

Primary Hyperoxaluria with Renal Failure and Bone Marrow Oxalosis in a young Patient in Pakistan

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Abstract

Primary hyperoxaluria is a rare condition characterized by recurrent kidney and bladder stones. It is estimated to affect 1 in 58,000 individuals worldwide. This condition is inherited in an autosomal recessive pattern. We are reporting a case of primary hyperoxaluria leading to renal failure and pancytopenia in Pakistan.

Introduction

High level of oxalate in urine is hyperoxaluria taken as a urinary oxalate levels >40mg in 24 hours or 40mg/24hours per gm of creatinine excreted. In women the criteria is stricter with 32mg/24hr. Oxalate is filtered through the kidneys and excreted as a waste product in urine, leading to abnormally high levels of this substance in urine (hyperoxaluria). During its excretion, oxalate can combine with calcium to form calcium oxalate, a hard compound that is the main component of kidney and bladder stones. Deposits of calcium oxalate can damage the kidneys and other organs and lead to hematuria, urinary tract infections, kidney damage, ESRD, and injury to other organs.

Hyperoxaluria is classically characterised in four categories according to the cause.[1]

1) Primary Hyperoxaluria: Primary Hyperoxaluria is caused by a rare autosomal recessive genetic defects in glycolate metabolism characterized by endogenous oxalate overproduction and elevated excretion.[2]

2) Enteric Hyperoxaluria: Associated with gastrointestinal problems causing Chronic Diarrhoea and malabsorption. Various causes like Inflammatory Bowel Disease, fat malabsorption, intestinal bacterial overgrowth syndrome, Chronic biliary or pancreatic diseases, surgical bowel resections can lead to increased absorption and subsequent urinary excretion of oxalate.

3) Dietary Hyperoxaluria: Dietary sources of oxalate have recently been given more importance as newer studies suggest dietary intake to be responsible for 50% of urinary oxalate [3-5] increased intake of oxalate rich food and a decreased intake of calcium and ascorbic acid lead to hyperoxaluria.

4) Idiopathic or mild: Idiopathic is considered the most common type of hyperoxaluria. The mechanism is unknown so far apart from a theory eluding to a genetic predisposition of stone formation causing nephrolithiasis.

Three genetic forms of Primary Hyperoxaluria have been defined, PH type 1, 2 and 3 are associated with mutations to *AGXT*, *GRHPR*, and *HOGA1*, respectively.[6,7] Type 1 is the most common and severe with the greatest mortality rate. Type 1 and 2 both involve Liver enzymes and as an aggressive disease pattern while the type 3 is less severe and is not associated with ESRD.[8] Here, we are reporting the second case documented in Pakistan of Primary Hyperoxaluria and the first case of primary Hyperoxaluria causing Pancytopenia.

Case Report:

A 15 year old female with ESRD was referred to our hospital for work up of recurrent nephrolithiasis, anemia and myalgia. 2 years back in Nowshera she developed epigastric pain alongwith an episode of non-bloody vomiting. Routine investigations were ordered by the local doctor. Her ultrasound abdomen revealed bilateral kidney stones. Further work up revealed right sided hydronephrosis and shrunken left kidney. She developed off and on pain in the lumbar region and was given NSAIDs on as per need. She underwent Right Ureteroscopic lithotripsy and DJ stenting followed by Left Percutaneous Nephrolithotomy 3 months later.[Figure1] Despite the surgeries her renal functions continued to deteriorate and Hemodialysis had to be done.

She was put on hemodialysis on 1-12-2014 and she is on twice weekly hemodialysis since then. She was referred to Military Hospital Rawalpindi for maintenance hemodialysis and remained admitted there for 1 month. Patient was started on Erthropeiotin analog (Epokine thrice weekly subcutaneous injections) along with Vitamin B12 and folate supplements. Phosphorous binders and Vitamin D3 supplement were also added to the treatment plan. One year into the treatment the patient tested positive for HbsAg and Anti HCV but seroconverted in a few months without any intervention. Subsequent tests showed patient negative for HCV PCR and HbsAg, Serum ALT at 20U/l and Total bilirubin at 11Umol/L, Alkaline Phosphate however was very high at 1809U/L. Abdominal Ultrasound revealed hepatosplenomegaly with moderate to severe liver fibrosis with abdominal ascites and therapeutic Ascitic tap was carried out. 6 months ago patient developed anemia and a complain of myalgia with arthralgias. Complete Blood Count test showed anemia with Hb 7.8g/dL and 2 units of red cell count were transfused, before patient was referred to our hospital CMH Lahore for further workup and management.

On examination the patient was a pale looking young girl with palpable spleen and no other pertinent findings. Her parents had a consanguineous marriage and she has three siblings. Her elder brother had a complain of nephrolithiasis and has had a nephrolithotripsy but since then has been asymptomatic. A repeat CBC showed HB of 8.7g/L TLC $3.5 \times 10^9/L$ and platelets $120 \times 10^9/L$. Peripheral smear used normochromic normocytic, poikilocytosis with tear drop cells and a Retic count of 3% and serum Ferritin at 963 (11-307ng/ml). Vitamin B12 and folate were within limits. A diagnosis of Pancytopenia was made and Bone marrow biopsy was done. Bone profile was also ordered and revealed normal serum Calcium, borderline high Serum Phosphate and elevated Parathyroid Hormone.

Bone Marrow Trepine Biopsy revealed crystalline deposits and extensive fibrosis consistent with oxalate morphology. Her funduscopy also revealed crystalline deposits in the retina although no visual symptoms were reports by the patient. A diagnosis of Primary Oxaluria was made of the basis of history and the biopsy results. Other test to confirm diagnosis included 24 hour urinary oxalate which turned out 31mg/dl of a 70m urine output. Due to lack of genetic testing available in the city the type could not be classified.

ECHO was done to rule out cardiac oxalosis. Pyridoxine was added to the regimen and maintenance dialysis continued. The patient has been put on the list for combined hepatorenal transplant. The younger siblings were also advised Ultrasound abdomen and 24 hour urinary oxalate testing. The results were negative.

At present her condition is stable on twice weekly hemodialysis.

Discussion

Primary Hyperoxaluria is a very rare condition and till now only three known reported cases of Primary Hyperoxaluria in people of Pakistani origins and two of which were diagnosed in Pakistani immigrant to

France [1] and to the United Kingdom [9] and only one is case from a private hospital in Lahore reported in 2015 [10]. The rarity of this disease makes it difficult to understand the disease pattern and clinical manifestation and subsequently develop treatment options. PH1, caused by deficiency of the liver-specific peroxisomal enzyme alanine-glyoxylate aminotransferase (AGT), is the most severe PH form, accounting for about 80% of genetically characterized patients.[11] Calcium oxalate oversaturation leads to recurrent urolithiasis and/or nephrocalcinosis, with reduced renal elimination due to renal damage resulting in oxalate deposition in all tissues (systemic oxalosis).[12] It can manifest as infantile oxalosis, resulting in early death, but a more typical course is recurrent urolithiasis with progressive nephrocalcinosis and ESRD by 20–30 years of age.[13] The classic presentation is recurrent urolithiasis and marked hypercalciuria in the first decade, but less active stone formation later.(14) Over time, kidney function decreases such that the kidneys can no longer excrete as much oxalate as they receive.(15) This result a false negative 24 hour urinary oxalate test in patients with advanced kidney disease. This is evidenced by the relatively borderline rise in urinary oxalate levels in our patient.PH2 is generally less severe than PH1 but with a similar age at first symptoms.(14) It is caused by deficiency of glyoxylate reductase/hydroxypyruvate reductase (GR/HPR), and accounts for about 10% of genetically characterized PH cases. PH3 is the least severe form, with good preservation of kidney function in most patients.

Systemic Oxalosis is a common complication of Primary Hyperoxaluria with High Oxalate plasma levels leading to deposition of oxalate in multiple organs. Oxalosis has been reported in myocardium, bone, retina and Bone marrow, leading to vascular diseases, oxalate osteopathy, conduction heart block, pancytopenia and more. (14)

Pancytopenia and anemia resistant to erythropoietin and B12 supplements is a rare complication of PH and an exhaustive PubMed search only a few researches studying the association between PH and Pancytopenia.(15-20) Bone Marrow oxalosis has been defined as the cause with oxalate crystal seen on Bone marrow biopsy similar to findings seen in this patient.(15) Reversal of Pancytopenia secondary to oxalosis hasn't been documented. Only one case report in 2004 in southern India showed a 50% decreased bone marrow involvement compared to pre kidney transplant biopsy.(21)

Till now the best treatment in a diagnosed case of PH type 1 and 2 with ESRD is a combined hepatic and renal transplant.(22-24) Hemodialysis and vitamin B6 supplements (starting from 5 mg/kg to a maximum dose of 20 mg/kg) have shown to be of some benefit in earlier stages of the disease but ultimately the patient would require transplant.(23) Gene therapy is also a been suggested as an option but it still an experimental rather than the standard treatment modality. (22-24)

We are seeing more and more cases of Primary Hyperoxaluria in our population here in Pakistan, along with other genetic illness due to continued consanguineous marriages in our culture. It is therefore imperative to study these in more detail and include such rare syndromes in our differential diagnosis to allow for prompt diagnosis and management. An increased awareness of Primary Hyperoxaluria and its clinical manifestations can allow for clinicians to have a high clinical suspicion necessary for early diagnosis of PH. Further genetic testing can also help us pin point exact mutations associated with primary Hyperoxaluria in our population and allow for improved outcomes by targeted genetic treatment.



Figure 1: Calcium Oxalate stones and Oxalate crystals in Bone Marrow at 40X magnification.

References

1. Cochat P. Primary hyperoxaluria type 1. *Kidney Int.* 1999 Jun. 55(6):2533-47.
2. Mukhin VN, Khomiakov KA. [Phenogenetics of offspring and their ancestors]. *Tsitol Genet.* 2003 Jul-Aug. 37(4):54-6.
3. Massey LK, Roman-Smith H, Sutton RA. Effect of dietary oxalate and calcium on urinary oxalate and risk of formation of calcium oxalate kidney stones. *J Am Diet Assoc.* 1993 Aug. 93(8):901-6.
4. Holmes RP, Goodman HO, Assimos DG. Contribution of dietary oxalate to urinary oxalate excretion. *Kidney Int.* 2001 Jan. 59(1):270-6.
5. Khan SR, Glenton PA, Byer KJ. Dietary oxalate and calcium oxalate nephrolithiasis. *J Urol.* 2007 Nov. 178(5):2191-6.
6. Beck B, Hoppe B: Is there a genotype-phenotype correlation in primary hyperoxaluria type 1? *Kidney Int* 70:984-996, 2006
7. Belostotsky R, Pitt JJ, Frishberg Y. Primary hyperoxaluria type III--a model for studying perturbations in glyoxylate metabolism. *J Mol Med (Berl).* 2012 Dec. 90(12):1497-504.
8. Milliner DS, Harris PC, Lieske JC, Pagon RA, Adam MP, Ardinger HH, et al. Primary Hyperoxaluria Type 3. 1993.
9. von Schnakenburg C, Hulton S, Milford D, Roper H, Rumsby G. Variable Presentation of Primary Hyperoxaluria Type 1 in 2 Patients Homozygous for a Novel Combined Deletion and Insertion Mutation in Exon 8 of the AGXT Gene. *Nephron.* 1998;78(4):485-488.
10. Ahmed W, Rehman A, Acharya S. Hyperoxaluria After Renal Transplantation. *Journal of the College of Physicians and Surgeons Pakistan.* 2017;27(03):33-35.
11. Danpure C. Advances in the enzymology and molecular genetics of primary hyperoxaluria type 1. Prospects for gene therapy. *Nephrology Dialysis Transplantation.* 1995;10(suppl8):24-29.
12. van Woerden C. Primary hyperoxaluria type 1 in The Netherlands: prevalence and outcome. *Nephrology Dialysis Transplantation.* 2003;18(2):273-279.
13. Harambat J, Fargue S, Acquaviva C, Gagnadoux M, Janssen F, Liutkus A et al. Genotype-phenotype correlation in primary hyperoxaluria type 1: the p.Gly170Arg AGXT mutation is associated with a better outcome. *Kidney International.* 2010;77(5):443-449.
14. Bhasin B. Primary and secondary hyperoxaluria: Understanding the enigma. *World Journal of Nephrology.* 2015;4(2):235.
15. Raju D, Cantarovich M, Brisson M, Tchervenkov J, Lipman M. Primary Hyperoxaluria: Clinical Course, Diagnosis, and Treatment After Kidney Failure. *American Journal of Kidney Diseases.* 2008;51(1):e1-e5.
16. Marangella M, Vitale C, Petrarulo M, et al: Bony content of oxalate in patients with primary hyperoxaluria or oxalosis-unrelated renal failure. *Kidney Int* 48:182-187, 1995
17. McKenna RW, Dehner LP: Oxalosis. An unusual cause of myelophthisis in childhood. *Am J Clin Pathol* 66:991- 997, 1976
18. Taşlı F, Özkök G, Ok ES, Soyer N, Mollamehmetoğlu H, Vardar E. Massive bone marrow involvement in an end stage renal failure case with erythropoietin-resistant anemia and primary hyperoxaluria. *Ren Fail* 2013;35:1167-1169.
19. M. J. Walter and C. V. Dang, "Pancytopenia secondary to oxalosis in a 23-year-old woman," *Blood*, vol. 91, no. 11, p. 4394, 1998
20. M. N. Hassan, W. S. W. Abd Rahman, Z. Zulkafli et al., "Bone marrow involvement in systemic oxalosis presenting as pancytopenia and uremia—a first reported case in Malay population," *Research*, vol. 1, article 1129, 2014.
21. SUD K, SWAMINATHAN S, VARMA N, KOHLI H, JHA V, GUPTA K et al. Reversal of pancytopenia following kidney transplantation in a patient of primary hyperoxaluria with bone marrow involvement. *Nephrology.* 2004;9(6):422-425.
22. Hoppe B. An update on primary hyperoxaluria. *Nat Rev Nephrol.* 2012;8:467-475.
23. Hoppe B, Latta K, von Schnakenburg C, Kemper MJ. Primary hyperoxaluria--the German experience. *Am J Nephrol.* 2005;25:276-281.
24. Cochat P, Hulton SA, Acquaviva C, Danpure CJ, Daudon M, De Marchi M, Fargue S, Groothoff J, Harambat J, Hoppe B, et al. Primary hyperoxaluria Type 1: indications for screening and guidance for diagnosis and treatment. *Nephrol Dial Transplant.* 2012;27:1729-1736.