Missed diagnosis of oxalosis with disastrous consequences. Case reports of a father and daughter

Durr-e-Sabih[1*], Udayakumar Ramachandran[2], Usman Khan[3], Quratulain Sabih[4], Kashif Rahim[5], M. Babar Imran[6]

European Journal of Medical Case Reports
Volume 6(3):52–57
https://doi.org/10.24911/ejmcr/173-1647277526

ABSTRACT

Background: Hyperoxalosis is a rare disease that originates from a defect in a liver enzyme and results in renal failure, if not diagnosed in time. Once end-stage renal disease is established, a transplant is the treatment of choice. But a kidney-only transplant can fail due to the mobilization of the excess oxalates in the tissue, and many authorities recommend a combined kidney-liver transplant.

Case Presentation: We describe a case where the diagnosis of oxalosis was missed, resulting in renal transplant failure and excision of the graft. The diagnosis was made only on noting florid heterotopic calcification. A renal transplant was performed due to end-stage renal disease, but graft failure occurred and had to be excised due to recurrent oxalosis, again without diagnosis, despite imaging and graft biopsy. It was only when muscle calcification was noted for an unrelated indication that a diagnosis was made. The case highlights the importance of excluding all causes of nephrocalcinosis, including rare ones like oxalosis, in the management of chronic renal disease.

Conclusion: We hope to alert the physician to consider primary hyperoxalosis as a differential diagnosis in renal failure patients with recurrent calcium oxalate renal stones and/or nephrocalcinosis.

Keywords: Hyperoxaluria, oxalosis, nephrocalcinosis, renal transplant failure, graft failure, case report.

Received: 14 March 2022 **Accepted:** 02 April 2022 **Type of Article:** CASE REPORT **Specialty:** Radiology

Correspondence to: Durr-e-Sabih
*Director, Multan Ultrasound Service, Multan, Pakistan.
Email: dsabih@yahoo.com
Full list of author information is available at the end of the article.

Background

Primary hyperoxaluria is a rare disease with a prevalence of 1-3 per million in the Western population, but a higher rifeness (1 per 58,000) is reported worldwide [1-3]. It is caused by an inborn enzymatic defect leading to impaired glycol-oxalate metabolism, resulting in enhanced oxalate production and disseminated systemic and visceral deposition of the insoluble calcium oxalate crystals. The disease presentation is extremely variable because of the marked heterogeneity of disease expression. We present an interesting case of a 36-year-old gentleman with renal transplant failure secondary to hyperoxalosis. His 8-year-old daughter also had primary hyperoxalosis with typical medullary calcification.

Case Presentation

A 36-year-old gentleman, known to have chronic renal failure, presented to the hospital with exacerbation of symptoms and oliguria. His previous imaging, performed a few years before the current admission, showed enlarged echogenic kidneys. No etiologic diagnosis was made and he was placed on chronic renal failure treatment. On admission, his creatine and BUN (blood urea nitrogen) were 5.8 and 108 mg/dl. He underwent a renal biopsy which was of very low yield, having few hyalinized glomeruli and mostly fibrosed tissue with a small focus of necrotizing glomerulonephritis. This was interpreted as tubulointerstitial nephritis with focal necrotizing glomerulonephritis. He was labeled as end-stage renal failure and was started on hemodialysis awaiting renal transplantation. Autoimmune work-up was not performed because of biopsy showing mostly fibrosed tissue. Subsequently, he underwent a living-related renal transplant with a good postoperative graft function and was discharged on cyclosporine, cellcept, and prednisone after initial graft care. During the second year of transplant, he started to show graft dysfunction with elevated serum creatinine of around 1.5-2. Ultrasound at that point showed mild-to-moderate hydronephrosis of the graft. No luminal obstructive lesions were noted. The patient underwent a ureteric reimplantation. Biopsy of the ureter showed nonspecific chronic inflammation, fibrosis, and occasional crystals. The patient's renal function continued to decline, despite excellent compliance with immunosuppression.

CT scan showed heavy calcification in the native kidneys (nephrocalcinosis) and severe hydronephrotic transplanted kidney with cortical thinning and few calcifications (Figure 1a and b). Renal osteodystrophy was also noted.

Graft core biopsy was performed which primarily showed transmural hyalinization, hyaline deposits in the adventitia, interstitial fibrosis, and tubular atrophy (Figure 2). Additionally, there were crystals in the tubules, the significance of which was not further elaborated. The interstitial inflammation was interpreted as chronic cell-mediated rejection. His immunosuppression was readjusted, but the patient continued to have worsened renal failure; he was started back on dialysis because of poor graft clearance functions. He developed ascites and the graft had to be excised.

Biopsy of the excised graft showed "almost complete necrosis of the graft with scanty atrophic and degenerate glomeruli with interstitial scarring" (Figure 3). Crystalline material was scattered throughout, but this was not commented upon in the final report. After about a year of graft excision, with the patient on hemodialysis, a Doppler of the right thigh was ordered for follow-up of a known iatrogenic femoral artery thrombosis. The Doppler scan showed recanalized thrombus in the right superficial femoral artery, but there were also multiple areas of focal calcification in the thigh muscles on both sides (Figure 4). The exam was extended to the abdomen and heavily calcified native kidneys were seen (Figure 5). The liver and thyroid showed punctate echogenicity, but no areas of macrocalcification could be seen. There was no ultrasound evidence of intrathyroidal parathyroid adenomas. A CT scan showed heavily calcified kidneys and multiple foci of calcification in the tongue and skeletal muscles (Figure 6). A ^{99m}Tc MDP (Methylene Diphosphonate) bone scan showed a "superscan" with low background and well-visualized appendageal skeleton (Figure 7). The patient's calcium, phosphorus, and

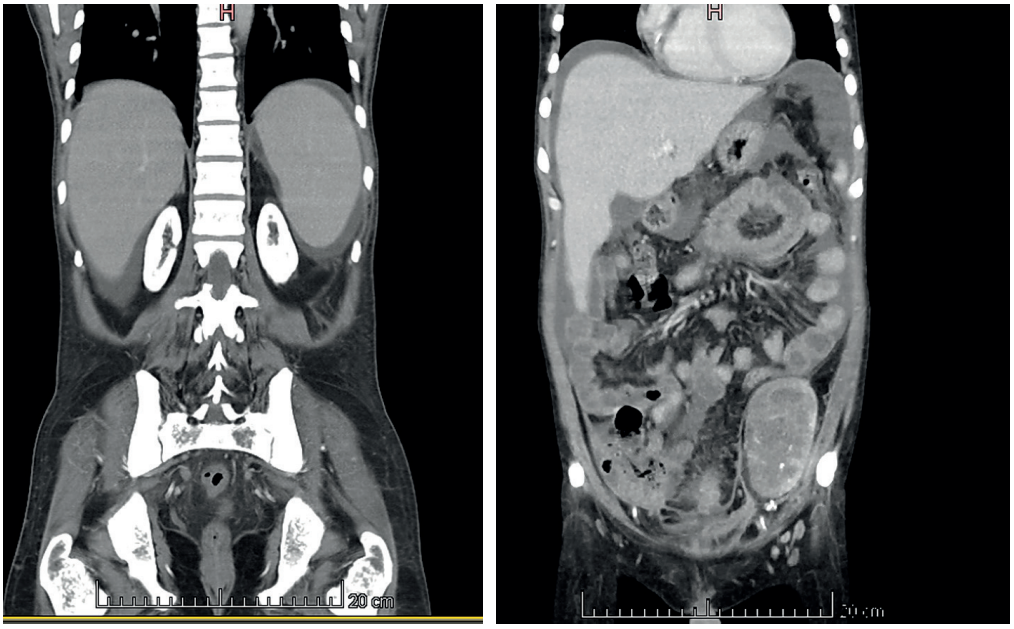

Figure 1. *(A) Coronal CT of native kidneys showing extensive calcification. (B) Coronal CT through the transplant in the left lower quadrant. The graft is severely hydronephrotic and a few calcifications are seen in the kidney, but no significant calcium deposits are noted in the skeletal muscles.*

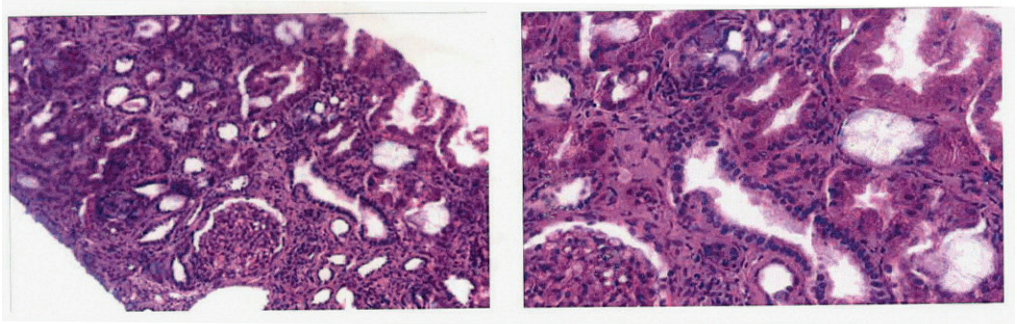

Figure 2. *Core biopsy of the failed transplant showing interstitial inflammation and vascular hyalinization. Tubular atrophy periglomular fibrosis, but no oxalate crystal deposition.*

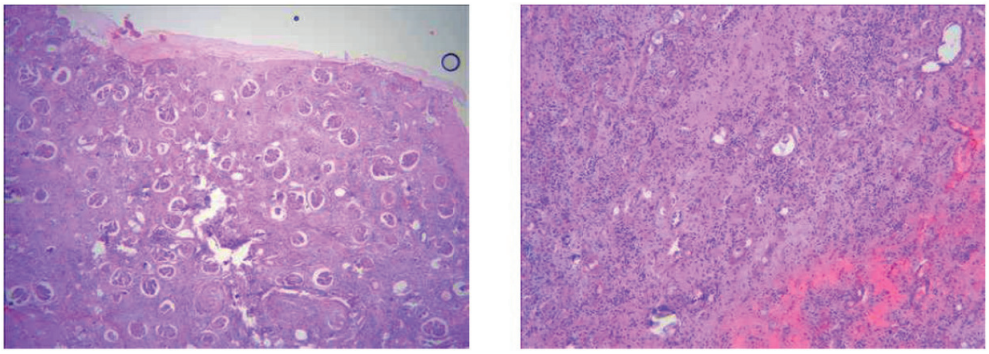

Figure 3. *Biopsy of the resected graft showing "almost complete necrosis of the graft with scanty atrophic and degenerate glomeruli with interstitial scarring." Crystalline material was found scattered throughout, but this was not commented upon in the final report.*

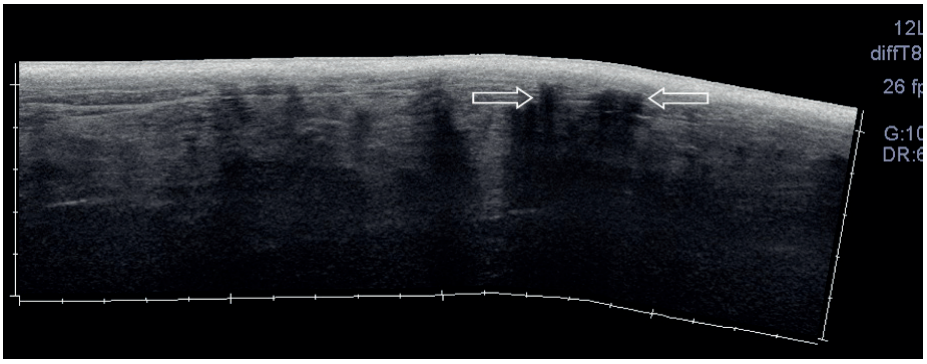

Figure 4. *Panoramic ultrasound image of the right thigh. Multiple heavily calcified areas (arrows) are seen in the muscles.*

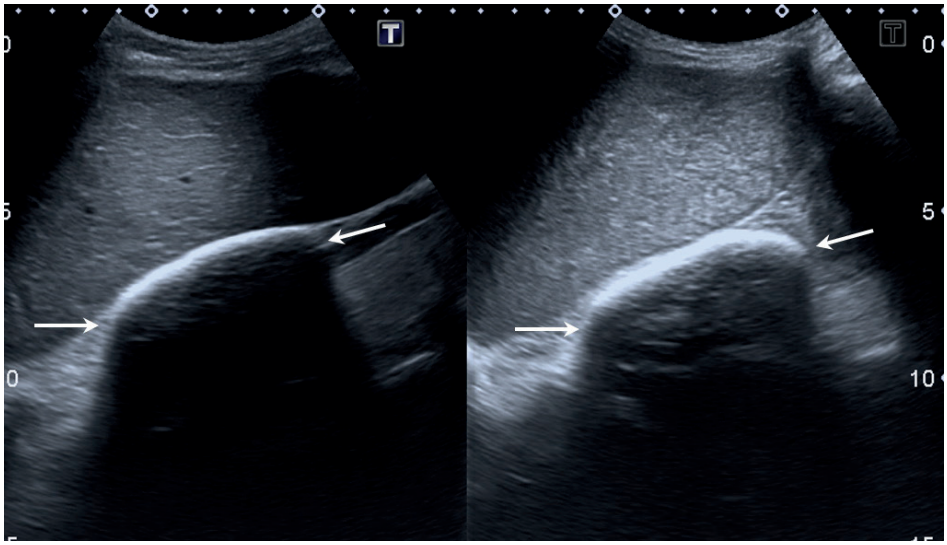

Figure 5. *Ultrasound of kidneys showing completely calcified, shrunken organs with no internal anatomy visible (arrows).*

vitamin D levels were within normal limits. Liver biopsy for alanine glyoxylate aminotransferase (AGT) deficiency (hyperoxalosis) was considered, but nationally immunoblotting to analyze the protein was not available. Interestingly, the patient's 8-year-old daughter had a diagnosis of primary oxalosis based on the 24-hour urinary oxalate levels and typical ultrasound features of medullary nephrocalcinosis on ultrasound and CT (Figures 8 and 9).

Discussion

Primary hyperoxaluria is a rare genetic disorder which is secondary to AGT deficiency, mostly inherited in the autosomal recessive pattern. Three types are described: type 1, present in 80% of the patients, results from a defect

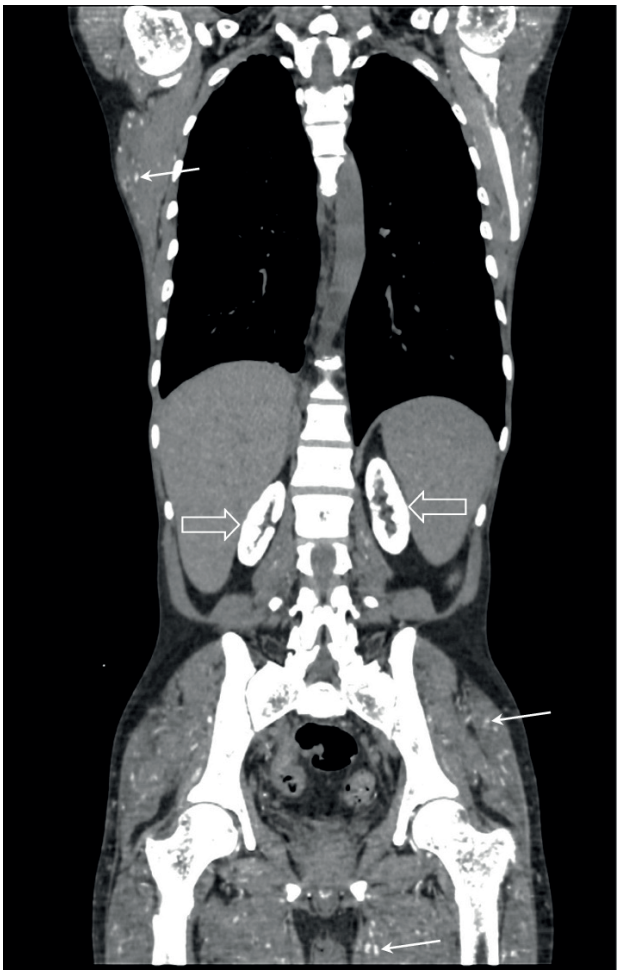

Figure 6. *CT scan with coronal reconstruction showing heavy cortical calcification of the kidneys (open arrow) and innumerable small calcifications in the skeletal muscles seen as punctate white spots (arrows).*

in vitamin B6-dependent hepatic peroxisomal enzyme, AGT; type 2 occurs in about 10% and is due to dysfunction of the enzyme glyoxalate/hydroxypyruvate reductase; and type 3, recently described, is seen in 10% of the cases and is due to error of mitochondrial 4-hydroxy 2-oxoglutarate aldolase [4].

Presentation can be variable, with 50% of the cases manifesting in infancy and early childhood [5,6]. Most patients present with chronic renal failure, but can also present as an acute renal failure too [7]. Many patients are diagnosed after transplant failure [8-10].

The error of metabolism is in the liver, secondarily affecting the kidneys. The treatment of choice is a combined liver-kidney transplant for type 1 hyperoxalosis that makes up for most cases. This is associated with a 5-year survival of 80%. A kidney-only transplant is recommended for those with pyridoxine-responsive type I disease, as well as for cases of type II disease. In this case, with a kidney-only transplant, the recurrence of renal oxalosis is probable due to mobilization of oxalates in tissues

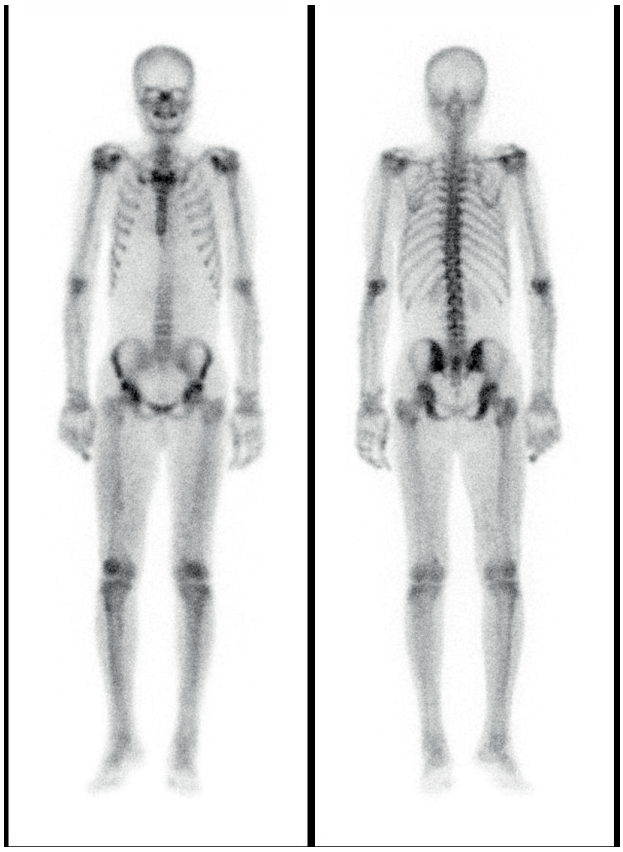

Figure 7. *Tc^{99m}-MDP bone scan showing a superscan with faintly visualized kidneys, but very clearly visualized skeleton; vertebrae are clearly seen as is the appendageal skeleton.*

[11]. This led to graft failure in our patient. The earliest reported case of graft failure after transplant for oxalosis occurred within a few hours of surgery [12], but typically it takes some time for graft failure to occur. In our case, the graft failed after 1 year and had to be excised after 18 months of the transplant.

Our case is unusual in that repeated imaging with ultrasound and CT and biopsies of the native kidneys and the excised failed transplant did not diagnose hyperoxalosis. Oxalate crystals were seen in the failed and excised graft, but given that oxalate crystals can be seen in graft failure without hyperoxalosis [13,14], the diagnosis was not made.

The condition progressed to extensive heterotopic skeletal muscle calcification, almost 1 year after graft excision, which led to the diagnosis retrospectively, strengthened by the fact that the daughter has typical medullary nephrocalcinosis and hyperoxaluria.

Nephrocalcinosis is a relatively easy diagnosis to make on ultrasound and CT, but most cases are of the medullary type, and cortical nephrocalcinosis is relatively rare. Oxalosis is differential in both medullary and cortical types of nephrocalcinosis. In this case, the father's disease progressed to complete calcification of

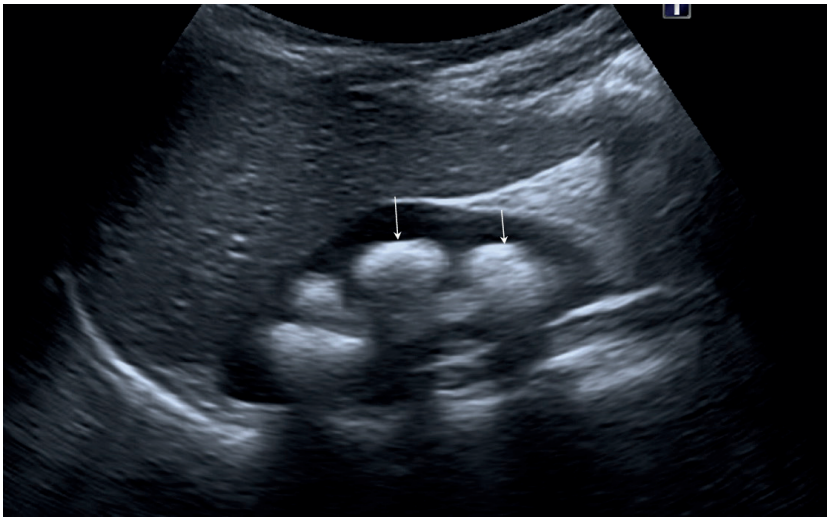

Figure 8. *Coronal ultrasound section of the daughter's kidney showing heavy calcification of the medullary pyramids (arrows) typical of medullary nephrocalcinosis.*

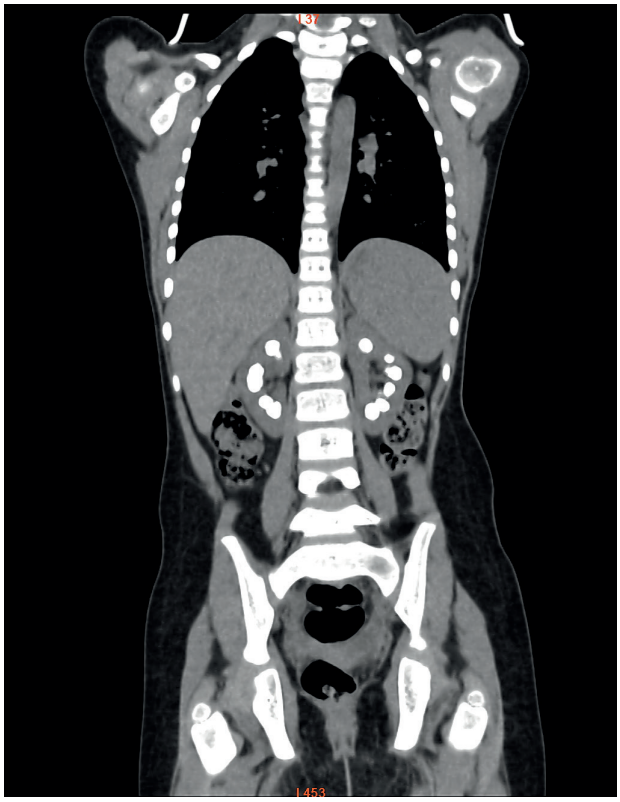

Figure 9. *Coronal CT scan of the daughter's kidneys showing heavy calcification of the medullary pyramids.*

the kidneys, while the daughter's kidneys showed medullary nephrocalcinosis.

Conclusion

We hope to alert the physician to consider primary hyperoxalosis as a differential diagnosis in renal failure patients with recurrent calcium oxalate renal stones and/or nephrocalcinosis.

What is new?

A renal transplant was performed due to end-stage renal disease, but graft failure occurred and had to be excised. The diagnosis of oxalosis was missed, despite imaging and graft biopsy. It was only when muscle calcification was noted for an unrelated indication that a diagnosis was made. The case highlights the importance of excluding all causes of nephrocalcinosis, including rare ones like oxalosis, in the management of chronic renal disease.

Acknowledgement

The authors gratefully acknowledge the contribution of Dr. Wajahat Ali, Radiologist at the Multan Institute of Kidney Disease (MIKD) for retrieving and sharing the CT images in Figure 1 (a) and (b).

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

None.

Consent for publication

Written and informed consent was taken from the patient to publish this case report.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

Author details

Durr-e-Sabih[1], Udayakumar Ramachandran[2], Usman Khan[3], Quratulain Sabih[4], Kashif Rahim[5], M. Babar Imran[6]

1. Director, Multan Ultrasound Service, Jail Road, Multan, Pakistan
2. Director, Genesis Scans, Chennai, India

3. Assistant Professor, Nephrology, University of Oklahoma Medical Centre, Oklahoma City
4. Fellow Breast Oncological Surgery, Roswell Park Cancer Center, New York
5. Principal Medical Officer and Head, Section of Ultrasound, Multan Institute of Nuclear Medicine and Radiotherapy, Multan, Pakistan
6. Director, Punjab Institute of Nuclear Medicine, Faisalabad, Pakistan

References

1. Levy M, Feingold J. Estimating prevalence in single-gene kidney diseases progressing to renal failure. Kidney Int. 2000;58(3):925–43. https://doi.org/10.1046/j.1523-1755.2000.00250.x
2. Cochat P, Deloraine A, Rotily M, Olive F, Liponski I, Deries N. Epidemiology of primary hyperoxaluria type 1. Société de Néphrologie and the Société de Néphrologie Pédiatrique. Nephrol Dial Transplant. 1995;10(Suppl 8): 3–7. https://doi.org/10.1093/ndt/10.supp8.3
3. Kopp N, Leumann E. Changing pattern of primary hyperoxaluria in Switzerland. Nephrol Dial Transplant. 1995;10(12):2224–7. https://doi.org/10.1093/ndt/10.12.2224
4. Bhasin B, Ürekli HM, Atta MG. Primary and secondary hyperoxaluria: Understanding the enigma. World J Nephrol. 2015;4(2):235–44. https://doi.org/10.5527/wjn.v4.i2.235
5. Hoppe B. Evidence of true genotype-phenotype correlation in primary hyperoxaluria type 1. Kidney Int. 2010;77(5):383–5. https://doi.org/10.1038/ki.2009.471
6. Cochat P, Liutkus A, Fargue S, Basmaison O, Ranchin B, Rolland MO. Primary hyperoxaluria type 1: still challenging! Pediatr Nephrol. 2006;21(8):1075–81. https://doi.org/10.1007/s00467-006-0124-4
7. Oli H, Davison AM. Adult systemic oxalosis presenting as acute renal failure. Postgrad Med J. 1979;55(639):44–5. https://doi.org/10.1136/pgmj.55.639.44
8. Cai R, Lin M, Chen Z, Lai Y, Huang X, Zhao G, et al. Primary hyperoxaluria diagnosed after kidney transplantation failure: lesson from 3 case reports and literature review. BMC Nephrol. 2019;20(1):224. https://doi.org/10.1186/s12882-019-1402-2
9. Spasovski G, Beck BB, Blau N, Hoppe B, Tasic V. Late diagnosis of primary hyperoxaluria after failed kidney transplantation. Int Urol Nephrol. 2010;42(3):825–9. https://doi.org/10.1007/s11255-009-9690-2
10. Talati JJ, Hulton SA, Garrelfs SF, Aziz W, Rao S, Memon A, et al. Primary hyperoxaluria in populations of Pakistan origin: results from a literature review and two major registries. Urolithiasis. 2018;46(2):187–95. https://doi.org/10.1007/s00240-017-0996-8
11. Cornell LD, Amer H, Viehman JK, Mehta RA, Lieske JC, Lorenz EC, et al; Rare Kidney Stone Consortium Primary Hyperoxaluria (RKSC PH) investigators. Posttransplant recurrence of calcium oxalate crystals in patients with primary hyperoxaluria: Incidence, risk factors, and effect on renal allograft function. Am J Transplant. 2022;22(1): 85–95. https://doi.org/10.1111/ajt.16732
12. Alsuwaida A, Hayat A, Alwakeel JS. Oxalosis presenting as early renal allograft failure. Saudi J Kidney Dis Transpl. 2007;18(2):253–6. PMID: 17496404.
13. Palsson R, Chandraker AK, Curhan GC, Rennke HG, McMahon GM, Waikar SS. The association of calcium oxalate deposition in kidney allografts with graft and patient survival. Nephrol Dial Transplant. 2020;35(5):888–94. https://doi.org/10.1093/ndt/gfy271
14. Geraghty R, Wood K, Sayer JA. Calcium oxalate crystal deposition in the kidney: identification, causes and consequences. Urolithiasis. 2020;48(5):377–84. https://doi.org/10.1007/s00240-020-01202-w

Summary of the case

1	**Patient (gender, age)**	Male, 36-year-old
2	**Final Diagnosis**	Hyperoxaluria leading to renal failure and extensive heterotopic calcification
3	**Symptoms**	Chronic renal failure
4	**Medications**	Chronic hemodialysis after graft failure
5	**Clinical Procedure**	Renal transplant
6	**Specialty**	Nephrology, Urology, Transplant medicine