

# Acute Kidney Injury and Anemia in Infants with Primary Hyperoxaluria: Two Case Reports

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## Abstract:

Primary hyperoxaluria is a rare hereditary disease that usually presents with renal stone, nephrocalcinosis and renal insufficiency. Anemia is usually expected secondary to chronic kidney disease or bone marrow oxalosis following hyperoxalemia. However, sudden onset of renal insufficiency and anemia is very unusual and not easily explained. In this report, we present two infants with histopathologic diagnosis of hyperoxaluria who presented with sudden onset of anuria and severe anemia that required blood transfusion. Both patients had normal body growth indices. Kidneys and urinary bladder x-rays in both infants and serial ultrasound evaluations in one of them did not reveal any renal stone or nephrocalcinosis. The other patient had multiple microcalculi in both kidneys on ultrasound. We may conclude that in any infant with unexplained acute kidney injury and anemia, hyperoxaluria must be considered and kidney biopsy can be conclusive.

**Keywords:** Primary hyperoxaluria; Anemia; Infant; Acute kidney injury; Renal insufficiency.

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## Introduction

Primary hyperoxaluria (PH) is a rare disease with autosomal recessive inheritance that mainly affects the kidneys. Based on the associated specific metabolic defects, three main types of PH are known. The most common and rapidly progressing form is type 1 which accounts for about 80% of all cases. This type of PH is due to mutation in a gene named AGXT encoding alanine-glyoxylate aminotransferase (1). Symptoms of PH type 1 vary in severity and can present from infancy to adulthood.

Overproduction of oxalate in liver in PH type 1 results in hyperoxaluria that can lead to urolithiasis, nephrocalcinosis and/or progressive renal insufficiency as oxalate is highly insoluble (2,3). With deteriorating kidney function, plasma levels of oxalate rises.

This leads to deposition of oxalate in all tissues including the bone marrow causing anemia (2,4). Chronic kidney disease (CKD) leading to erythropoietin deficiency is another potential cause of anemia in these patients (5).

However, to our knowledge, sudden onset of renal insufficiency and anemia that was observed in our patients is very unusual and not easily explained.

## Case Reports

### Case 1:

A 5-month-old male infant, product of a twin delivery, was quite well up to one day prior to admission when he developed anuria. On admission, he had normal growth indices and his blood pressure was 100/70 mm Hg.

The only positive physical findings were pallor and periorbital edema.

On arrival, hemoglobin (Hb) level was 5 g/dl with normal red blood cell (RBC) indices for his age. White blood cell (WBC) count was 4400/mm<sup>3</sup> with 63% lymphocytes and platelet count was 643000/mm<sup>3</sup>. Other laboratory measurements on arrival included: Blood urea nitrogen (BUN)= 83 mg/100 ml, serum creatinine (Cr)=7.8 mg/dl, serum sodium (Na)= 122 mEq/lit, serum potassium (K)= 4 mEq/lit, lactate dehydrogenase (LDH)= 627 IU/ml (normal range: up to 1100IU/ml), serum bicarbonate (HCO<sub>3</sub>) =13.4 mEq/lit, pH= 7.41 and PCO<sub>2</sub>= 21 mm Hg. Peripheral blood smear revealed 1% fragmented RBC. Antinuclear antibody, C3 and C4 were in normal range.

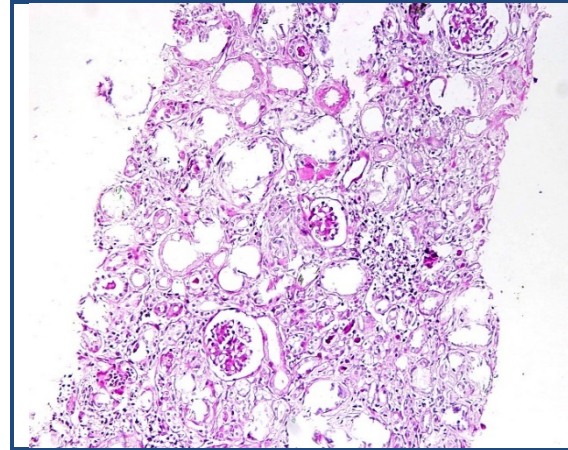
Blood transfusion was done and peritoneal dialysis was started. He gradually developed urine output but it was within the oliguric range. Urinalysis revealed 3+ protein and 3+ blood with many WBC/ high-power field (HPF) and many RBC/ HPF. Urine culture was negative.

Kidneys and urinary bladder x-ray did not show any renal stone or nephrocalcinosis. Ultrasonography revealed normal size kidneys with severely increased echogenicity and decreased corticomedullary differentiation without stone or nephrocalcinosis. Echocardiography was normal.

His parents were not related and his twin sister was normal. He had a 9-year old brother with renal stone and hyperoxaluria with documented AGXT mutation. Considering the family history, genetic study for the patient and his twin sister was done. He also had AGXT mutation but genetic study of his sister was normal. Thus, vitamin B6 was started and percutaneous kidney biopsy was done.

On the biopsy, all the 67 glomeruli were normal for his age, but the tubules were dilated and filled with calcium oxalate crystals. Severe deposition of calcium oxalate crystals with infiltration of chronic inflammatory cells (about 25%) in the interstitium was also reported (Figure 1). Immunofluorescent study was negative.

Proteinuria was disappeared early on follow-up. During 18 months of follow-up, the patient remained oliguric and dialysis dependent.



**Figure 1.** Renal biopsy shows fan-shaped birefringent calcium oxalate crystals in tubules and interstitium (H&E, polarizing 100x)

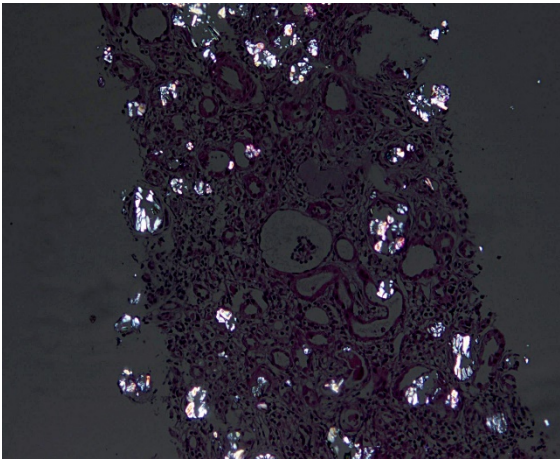
### Case 2:

An 11-month-old male infant was admitted following three days of diarrhea and vomiting. He had been completely healthy with normal growth and development until three days before the admission. He was the first child of a first degree related young couple. On admission, he had periorbital edema and pallor with normal blood pressure and normal body temperature. Laboratory findings on admission were as follows: BUN=91mg/dl, serum Cr=8.7 mg/dl, Na= 135 mEq/l, K=4 mEq/l, Hb=6.2 g/dl, WBC count=10000/mm<sup>3</sup> with 54% PMN, platelet count=292000/mm<sup>3</sup>, LDH=603 IU/ml, pH=7.46 and HCO<sub>3</sub>=16.4mEq/lit. Prothrombin time, partial thromboplastin time and liver function tests were normal. Urinalysis showed 1+protein, many WBC/HPF and 2-4 RBC/HPF. Peripheral blood smear showed 1% nucleated RBC. Antinuclear antibody, C3 and C4 were in normal range.

Kidneys and urinary bladder x-ray did not show any renal stone or nephrocalcinosis. Ultrasonography revealed normal sized kidneys with increased parenchymal echogenicity and bilateral multiple microcalculi but no hydronephrosis. Blood transfusion was done and peritoneal dialysis was started. Finally, percutaneous kidney biopsy was performed. There were 40 normal glomeruli and moderate to severe mononuclear cell as well as calcium oxalate deposition in the interstitium on the biopsy.

Most of the tubules were dilated and filled with calcium oxalate crystals (Figure 2). There was less than 5% of interstitial fibrosis or tubular atrophy. High dose of vitamin B6 was started for the patient.

Due to financial issues, genetic study for PH could not be done for this patient. During 19 months of follow-up, the patient was anuric and dialysis dependent.



**Figure 2.** Renal biopsy shows chronic interstitial inflammation and mild tubular atrophy (PAS, 200x)

## Discussion

Both of our patients with PH presented with sudden onset of anuria and anemia requiring dialysis and blood transfusion. PH type 1 was documented by genetic study and kidney biopsy in the first case and the presence of renal stone in both kidneys and the pathologic report were highly suggestive of PH in the second case. PH is an autosomal recessive disorder (1); therefore, it is more prevalent in the societies with consanguineous unions. Although consanguineous unions are common in our society (6), there was no consanguinity between parents of our first patient.

The presenting symptoms and the severity of PH type 1 is variable. The symptoms can begin from neonatal period to adulthood although the median age of symptom onset is 5.5 years (7). On an international registry for PH including 95 patients, 90% of patients had urolithiasis, 48% had nephrocalcinosis and 15% were asymptomatic at the time of diagnosis. About

80% of the patients had PH type 1 on this registry (7).

Less than 20% of patients with PH type 1 present during the first few months of life (8). These patients usually have a severe form of the disease with poor prognosis (9). Anemia is usually expected in these patients following either chronic kidney disease (5) or bone marrow involvement secondary to oxalosis (2,4). Although some chronic and irreversible histopathologic changes were observed in the tubulointerstitial areas of our cases, normal glomeruli in the renal tissue of both infants are not fully explained by chronic kidney disease. Moreover, normal physical growth, normal size of the kidneys and acute clinical presentation in our patients were in favor of acute kidney injury rather than chronic kidney disease. Considering bone marrow involvement, although serum oxalate level measurement or bone marrow aspiration were not done in our patients, lack of pancytopenia, leukoerythroblastic picture and hepatosplenomegaly makes bone marrow oxalosis less likely (10). Increased extracellular water volume secondary to acute kidney injury can cause hemodilution and lower Hb concentration (11). However, significantly low Hb in our patients cannot be explained by hemodilution. Thus, anemia was not expected in our patients and cannot be fully explained.

In a study from India, two similar cases with primary infantile hyperoxaluria leading to acute kidney injury and anemia were reported. However, there was no genetic testing in that study and development of anemia in those patients was not discussed (8).

PH type 1 is a rare disease with variable presentation (12). Therefore, the diagnosis is often challenging especially in the infants and children. Another reason might be that normal ranges of serum and urine oxalate levels in infants and children are not clearly defined (8). There are some reports in the literature that the diagnosis of PH was delayed or even missed and led to death of the patient (8,13). Thus, high clinical suspicion is a key element for timely diagnosis of PH and efficacy of the treatment (3,8).

Different treatment options for PH type 1 have been considered to achieve the goal of increased urine flow and decreased crystallization of oxalate in kidney tubules (14). These measures

include high fluid intake, urinary alkalization, pyridoxine supplementation, dialysis and liver-kidney transplantation (3). High dose of pyridoxine is expected to reduce oxalate excretion or even normalize it in about 30% of patients with PH type I (15). Therefore, it was prescribed to our patients.

### Conclusion

We may conclude that in any infant with unexplained acute kidney injury, even with anemia and nonconsanguineous parents, evaluation for PH is indicated.

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### Conflict of Interest

Authors declared no conflict of interest to declare.

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