

**PRIMARY HYPEROXALURIA TYPE1: THE BONE MARROW BIOPSY MAKES THE DIAGNOSIS IN 2 CASES****A. Abouzoubair\*<sup>1</sup>, L. Boualla<sup>2</sup>, S. Belmokadem<sup>1</sup>, Z. Alhamany<sup>3</sup>, T. Bouattar<sup>1</sup>, L. Benamar<sup>1</sup>, R. Bayahia<sup>1</sup>, A. Sefiani<sup>2</sup> and N. Ouzeddoun<sup>1</sup>**<sup>1</sup>Department of Nephrology-Dialysis and Kidney Transplantation, Ibn Sina University Hospital. Rabat. Morocco.<sup>2</sup>Center for Human Genomics, Faculty of Medicine and Pharmacy, Mohamed V University. Rabat. Morocco.<sup>3</sup>Department of Pathological Anatomy and Cytology. Ibn Sina University Hospital. Rabat Morocco.**\*Corresponding Author: Dr. Abouzoubair A.**

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**ABSTRACT**

Primary hyperoxaluria type 1 (PH1) is a rare autosomal-recessive disease caused by mutations in the gene AGXT. That induces overproduction of oxalate due to the liver specific enzyme, alanine-glyoxylate aminotransferase, deficiencies. As glomerular filtration rate decreases, systemic oxalate storage occurs throughout all the body, and mainly in the skeleton. The diagnosis is first based on urine oxalate measurement, then on genotyping. Conservative measures including hydration, crystallization inhibitors and pyridoxine may allow long lasting renal survival and should be undertaken as early as possible. Treatment based on liver or liver and kidney transplant, which may supplement enzymatic activity and kidney function respectively. Promising therapeutic agents are currently under study. We report two cases of chronic hemodialysis patients (CHD) for whom late diagnosis of PH1 was made by a bone marrow biopsy (BMB). These cases illustrate the harmful consequences associated with the delayed diagnosis of this rare disease.

**KEYWORDS:** Primary hyperoxaluria type 1, alanine-glyoxylate aminotransferase, oxalate, diagnosis, treatment.**INTRODUCTION**

Primary hyperoxaluria type 1 (PH1) is a rare autosomal-recessive disease caused by mutations in the gene AGXT. That induces overproduction of oxalate due to the liver specific enzyme, alanine-glyoxylate aminotransferase, deficiencies. Recurrent urolithiasis and nephrocalcinosis are the first signs, then come the end-stage renal failure and systemic oxalosis.

We report two cases of chronic hemodialysis patients (CHD) for whom late diagnosis of PH1 has been reported on bone marrow biopsy (BMB).

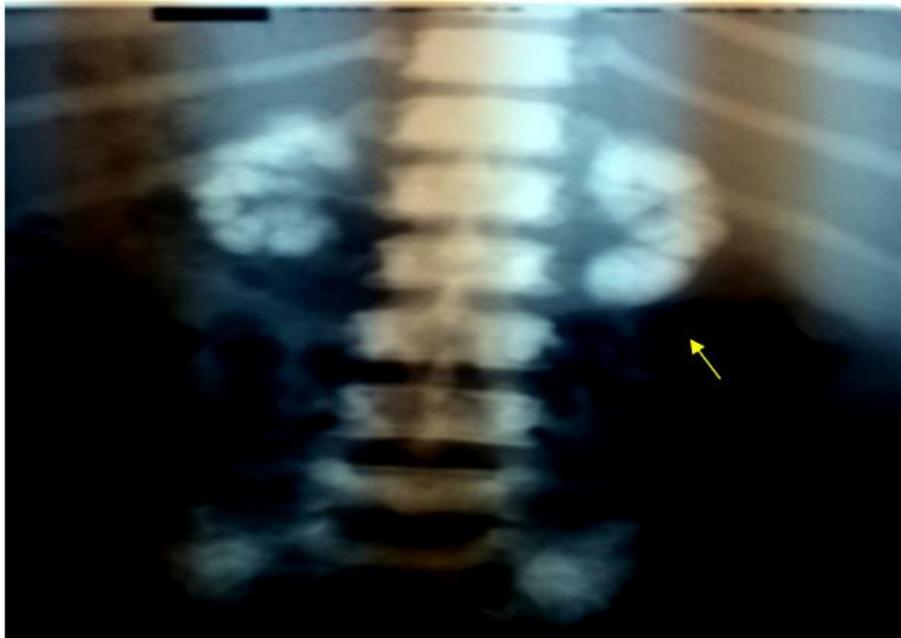
**CASE 1**

Y.G. is a young patient of 16 years old, in chronic hemodialysis since the age of 7, secondary to nephrocalcinosis. His parents were second degree cousins. The patient was hospitalized for abdominal distension associated to a bone pain and deterioration of his general condition. Physical examination revealed hepatosplenomegaly with ascites and lymphadenopathy in femoral, cervical and axillary nodes. The blood test finds a pancytopenia. The anaemia (haemoglobin level at 9.1 g/dl) was resistant to erythropoietin (EPO). The phosphocalcic balance was normal with a parathormon at

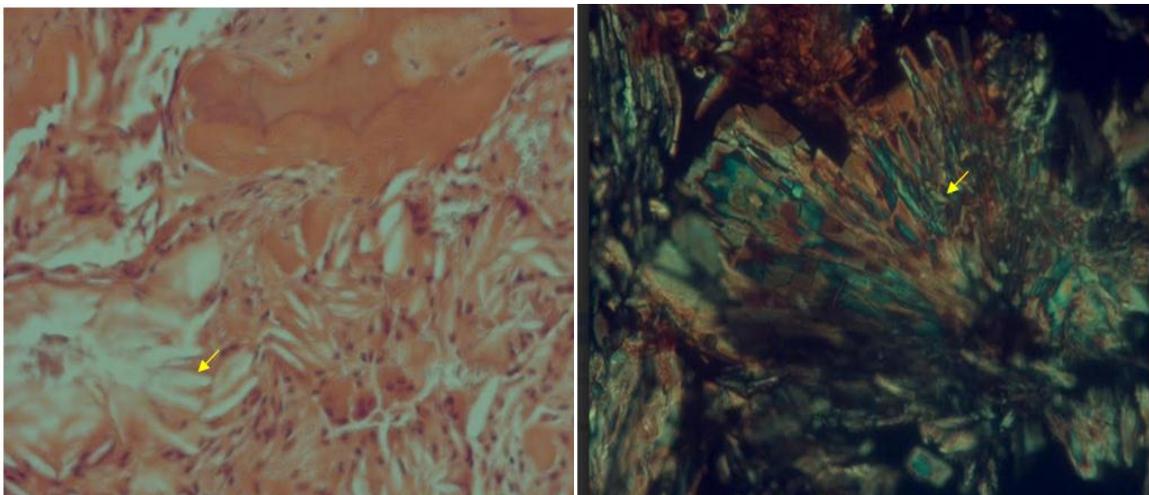
182 pg/ml. The hand radiograph shows a diffuse bone condensation (a). Kidney-ureter- bladder x-ray (KUB) shows nephrocalcinosis (b). The thoraco-abdomino-pelvic computed tomography scan shows a homogeneous hepato-splenomegaly with mid-abundance ascites and diffuse condensing bone lesions. The scan doesn't reveal a deep adenopathies (ADP) or a pulmonary parenchymatous lesion. The biopsy of cervical ADP reveals reactional adenitis. Examination of BMB specimen showed that the marrow was extensively replaced with oxalate crystals (c) and fibrous connective tissue with severe decrease of hematopoietic cells. The Genetic testing proved diagnosis by showing the recurrent mutation in Morocco: c.731T > C in exon 7 of AGXT gene in the homozygous state which confirms the diagnosis of HP1.



**A: Hand radiograph: Metaphyseal condensation on the wrist.**



**B: KUB: nephrocalcinosis.**

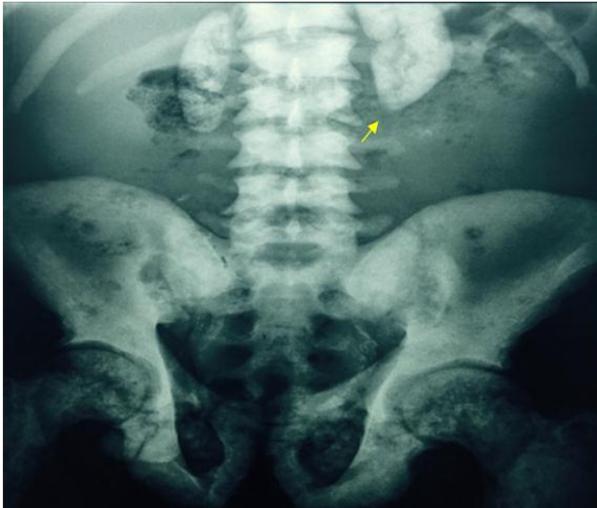


**C: BMB: oxalate crystals.**

**CASE 2**

Mr R.E. is 35 years old, from a non-consanguineous marriage and in chronic hemodialysis since the age of 29, secondary to nephrocalcinosis.

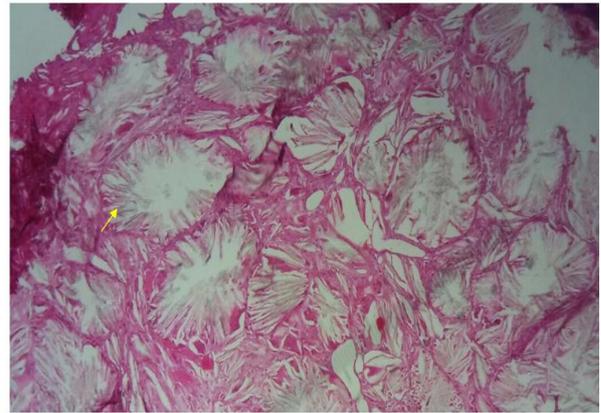
The patient was hospitalized for abdominal distension associated to a bone pain and deterioration of his general condition. Physical examination revealed splenomegaly with ascites and thoracic deformity. The blood test reveals a pancytopenia. The anaemia (haemoglobin level at 6.7 g/dl) was resistant to EPO. No infectious biological signs. KUB objectified a nephrocalcinosis with bone demineralization (d). The abdominal ultrasound noted ascites of great abundance, splenomegaly without hepatomegaly. There was no sign of portal hypertension. The abdominopelvic CT objectified the same images, in addition to bone remodeling and calcifications of the soft tissues (e). On the BMB there is a massive medullary infiltration by oxalate crystals (f). The patient died before taking the genetic test.



**D: KUB: nephrocalcinosis with bone demineralization.**



**E: Pelvic CT showing calcification in the soft parts.**



**F: BMB Massive medullary infiltration by oxalate crystals.**

**DISCUSSION**

Primary hyperoxaluria type 1 is a rare autosomal-recessive disease. It has an estimated prevalence ranging from 1 to 3 three per million and an estimated incidence rate of ~1.100 000 live births per year in Europe.<sup>[1-2]</sup> In contrast, PH is more prevalent in countries where consanguineous marriages are common. Almost 10% of Kuwaiti and ~13% of Tunisian children with end stage renal diseases have been reported to have PH. PH1 results from an enzymatic deficiency in alanine-glyoxylate aminotransferase in the peroxisomes of the liver, causing hyperoxaluria.<sup>[5]</sup> The calcium oxalate formed being insoluble in urine, the first symptoms usually concern the urinary tract in the form of urinary lithiasis, nephrocalcinosis and renal insufficiency. The latter accentuates systemic tissue precipitation by default of excretion of oxalate leading to a systemic oxalosis.<sup>[6,7,8]</sup> Different tissues and organs are the seat of crystal deposition such as kidneys, bones, heart, eyes, skin, blood vessels and others.<sup>[9,10,11,12]</sup>

Patients should undergo a metabolic screening for PH1 at presentation of a first kidney stone (in a child) or recurrent or familial stone disease (at any age) or if nephrocalcinosis is detected.<sup>[9]</sup>

Stone analysis may reveal characteristic morphology and contain >95% calcium oxalate (CaOx) monohydrate (whewellite) often presenting with a particular morphology. Preliminary PH1 diagnostic workup should include 24-h urine collection for oxalate, creatinine and glycolate; plasma oxalate (POx) when GFR is < 60 mL/min/1.73m<sup>2</sup>.<sup>[9]</sup> In the end stage fo renal failure, the oxalate/creatinine and glycolate/creatinine plasma ratios are useful.<sup>[5]</sup> When the phenotype is evocative, it makes sense to propose genotyping targeting the most frequent mutations according to the geographical and ethnic origin of the patient.<sup>[13]</sup>

Conservative treatment (hyperhydration, crystallization inhibitors, pyridoxine) is essential and should be undertaken as early as possible. No dialysis method is effective enough to compensate for the overproduction of

oxalate. Liver and kidney transplantation should be planned relatively early, before the advanced renal failure stage, to limit the damage.<sup>[5]</sup>

There is light on the horizon that new treatment options will be available in due time, as there are several promising therapeutic agents currently under investigation, some being at the first levels of drug development, but some already in ongoing clinical trials (phase I-III).<sup>[14]</sup>

## CONCLUSION

HP1 should be discussed very early in the case of any child with renal lithiasis. The diagnosis is confirmed in the genetic study. In chronic kidney disease Stages 4 and 5, the best outcomes to date were achieved with combined liver–kidney transplantation.

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