Educational Case Report

Primary Hyperoxaluria Type 1 (PH1) Presenting With End-Stage Kidney Disease and Cutaneous Manifestations in Adulthood: A Case Report

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Abstract

Rationale: Primary hyperoxaluria (PH) is a rare autosomal recessive disorder more commonly diagnosed in children or adolescents. Owing to its rarity and heterogeneous phenotype, it is often underrecognized, resulting in delayed diagnosis, including diagnosis after end-stage kidney disease (ESKD) has occurred or recurrence after kidney-only transplantation.

Case Presentation: A 40-year-old Caucasian Canadian woman with a history of recurrent nephrolithiasis since age 19 presented with ESKD and cutaneous symptoms. She had no known prior kidney disease and no family history of kidney disease or nephrolithiasis.

Diagnosis: A diagnosis of primary hyperoxaluria type 1 (PH1) due to homozygous splice donor mutation (AGXT c.680+1G>A) was made with kidney and cutaneous pathology demonstrating calcium oxalate deposition and ultrasound suggestive of nephrocalcinosis.

Interventions: She was initiated on frequent, high-efficiency, high-flux conventional hemodialysis and oral pyridoxine. Lumasiran was added 11 months later, after she developed bilateral swan-neck deformities.

Outcomes: After 14 months of high-intensity dialysis and 3 months of lumasiran, there have been no signs of renal recovery, and extra-renal involvement has increased with progressive swan-neck deformities, reduced cardiac systolic function, and pulmonary hypertension. The patient has been waitlisted for kidney-liver transplantation.

Teaching Points: This case report describes an adult presentation of PH1. The case highlights the importance of timely workup of metabolic causes of recurrent nephrolithiasis or nephrocalcinosis in adults which can be a presenting sign of PH and genetic testing for PH to facilitate early diagnosis and treatment especially in the era of novel therapeutics that may alter disease course and outcomes. The case also demonstrates the value of testing for PH in adults presenting with unexplained ESKD and a history of recurrent nephrolithiasis or nephrocalcinosis due to implications for organ transplantation strategy and presymptomatic family screening.

Abrégé

Justification : L'hyperoxalurie primaire (HP) est un trouble récessif autosomique rare plus souvent rencontré chez les enfants ou les adolescents. En raison de sa rareté et de son phénotype hétérogène, cette affection est fréquemment sous-reconnue, ce qui entraîne un retard dans le diagnostic, et ce, même après l'apparition d'une insuffisance rénale terminale (IRT) ou une récidive suivant une greffe simple de rein.

Présentation du cas : Nous présentons le cas d'une Canadienne de race blanche âgée de 40 ans avec des antécédents de néphrolithiase récurrente depuis l'âge de 19 ans. La patiente était atteinte d'IRT et présentait des symptômes cutanés. Elle n'avait aucun antécédent connu de maladie rénale ou antécédent familial de maladie rénale ou de néphrolithiase.

Diagnostic : Une pathologie rénale et cutanée montrant des dépôts d'oxalate de calcium et une échographie suggérant une néphrocalcinose ont permis de poser un diagnostic d'hyperoxalurie primaire de type 1 (HP1) due à une mutation de donneur d'épissage homozygote (AGXT c.680+1G>A).

Interventions : La patiente a amorcé des traitements d'hémodialyse conventionnelle à grande fréquence, à haut rendement et à flux élevé, et a reçu de la pyridoxine par voie orale. Un traitement par lumasiran a été ajouté 11 mois plus tard, après le développement de déformations bilatérales en col de cygne.

Résultats : Après quatorze mois de dialyze à haute intensité et trois mois de lumasiran, aucun signe de récupération rénale n'a été observé. L'intervention d'épuration extra-rénale a été augmentée en raison de déformations progressives en col de cygne, d'une réduction de la fonction cardiaque systolique et d'une hypertension pulmonaire. La patiente a été placée sur la liste d'attente pour une transplantation rénale et hépatique.

Enseignements tirés : Ce rapport de cas décrit une présentation adulte d'HP1. Ce cas souligne l'importance de traiter rapidement les causes métaboliques de la néphrolithiase ou de la néphrocalcinose récidivante chez les adultes, car celles-ci peuvent être des signes d'hyperoxalurie primaire (HP). Ce cas souligne en outre l'importance de procéder à des tests génétiques pour l'HP afin de permettre le diagnostic et le traitement précoces, en particulier à l'ère de nouveaux traitements susceptibles d'infléchir l'évolution et les résultats de la maladie. Enfin, il démontre la valeur du dépistage de l'HP chez les adultes présentant une IRT inexpliquée et des antécédents de néphrolithiase ou de néphrocalcinose récidivante, en raison de ses implications sur la stratégie de transplantation d'organes et sur le dépistage pré-symptomatique de la famille.

Introduction

Three types of primary hyperoxaluria have been described, each with enzyme deficiencies affecting different hepatocyte organelles and enzymes involved in glyoxylate metabolism. The enzyme deficiency in PH1 is the hepatocyte-specific peroxisomal alanine-glyoxylate aminotransferase (AGT) (OMIM 259900),[1] whilst primary hyperoxaluria type 2 (PH2) (OMIM 260000)[1] is characterized by a deficiency in glyoxylate reductase-hydroxypyruvate reductase (GRHPR) found mainly in hepatic cytoplasm and to some extent in mitochondria. Primary hyperoxaluria type 3 (PH3) (OMIM 613616)[1] arises from deficiencies in hepatic mitochondrial 4-hydroxy-2-oxoglutarate aldolase (HOGA).

Primary hyperoxaluria type 1 is an autosomal recessive genetic disorder caused by a homozygous or compound heterozygous mutation in the AGXT gene on chromosome 2q37.3 which encodes hepatic-specific peroxisomal AGT.[1] The mutation results in absent or reduced AGT activity. In some cases, AGT is formed but mistargeted to mitochondria where it is inactive. In hepatic peroxisomes, glycolate oxidase (GO) metabolizes glycolate to glyoxalate, which in turn is metabolized to glycine by AGT. When AGT is deficient, glyoxalate accumulates, and in the hepatic cytoplasm, is converted into glycolate by glyoxylate reductase (GR) and into oxalate by lactate dehydrogenase (LDH).[2] High intracellular production of oxalate results in extracellular transport and hyperoxaluria. Calcium oxalate is insoluble and causes nephrolithiasis, nephrocalcinosis, kidney dysfunction, and kidney failure. Independent of nephrolithiasis, intratubular calcium oxalate crystal deposition along with nucleotide-binding domain, leucine-rich repeat (NALP3)-mediated inflammasome activation have been demonstrated to drive tubulointerstitial inflammation, fibrosis, and progressive kidney failure in oxalate nephropathy.[3] When the plasma oxalate load exceeds urinary excretion, oxalate deposition occurs in multiple tissues, in a process called oxalosis.[4] In contrast, secondary oxalosis (SO) is caused by ingestion of high oxalate foods, excess vitamin C, ethylene glycol, enteric hyperoxaluria, low calcium intake, and decreased oxalate excretion in patients with kidney dysfunction.[5]

Primary hyperoxaluria type 1 is the most common (70-80%) and severe type of primary hyperoxaluria.[6-8] The estimated prevalence of PH1 is 1 to 3 cases per 1 million population in Europe.[4,7,9] The true prevalence is unknown due to underdiagnosis.[4]

Screening for metabolic causes of recurrent nephrolithiasis in adults does not always include PH due to its perception as a childhood condition or presumption of benign etiology. While many PH1 cases are diagnosed by age 18, 30% of PH1 cases were diagnosed in adults, and of these 59% presented in kidney failure in the Netherlands.[7]

We describe a patient with an AXGT gene splice donor mutation, negative family history, and recurrent nephrolithiasis, presenting with end-stage kidney disease and cutaneous

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complications in adulthood. The case highlights the importance of timely workup of metabolic causes of recurrent nephrolithiasis or nephrocalcinosis in adults.

Presenting Concerns

A 40-year-old Caucasian woman presented to the Emergency Department (ED) with a 2-week history of vomiting, malaise, 1-week history of cold and painful blue toes, and 1-day history of chest pain. Two days earlier, her family physician prescribed aspirin 81 mg orally daily and referred her to vascular surgery for lower limb ischemia. Her only other medication was levonorgestrel and ethinyl estradiol 100-20 mcg orally daily.

Her childhood and adolescent history were unremarkable. She had nephrolithiasis at age 19 and 33 which required lithotripsy on both occasions. The stones were composed of calcium, magnesium, oxalate, and phosphate. Urologic evaluation with the second lithotripsy revealed no residual stones, but a punctate calcification in the left hemipelvis. She was referred to urology after moving to another province for further workup of metabolic causes. No information is available on her out-of-province management. There was no maternal family history of kidney disease or nephrolithiasis, and paternal history was unknown. She had no siblings or offspring. Past history included cold-induced pain and sensory deficits in the right ulnar distribution, with normal electromyography (EMG) and brain magnetic resonance imaging (MRI) at age 26. Her creatinine was 103 μmol/L 19 months prior to presentation.

Clinical Findings

Physical examination revealed new hypertension (145/77 mmHg), and otherwise normal vital signs, cardiac, respiratory, and abdominal examinations. Dorsalis pedis pulses were not palpable, and there was bilateral acrocyanosis of the toes although distal extremities were warm.

Diagnostic Focus and Assessment

Table 1 summarizes notable laboratory findings at initial presentation.

The following serologies were normal or negative: antinuclear antibody panel, rheumatoid factor, C3, C4 complements, cryoglobulins, ANCA, anti-GBM, antistreptolysin O titer, HIV antigen and antibody, Hepatitis C, syphilis, and Hepatitis B surface antigen. Hepatitis B surface antibodies revealed immunity. Serum protein electrophoresis showed no monoclonal gammopathy. Serum immunoglobulin free light chain κ/λ ratio was 2.83.

Urinalysis showed 0.3 g/L albuminuria, 25 erythrocytes/μL, and pyuria 5-10 cells/high power field. Urine cultures grew multidrug-sensitive *Escherichia coli*. Blood cultures showed no growth. COVID-19 nasopharyngeal swab polymerase chain reaction (PCR) was negative.

Thrombosis workup was negative including protein C activity, protein S levels, antithrombin levels, Factor V Leiden levels, Lupus anticoagulant ratio, and anticardiolipin IgG antibody.

High sensitivity troponin-T was elevated at 233 ng/L (normal $\leq$ 14) in keeping with renal failure, with stable serial sampling at 3 h and 30 h. There were no signs of ischemia or conduction abnormalities on serial electrocardiograms, and no further episodes of chest discomfort.

Diagnostic Imaging

Computed tomography thorax angiography showed no atheromatous disease of the aorta and no embolic source. There were no other abnormalities.

Transthoracic echocardiogram revealed normal left and right ventricular size and systolic function. There was no interatrial shunt upon injection of agitated saline and no intracardiac thrombus.

Arterial Doppler ultrasound of the lower limbs revealed normal peripheral vascular resistance (PVR) below the knees, mildly abnormal PVR at the ankles, and severe ischemia at the metatarsals and digits bilaterally. When repeated 10 days later, after warming the feet, there was no improvement in perfusion of the second to fifth digits bilaterally, and improvement to moderate ischemia in the great toes bilaterally.

X-rays of bilateral hands and feet showed no vascular or extra-osseus calcification.

Renal ultrasound showed bilateral cortical thinning and marked echogenicity with pronounced corticomedullary differentiation. The medullary pyramids were diffusely echogenic suggesting medullary nephrocalcinosis. There was no hydronephrosis or nephrolithiasis.

Therapeutic Focus and Assessment

A vascular surgeon recommended sildenafil 20 mg orally twice daily and long-acting nifedipine 20 mg orally daily for lower limb microvascular ischemia to no benefit. Simvastatin was started.

A right tunneled internal jugular central venous catheter was inserted, and 4 h, thrice weekly, high-efficiency and high-flux hemodialysis treatments were started. A week later, a kidney biopsy was performed (Figures 1 and 2), and following those results, dialysis frequency was increased to 6 days per week. Genetic testing was performed.

A dialysis multivitamin containing pyridoxine (10 mg/day) was started. Dietary history did not reveal high oxalate intake. The patient was advised to avoid oxalate-rich foods, maintain adequate calcium intake, and avoid excessive intake of ascorbic acid. Following genetic test results,

Table 1. Laboratory Results on Initial Presentation.

Serum chemistry	Result	Reference range
Creatinine	1644	49-90 µmol/L
Urea	42.2	2.5-9.2 mmol/L
Total CO_2	13	22-29 mmol/L
Chloride	107	100-110 mmol/L
Sodium	140	136-145 mmol/L
Potassium	4.7	3.4-5.0 mmol/L
Anion gap	20	5-15
Lactate	0.8	0.5-2.2 mmol/L
Random blood glucose	5	3.8-7.8 mmol/L
Albumin	31	35-50 g/L
Total calcium	1.65	2.20-2.60 mmol/L
Ionized calcium	0.75	1.15-1.27 mmol/L
Phosphorus	2.92	0.74-1.52 mmol/L
Intact parathyroid hormone	60.5	1.9-8.7 ρmol/L
Total bilirubin	5	0-20.4 µmol/L
Aspartate aminotransferase	8	5-45 U/L
Alanine aminotransferase	6	0-44 U/L
Alkaline phosphatase	84	38-150 U/L
International normalized ratio	1.0	0.8-1.2
Lactate dehydrogenase	238	120-230 U/L
C-reactive protein	43.97	0-7.99 mg/L
Hematology		
White blood count	14.45	$4.5-11 \times 10^9$/L
Hemoglobin	87	120-160 g/L
Platelet	286	$150-350 \times 10^9$/L
Haptoglobin	3.34	0.47-2.03 g/L
Peripheral smear	No schistocytes	
Reticulocyte count	33	$28.8-94.1 \times 10^9$/L
24-h urine collection[a]		
TV	1025 mL	
Urine creatinine	1.2	6.3-14.6 mmol/TV
Oxalate	319	40-320 µmol/TV
Citrate	undetectable	≥1.7 mmol/TV
Protein	0.2	0.05-0.150 g/TV

Note. TV = Total urine volume.
[a]24-h urine collection 4 days after presentation and prior to dialysis initiation. Plasma oxalate levels were not available.

pyridoxine 50 mg orally daily was added, with dose escalation to 1400 mg/day (20 mg/kg/day) over 2 months.

The livedo reticularis, acrocyanosis, and toe pain improved post-hemodialysis and worsened during the interdialytic break. A dermatologist performed a punch biopsy. A rheumatologist found no evidence of Raynaud's phenomena.

Renal Pathology

Light microscopy showed a core of cortex with 29 glomeruli, 10 of which were globally sclerosed, and the remainder of which showed glomerulomegaly and minimal variable ischemic glomerular basement wrinkling. Extensive deposition of calcium oxalate crystals was noted. There was a prominent interstitial lymphoid infiltrate in a background of marked chronic tubular atrophy, interstitial fibrosis, and sclerosis of small arteries and arterioles. Electron microscopy was unremarkable. Immunofluorescence was negative.

Skin Pathology

A punch biopsy of skin and subcutis from the leg revealed mural deposits of refractile calcium oxalate crystal (with blue-yellow birefringence under polarized light) in dermal and subcutaneous vessels. Microscopic evidence of other vasculopathies was absent.

Genetic Testing

DNA testing was done using sequence analysis and copy number variation analysis of AGXT, GRHPR, and HOGA1
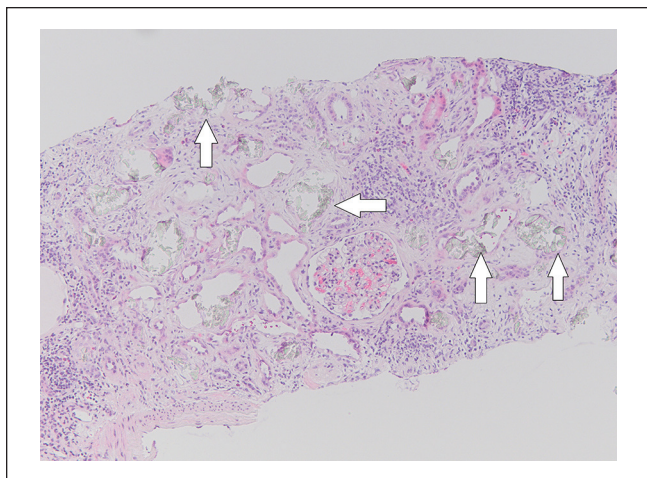
Figure 1. Renal tissue with oxalate crystals in renal tubules (arrows), hematoxalin and eosin stain, 100× magnification 1299 × 974 mm (96 × 96 dots per inch).
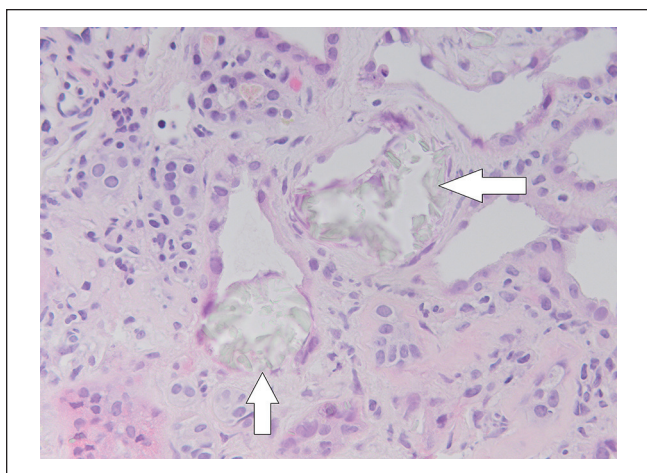

Figure 2. Renal tissue with oxalate crystals in renal tubules (arrows), hematoxalin and eosin stain, 400× magnification 1299 × 974 mm (96 × 96 dots per inch).

genes. The patient was homozygous for AGXT c.680+1G>A, which is pathogenic and associated with a phenotype of PH1.

Follow-Up and Outcomes

Medical genetics were consulted. The patient was maintained on oral pyridoxine and high-intensity hemodialysis. Eight months after dialysis initiation, she was waitlisted for kidney and liver transplantation. She developed bilateral swan-neck deformities of the fingers and limited grasp. Lumasiran (Alnylam [Oxlumo™] Pharmaceuticals Inc, Cambridge MA, USA) 1 mg/kg subcutaneously monthly for 3 months, then every 3 months was started on a compassionate basis 11 months after presentation. After 3 months of lumasiran, there have been no adverse effects, and the patient remains dialysis-dependent. Predialysis plasma oxalate levels fell by 36% from 98.2 to 62.8 μmol/L prelumasiran and postlumasiran, respectively. Extra-renal involvement increased despite high-intensity dialysis and lumasiran, with progressive swan-neck deformities, reduced cardiac systolic function, and pulmonary hypertension.

Discussion

Primary hyperoxaluria can present at any age. There is genotypic heterogeneity and variable phenotypic expression.[10,11] Severe kidney disease can develop insidiously with 30% of patients having kidney failure at diagnosis.[7,12] Adult-diagnosed PH1 was reported in 38% of all PH1 patients.[4] There is a high prevalence (59%) of end-stage kidney disease at presentation in adult-diagnosed PH1.[7,10] Late diagnosis is due to the inadequate metabolic screening in adult stone-formers, and inadequate presymptomatic genetic testing in individuals with a family history of PH1. Cumulative renal survival was 59, 41, and 10% at age 20, 30, and 50 years, respectively, in 155 patients of Western European, North African, or the Middle Eastern origin.[10]

Infantile PH1 is associated with early nephrocalcinosis and kidney failure. Children or adolescents present with recurrent nephrolithiasis and progressive renal failure. Late-onset PH1 presents with occasional nephrolithiasis in adulthood.[7] Some patients are diagnosed after developing recurrent disease post kidney-only transplantation.[4,12] Presymptomatic diagnosis is done through screening individuals with a family history of PH1.[12]

The heterogeneity in presentation challenges timely diagnosis.[4,7] The OxalEurope group published guidelines recommending screening for PH in children with first kidney stone, adults with recurrent stone disease, nephrocalcinosis (especially if associated with decreased glomerular filtration rate), individuals with calcium oxalate monohydrate crystals in any biological tissue or fluid, and relatives of index cases.[12]

Over 190 pathogenic variants in the AGXT gene have been described. The majority (67%) are missense mutations. Nonsense and splice site alterations are also reported. Deletions and insertions account for 25% of known mutations.[9,11] The p.Gly170Arg (c.508G > A) mutation is the most common mutation reported in Europe and is associated with better renal outcomes.[10] The 4 most common pathogenic variants p.Gly170Arg, p.Phe152Ile, and p.Ile244Thr and c.33dupC account for more than 65% of PH1-causing alleles.[10] Individuals with higher urinary oxalate excretion rates have poor renal outcomes.[8]

Mutations in the AGXT gene have been found in more than 99% of individuals with PH1; however, some cases of PH1 cannot be confirmed by detection of a known AGXT mutation and require diagnosis by liver biopsy confirming AGT deficiency, or by significant hyperoxaluria in combination with hyperglycolic aciduria in the absence of identifiable secondary causes.

About 30% of patients with PH1 are pyridoxine-responsive, with responsiveness noted in p.Gly170Arg (c.508G>A) and p.Phe152Ile (c.454T>A) mutations.[10,13] Pyridoxal phosphate is the essential cofactor of AGT and works by increasing catalytic activity, functioning as a chaperone by increasing peroxisomal targeting and increasing enzymatic net expression.[14] Three patients homozygous for the p.Gly170Arg (c.508G >A) mutation with severe oxalate nephropathy were able to discontinue dialysis after treatment with pyridoxine.[15] The p.Gly170Arg (c.508G >A) mutation results in functional but mistargeted AGT, such that enzyme activity can be enhanced when pyridoxine is supplemented. Our patient, who had the rare splice-site variant mutation AGXT c.680+1G>A,[11] was treated with pyridoxine with no signs of renal recovery due to irreversible kidney damage at diagnosis, and probable pyridoxine nonresponsiveness due to severely deficient AGT activity predicted by a splice variant mutation. Her mild kidney disease until age 38 is not out of keeping with other PH1 mutations that have better renal outcomes.[10,11] However, the development of end-stage kidney disease by age 40 is in keeping with that reported in other PH1 cases.[10] Her normal urine oxalate level at presentation was due to reduced estimated glomerular filtration rate (eGFR) of 2 mL/min/1.73 m^2.

Management of PH1 is supportive including fluid intake >3L/day, pyridoxine and citrate in nondialysis patients. Dialysis patients are treated with pyridoxine, early and daily high-efficiency and high-flux hemodialysis, plus or minus nocturnal peritoneal dialysis, and combined liver and kidney transplantation.[12,16] Lumasiran, a novel therapeutic recently granted US Food and Drug Administration (FDA) approval under orphan drug and breakthrough therapy designation for PH1, is a double-stranded small interfering ribonucleic acid (siRNA) that targets the messenger RNA for hepatocyte hydroxyacid oxidase 1 (HAO1), thus reducing GO enzyme levels, which results in decreased glyoxylate formation and decreased oxalate production. Due to GO being upstream of AGT, the mechanism of action of lumasiran is independent of AGT deficiency. The ILLUMINATE-A study and preliminary results of ILLUMINATE-B study showed reduction in urinary oxalate excretion rates, portending a possible beneficial effect on long-term outcomes, such as kidney failure.[17,18] A recent study in adults demonstrated reduction in 24 urinary oxalate excretion rates to normal or near normal levels in patients treated with lumasiran.[19] There are no published studies yet on the use of lumasiran in patients with eGFR under 30 mL/min/1.73 m^2.

Vascular oxalosis is typified by the findings in this case. Our patient was initially thought to have peripheral vascular disease. A skin biopsy was helpful to distinguish it from other vasculopathies including calcific uremic arteriolopathy.[20] The amelioration of her livedo reticularis, acrocyanosis, and toe pain with hemodialysis was due to reduction of calcium oxalate burden by hemodialysis.[6,12]

Individuals meeting OxalEurope criteria for PH screening should undergo initial workup including stone analysis, and 24-h urine measurements of calcium, oxalate, glycolate, creatinine, and citrate.[12] The latter may be repeated while on low oxalate, and high oxalate diets. Patients with PH have high urinary oxalate levels irrespective of dietary oxalate intake. Plasma oxalate levels should be measured if eGFR < 60 mL/min/1.73 m^2. If initial investigations are in keeping with PH, then early referral to a center with expertise in genetic testing, performing liver biopsies, PH management, dialysis, and transplantation is recommended.

Conclusions

This case illustrates an example of PH1 presenting with kidney failure in the 4th decade of life. It highlights the value of evaluating for PH in adults with recurrent calcium oxalate nephrolithiasis or nephrocalcinosis as per current European guidelines.[12]

This case demonstrates the value of performing a kidney or skin biopsy to detect calcium oxalate crystals and genetic testing to make the correct diagnosis. This had implications for management, including transplantation strategy, given the risk of recurrent disease after kidney-only transplantation, ruling out other cutaneous vasculopathies with different treatment approaches, and offering earlier PH screening in pre-symptomatic family members.

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