Clinical Kidney Journal, 2021, vol. 14, no. 1, 435–438

doi: 10.1093/ckj/sfz190
Advance Access Publication Date: 18 January 2020
Exceptional Case

EXCEPTIONAL CASE

Calciphylaxis or vascular oxalosis?

Skye El-Saygeh[1], Douglas Roese[2] and Sharon M. Moe[1]

[1]Division of Nephrology, Indiana University School of Medicine, Indianapolis, IN, USA and [2]Department of Surgery, Columbus Regional Hospital, Columbus, IN, USA

Correspondence to: Sharon M. Moe; E-mail: smoe@iu.edu

ABSTRACT

We report the case of a 31-year-old female with primary hyperoxaluria type 1 with end-stage kidney disease who developed severe peripheral vascular disease leading to limb amputation initially thought to be secondary to calciphylaxis. However, polarized review of the pathologic specimen revealed calcium oxalate deposition in the lumen of blood vessels. This unusual presentation of systemic oxalosis demonstrates the adverse consequences of elevations of serum oxalate in patients with hyperoxaluria and that levels can acutely worsen with abrupt onset of kidney failure.

Keywords: calciphylaxis, hyperoxaluria, oxalosis, primary hyperoxaluria, primary hyperoxaluria type 1, vascular oxalosis

BACKGROUND

Primary hyperoxaluria (PH) is a rare autosomal recessive disorder of oxalate overproduction due to genetic defects in enzymes critical in the metabolism of oxalate in the liver. PH type 1 (PH-1), the most severe type, is caused by the deficiency of the liver-specific peroxisomal enzyme alanine-glyoxylate aminotransferase (AGXT) [1]. Clinical presentation ranges from infantile nephrocalcinosis and failure to thrive secondary to renal dysfunction to recurrent nephrolithiasis in adulthood. Oxalosis is the term describing the deposition of calcium oxalate crystals in multiple tissues with resulting damage.

CASE REPORT

A 31-year-old white female presented in infancy with nephrocalcinosis, hyperoxaluria and kidney failure. She carried a presumed diagnosis of PH but genetic testing was not done. She underwent two kidney transplants, the first from her father at 15 months of age, with subsequent failure due to severe cytomegalovirus infection. She restarted dialysis and had a second transplant from her mother at 23 months of age. She did well until she became pregnant at the age of 31 years and self-discontinued her immunosuppression, leading to the rapid onset of end-stage kidney disease (ESKD) requiring hemodialysis (HD) thrice weekly. Shortly after dialysis initiation, she presented with acute lower extremity deep vein thrombosis (DVT) and a negative workup for clotting disorders and was treated with warfarin. A few months later she developed non-healing wounds on both lower extremities that were felt to be calciphylaxis exacerbated by warfarin, a known risk factor for calciphylaxis [2]. Due to the severe peripheral vascular disease and the worsening ulcerated lesions, the patient underwent a right below the knee amputation and left transmetatarsal amputation.

She was then evaluated for a kidney transplant and genetic testing was done, revealing type I PH with two *AGXT* gene mutations: c.33dupC and Gly170Arg type I (courtesy of the Rare Kidney Stone Consortium). The histology collected from tissue at the time of amputation was retrieved and revealed heavy deposition of calcium oxalate crystals in the medial layer of arteries (Figure 1), demonstrating the etiologies of the vascular occlusions and amputations were likely due to widespread oxalate deposition from acute rejection/kidney failure in a setting of PH-1. The patient was listed for a combined kidney–liver transplant and underwent HD six times per week to optimize oxalate removal. Pyridoxine was added to her treatment regimen since it has been found that patients with PH-1 with the

Received: 4.11.2019; *Editorial decision:* 9.12.2019

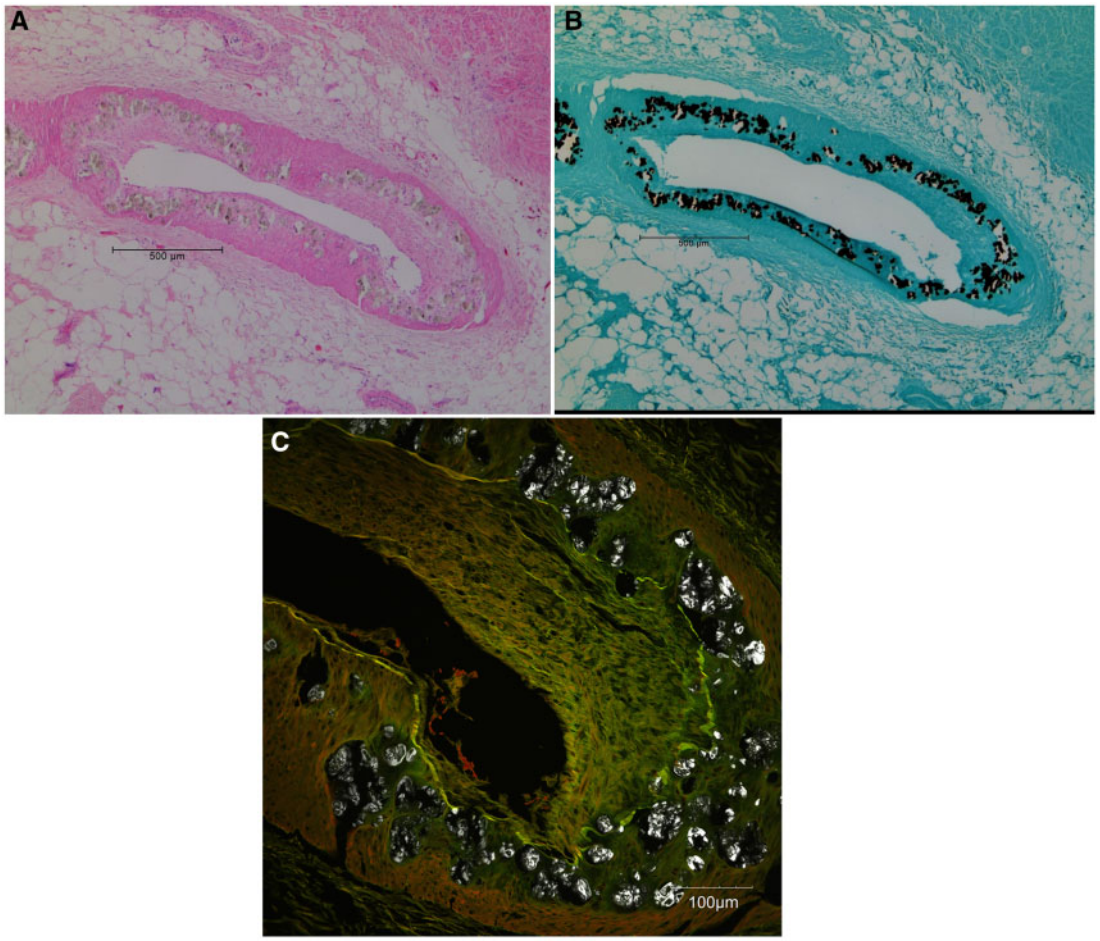

FIGURE 1: Histopathology of a blood vessel from the distal amputation. (**A**) Disruption of the medial layer of the artery with deposition of a brownish substance (black arrow; hemotoxylin and eosin). (**B**) The same vessel stained with von Kossa stain (calcification is black) and toluidine blue. (**C**) The same vessel imaged by confocal microscopy at a higher magnification under polarized light using the green channel. The calcified crystals polarize and thus are calcium oxalate. The green color is generated from autofluorescence of collagen and elastin fibers in the intimal layer and the bright line of fluorescent green is the internal elastic lamina (white arrow).

Gly170Arg and Phe152Ile gene mutations are highly responsive to pyridoxine supplementation, which is a cofactor to the AGXT enzyme, leading to a significant reduction of urinary oxalate levels [1, 3]. The liver–kidney transplant was done and she is doing well 5 years posttransplant.

DISCUSSION

Our patient had an unusual presentation of vascular oxalosis mimicking calciphylaxis, thought to be precipitated from warfarin administered for a DVT. Vascular oxalosis is extremely rare in PH, with only a few case reports (Table 1). Table 2 compares the histologic characteristics of vascular oxalosis with those of calciphylaxis. It is important to note that routine staining for calcium deposition with alizarin red or silver stain on biopsy would demonstrate medial calcification in both disease states; visualization under polarized light is needed to differentiate the crystal type and the etiology. Systemic deposition of calcium oxalate occurs in every organ and begins once the saturation point of plasma oxalate is reached. Urine is the primary route of oxalate clearance and thus the saturation is accelerated in patients with chronic kidney disease. In patients with PH-1 and ESKD, oxalate levels remain supersaturated despite aggressive HD, leaving patients at high risk of progressive systemic oxalosis [4]. Unfortunately, thrice-weekly HD and even peritoneal dialysis are unable to alleviate the burden of excess oxalate production; weekly oxalate elimination with either modality equals only 2–3 days of oxalate production [5]. Therefore the ultimate treatment in PH-1 to limit the progression of systemic oxalosis is combined liver–kidney transplantation coupled with daily HD to maximize the dialytic clearance of oxalate postoperatively.

In summary, vascular presentations in patients with hyperoxaluria, especially those with impaired renal function limiting excretion, should be biopsied to determine the diagnosis.

ACKNOWLEDGEMENTS

The authors would like to thank Dr Dawn S. Milliner from the Mayo Clinic Hyperoxaluria Center for providing genetic analysis for our patient, Drs Neal Chen and Gosia Komacka for help in taking the pathology photos and Dr Maryann Bridge at Columbus Regional Hospital for helping us obtain the pathology samples.

CONFLICT OF INTEREST STATEMENT

The results presented in this article have not been published previously in whole or part. The authors have no conflicts of interest related to this study.

Table 1. Comparison of our patient with other published case reports

References	Patient	Past medical history	Manifestations	Course of disease
Baethge *et al.* [6]	38-year-old white male	Recurrent nephrolithiasis, ESRD on HD status post-renal transplant, later diagnosed with PH-1	Severe peripheral ischemia with livedo reticularis	Vasodilator, pyridoxine and HD; later required left foot and right metatarsal amputation
Spiers *et al.* [7]	45-year-old white female	Recurrent nephrolithiasis with acute renal failure later diagnosed with PH	Livedo reticularis of upper and lower extremities	Dialysis, then died from cardiac complications
Somach *et al.* [8]	38-year-old white female	ESRD secondary to milk-alkali syndrome initially on PD then HD, later diagnosed with PH-1	Proximal lower extremity cutaneous necrosis	Pyridoxine initiated; however, the patient died shortly after due to the rapid progression of cutaneous necrosis complicated by fatal sepsis
Farrell *et al.* [9]	22-year-old white female	Unknown cause of ESRD on HD later diagnosed with PH-1	Livedo reticularis, retinopathy and peripheral sensory neuropathy	Combined liver–kidney transplantation with improvement
Marconi *et al.* [10]	40-year-old white female	Nephrolithiasis, ESRD on HD later diagnosed with PH-1	Livedo reticularis and distal ischemia	Not reported
Bogle *et al.* [11]	27-year-old Latin American female	Nephrolithiasis and ESRD on PD, later diagnosed with PH-1	Raynaud's phenomenon of the toes, livedo reticularis on the upper and lower extremities and small ulcerations on the bilateral knees and left buttock	Ongoing dialysis while awaiting combined liver–kidney transplantation
Rubenstein *et al.* [12]	30-year-old Latin American female	PH-1 with ESRD requiring PD until a combined liver–kidney transplantation	Livedo reticularis and ischemic cutaneous ulcerations on the lower extremities 16 months after successful transplantation	Supportive care with surgical debridement; later died from cardiac complications
Blackmon *et al.* [13]	38-year-old white female	Recurrent nephrolithiasis, ESRD on HD, later diagnosed with PH	Livedo reticularis, eschar and acrocyanosis	Not reported
Triki *et al.* [14]	27-year-old white male	Recurrent nephrolithiasis, ESRD on PD, later diagnosed with PH-1	Livedo reticularis	HD while awaiting combined liver–kidney transplantation
El-Saygeh *et al.* [current article]	31-year-old white female	PH-1, ESRD on HD status after two kidney transplants	Severe peripheral vascular disease requiring right above the knee amputation and left transmetatarsal amputation	Warfarin, sildenafil, pyridoxine and eventually combined liver–kidney transplantation

ESRD: end-stage renal disease; PD: peritoneal dialysis.

Table 2. Histologic manifestations

Histology	Vascular oxalosis	Calciphylaxis
Vessel distribution	Variable in location and size of arteries	Dermal and subcutaneous arteries and capillaries
Crystal deposition	Medial layer	Medial layer of the artery, sometimes within the fat
Crystal characteristics	Calcium oxalate (birefringent under polarized light)	Calcium phosphate (nonbirefringent)
Thrombosis	Reported	Almost always
Other findings	Too few case reports to determine	Inflammation and necrosis

REFERENCES

1. Cochat P, Rumsby G. Primary hyperoxaluria. *N Engl J Med* 2013; 369: 649–658
2. Portales-Castillo I, Kroshinsky D, Malhotra C *et al.* Calciphylaxis-as a drug induced adverse event. *Expert Opin Drug Saf* 2019; 18: 29–35
3. Milliner D, Eickholt J, Bergstralh E *et al.* Results of long-term treatment with orthophosphate and pyridoxine in patients with primary hyperoxaluria. *Pediatr Nephrol* 1995; 9: 446–446
4. Hoppe B, Kemper M, Bökenkamp A *et al.* Plasma calcium oxalate supersaturation in children with primary hyperoxaluria and end-stage renal failure. *Kidney Int* 1999; 56: 268–274

Clinical Kidney Journal
ckj

5. Hoppe B, Graf D, Offner G *et al*. Oxalate elimination via hemodialysis or peritoneal dialysis in children with chronic renal failure. *Pediatr Nephrol* 1996; 10: 488–492
6. Baethge B, Daniel Sanusi I, Landreneau M *et al*. Livedo reticularis and peripheral gangrene associated with primary hyperoxaluria. *Arthritis Rheum* 1988; 31: 1199–1203
7. Spiers E, Sanders D, Omura E. Clinical and histologic features of primary oxalosis. *J Am Acad Dermatol* 1990; 22: 952–956
8. Somach SC, Davis BR, Paras FA *et al*. Fatal cutaneous necrosis mimicking calciphylaxis in a patient with type 1 primary hyperoxaluria. *Arch Dermatol* 1995; 131: 821–823
9. Farrell J, Shoemaker J, Otti T *et al*. Primary hyperoxaluria in an adult with renal failure, livedo reticularis, retinopathy, and peripheral neuropathy. *Am J Kidney Dis* 1997; 29: 947–952
10. Marconi V, Mofid M, McCall C *et al*. Primary hyperoxaluria: report of a patient with livedo reticularis and digital infarcts. *J Am Acad Dermatol* 2002; 46: S16–S18
11. Bogle M, Teller C, Tschen J *et al*. Primary hyperoxaluria in a 27-year-old woman. *J Am Acad Dermatol* 2003; 49: 725–728
12. Rubenstein MC, Martinelli PT, Bayer-Garner IB *et al*. Persistent cutaneous manifestations of hyperoxaluria after combined hepatorenal transplantation. *Dermatol Online J* 2004; 10
13. Blackmon JA, Jeffy BG, Malone JC, Knable AL. Oxalosis involving the skin: case report and literature review. *Arch Dermatol* 2011; 147: 1302–1305
14. Triki M, Ksentini M, Kallel R *et al*. Oxalosis in a patient with livedo reticularis. *Skinmed* 2017; 15: 303–305

Clinical Kidney Journal
ckj