EXCEPTIONAL CASE

Calciphylaxis or vascular oxalosis?

Skye El-Saygeh¹, Douglas Roese² and Sharon M. Moe¹

¹Division of Nephrology, Indiana University School of Medicine, Indianapolis, IN, USA and ²Department 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...
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 postrenal 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-1 | 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
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, Mofd 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. Skimed 2017; 15: 303–305