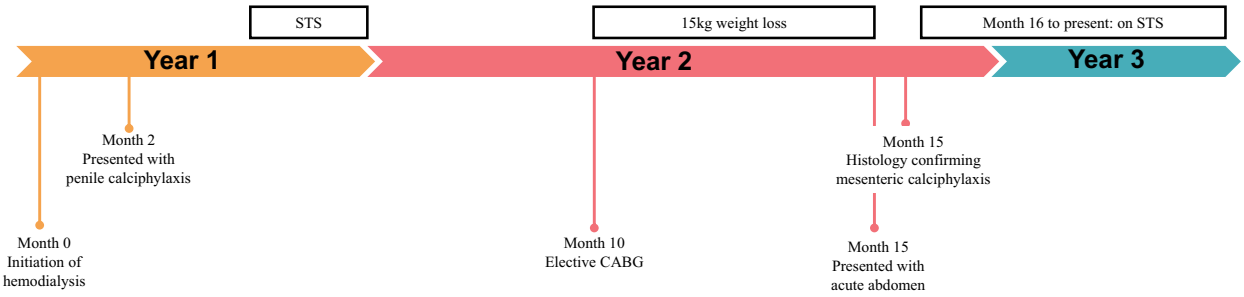
A recent systematic review showed that the location of CUA influenced clinical outcome; proximal lesions had a higher mortality rate of 60.3% to 70% compared with distal lesions with a mortality rate of 46.9% to 47.7%.[3] The typical cutaneous presentation is with painful skin lesions,[4] with histology showing vascular calcification of small and medium-sized arteries and arterioles, intimal hyperplasia, and microthrombi.[5] There are reports of visceral calciphylaxis occurring in patients with active cutaneous lesions, and these have all been fatal.[1,6–12] We present a hemodialysis patient presenting with mesenteric calciphylaxis without active cutaneous disease.

CASE REPORT

The patient was a white man in his 40s with chronic kidney failure presumed secondary to long-standing type 2 diabetes that had been present for 20 years. Before dialysis initiation, he had metabolic bone disease, with previous tibia and femur fractures. Two months after initiation of hemodialysis, he presented with penile calciphylaxis. Histopathologic examination showed areas of necrosis with adjacent organizing granulation tissue and an occasional artery exhibiting mural calcification and prominent fibrointimal thickening with almost complete luminal occlusion. It was treated with multiple surgical debridements, split skin grafts, and a month of sodium thiosulfate therapy, with complete resolution.

The patient's other history included coronary artery disease with a coronary artery bypass, hypertension, hyperlipidemia, obstructive sleep apnea, hypothyroidism, and depression. He was a reformed smoker with a 25–pack-year history. His body mass index was 26 kg/m^2, with weight of 75 kg. There was a 15-kg weight loss following cardiac bypass in a period of 5 months before his current presentation. Medications included cinacalcet, lanthanum, calcitriol, aspirin, rosuvastatin, perindopril, metoprolol, thyroxine, fluoxetine, levemir, and epoetin lambda. Corrected serum calcium, phosphate, and PTH levels were 9.26 mg/dL, 7.18 mg/dL, and 114.3 pg/mL, respectively, 14 months after initiation of hemodialysis. Figure 1 demonstrates the trend of his metabolic results.

Thirteen months after the patient's initial presentation of penile calciphylaxis, he presented with an acute abdomen. Computed tomography of the abdomen demonstrated free air and fluid throughout the peritoneal cavity. Laparotomy demonstrated a perforated caecum



Month / Serum	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Parathyroid hormone (pg/mL)	105.7	N/A	155.7	133	N/A	N/A	217.9	109.4	62.3	93.4	88.7	117	114.3	108.5	339.6	91.5	37.7	21.7	27.4	99.1
Corrected Calcium (mg/dL)	9.82	10.14	9.90	10.14	N/A	9.42	8.90	9.14	8.42	9.66	9.14	9.86	9.26	8.70	10.30	11.26	9.94	9.98	9.82	9.7
Phosphate (mg/dL)	2.91	4.96	3.10	4.06	N/A	6.13	4.55	5.95	6.78	5.39	6.41	7.37	7.18	7.62	4.89	4.68	7.40	3.65	10.34	9.76
Alkaline phosphatase (U/L)	112	171	137	N/A	N/A	138	115	120	80	114	109	112	108	109	450	319	289	353	338	370

Figure 1. Timeline shows progression of events that demonstrate parathyroid hormone (PTH), corrected calcium, phosphate, and alkaline phosphatase levels from initiation of hemodialysis (month 0) to month 21. The normal reference ranges are as follows: PTH, 7.5 to 51.9 pg/mL; serum corrected calcium, 8.42 to 10.42 mg/dL; serum phosphate, 2.32 to 4.65 mg/dL; and alkaline phosphatase, 30 to 110 U/L. The acceptable upper threshold for PTH level in chronic kidney failure receiving dialysis is 2 to 9 times the upper limit of normal for an assay.[18] Conversion factors for units: corrected calcium in mg/dL to mmol/L, ×0.2495; serum phosphate in mg/dL to mmol/L, ×0.3229. Abbreviations: STS, sodium thiosulfate; N/A, not available.

with an indurated mass at the cecal pole. Ileocolic resection and end-ileostomy were performed.

Histologic examination of the resected bowel showed architectural simplification and inflammation within the bowel mucosa and mesenteric arterial narrowing associated with mural calcifications and intimal/medial hyperplasia consistent with CUA (Fig 2). The patient's vitamin K levels were reported low at 0.09 (reference range, 0.14-1.17) ng/mL. He was started on 25 g of intravenous sodium thiosulfate and 10 mg of intravenous vitamin K 3 times a week during hemodialysis. His calcium dialysate bath remained the same at 5.01 mg/dL. Calcitriol and cinacalcet treatment were ceased. His corrected serum calcium, phosphate, and PTH levels ranged from 8.70 to 11.26 mg/dL, 4.68 to 10.34 mg/dL, and 21.7 to 339.6 mg/mL, respectively, following his resection (Fig 1). His incision sites healed well and to date, there has been no relapse of CUA.

DISCUSSION

CUA typically presents as painful skin lesions, initially as induration, subcutaneous plaques, nodules, livedo, or purpura before becoming malodorous ulcers with black eschars.[4] The main cutaneous histopathologic findings are

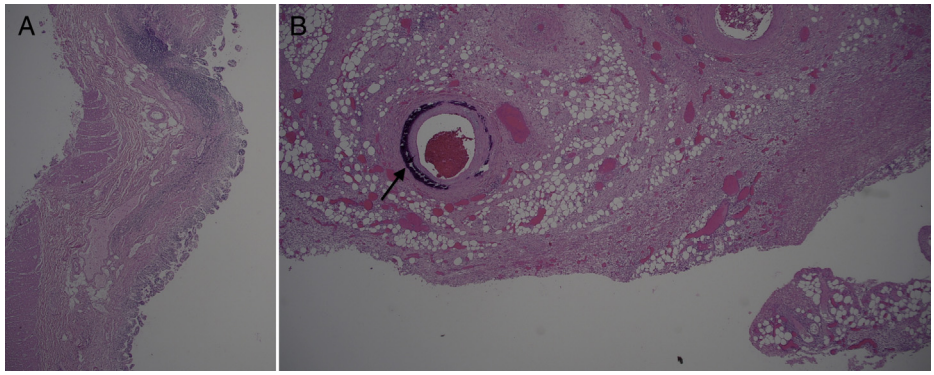


Figure 2. (A) Architectural simplification and associated inflammation in bowel wall indicating ischemia (hematoxylin and eosin stain; original magnification, ×4). (B) A mesenteric vessel shows circumferential mural calcifications and intimal/medial hyperplasia narrowing the lumen (black arrow) (hematoxylin and eosin stain; original magnification, ×10).

vascular calcification of small and medium-sized arteries and arterioles, intimal hyperplasia, and microthrombi, which lead to occlusion, dermal-epidermal separation, necrosis, and ulceration.[5] There are case series of biopsy-confirmed mesenteric calciphylaxis in hemodialysis patients presenting with intestinal ulceration, bleeding, or ischemia. This challenges the concept that CUA is a disorder of cutaneous microvascular occlusion. Of the 8 reported cases of biopsy-proven mesenteric calciphylaxis in the dialysis population in the English literature,[1,7-12] 7 patients were female. Half the cases had chronic kidney failure due to diabetes, with the mean age of 54 years. All 8 patients had cutaneous skin lesions and died during or within 3 months after hospital discharge. This is in contrast with our patient, who is a man, is approximately 10 years younger than the mean age, and with no active cutaneous lesions of CUA.

The cause of calciphylaxis is not well understood. The pathologic lesions include calcification of the small and medium-sized arteries and arterioles, intimal hyperplasia, and microthrombi formation, which results in ischemia and necrosis. While typically presenting in the skin, we presume the pathologic process occurring in the mesentery circulation is the same. However, the presentation of these calciphylactic lesions in different organs at different times is not understood.

Apart from chronic kidney failure, risk factors for CUA include diabetes; rapid weight loss; medications including warfarin, calcium, and vitamin D analogues; and biochemical evidence of elevated serum calcium, phosphate, PTH, and alkaline phosphatase levels have been associated with increased risk.[1,2] Vitamin K deficiency has also been implicated as a risk factor for CUA, which is likely multifactorial in the hemodialysis population. Previous studies have demonstrated subclinical vitamin K deficiency in hemodialysis patients due to dietary restriction that limits vitamin K ingestion by following a low-potassium and low-phosphate diet.[13] In addition, in a cohort study of 20 hemodialysis patients with and without CUA, vitamin K deficiency was associated with lower relative carboxylated matrix G1a protein concentration, which is a potent inhibitor of vascular calcification.[14] Our patient was receiving treatment with vitamin D analogues for management of his high fracture risk and had relatively low vitamin K levels.

In addition to wound care, analgesia, and elimination of risk factors, evidence-based therapeutic options are limited. Sodium thiosulfate is frequently used as first-line treatment but there has not been a prospective trial to evaluate its efficacy. The current recommendation for hemodialysis patients with CUA is 25 g of sodium thiosulfate intravenously after each dialysis session for 3 months.[15] This regimen is based on the largest retrospective study involving 53 hemodialysis patients who received intravenous sodium thiosulfate at a median dose of 25 g with a median of 38 doses. Complete remission was observed in 26% of patients, and 19% had marked improvement in skin lesions.[16] Of the 8 reported cases, only 1 case was administered sodium thiosulfate treatment. Despite this, the patient died of sepsis and intestinal bleeding.[11] It can be speculated that the reasons for not administering sodium thiosulfate in other cases are that the patients were too unwell to receive sodium thiosulfate or the diagnosis of bowel calciphylaxis was not considered. In our patient, he was managed with surgical resection of ischemic bowel. In addition, 25 g of intravenous sodium thiosulfate and 10 mg of intravenous vitamin K were initiated on hemodialysis 3 times a week. The patient remains on vitamin K and sodium thiosulfate treatment at 9 months post presentation with mesenteric calciphylaxis. It is uncertain when it should be stopped given the difficulty monitoring for disease activity with mesenteric calciphylaxis compared with cutaneous calciphylactic lesions.

The outcomes for mesenteric calciphylaxis with ischemic bowel in patients receiving dialysis and with a kidney transplant are universally poor, with mortality reported approaching 100%. Of the 10 case reports, only 1 patient with a kidney transplant survived. Half the patients died of sepsis, with 2 patients who died of myocardial infarction and 1 patient who died of a gastrointestinal bleed and pneumonia, respectively.[17]

Mesenteric calciphylaxis should be considered as a differential diagnosis for intestinal bleeding or perforation in patients with underlying risk factors for developing CUA. This is the first case we are aware of mesenteric calciphylaxis presenting with ischemic colitis in a patient who does not present with the typical cutaneous lesions. Interestingly, the patient had cutaneous penile calciphylaxis previously that was healed at the time of the current presentation. This case raises the clinical question of the duration to continue sodium thiosulfate and vitamin K treatment, monitoring of disease activity, and whether these patients should be considered for a kidney transplant.

ARTICLE INFORMATION

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