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Primary Hyperoxaluria Type 1 in Adulthood: Case Series

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Abstract

Introduction: Primary hyperoxaluria type 1 (HP1) is a rare lithiasis with systemic involvement, due to the accumulation of calcium oxalate crystals. In the absence of therapeutic management, it progresses to end-stage chronic renal failure. The aim of this study is to describe and analyse the observations of our patients with HP1. **Patients and methods:** This is a retrospective study carried out between 2014 and 2023 in the Nephrology-Dialysis Transplant Department of the Ibn Sina University Hospital in Rabat. The clinical, paraclinical and evolutionary elements were taken from the patients' medical records. **Results:** We collected 11 cases, with a mean age of 27 ± 8.5 years and a M/F sex ratio of 1.7. The diagnosis of HP1 was made on the basis of genetic analysis in 8 patients, morphological and spectro-photometric analysis of the calculus in one patient, biopsy of the graft in one patient and crystalluria and a family history of PH1 in one patient. Two patients died, and 8 patients were on chronic haemdialysis with systemic damage. Only one patient maintained a stable GFR at 60 ml/min. **Conclusion:** Early diagnosis combined with conservative treatment is the only way to limit the rapid progression of this disease. This requires awareness and collaboration between nephrologists, urologists and biologists within a specialised team.

Keywords

Primary Hyperoxaluria, Adulthood, Kidney Disease

1. Introduction

Primary hyperoxaluria type 1 (PH1) is a rare hereditary autosomal recessive kidney stone disease. It is often underdiagnosed or diagnosed late.

Its prevalence remains higher in countries with high rates of consanguinity,

such as Tunisia, the Canary Islands, and the Middle East [1]-[4].

PH1 is caused by a dysfunction of alanine-glyoxylate aminotransferase (AGT), an hepatic enzyme, leading to oxalate over accumulation and formation of calcium oxalate crystals [1]. These insoluble crystals precipitate within the kidneys, resulting in end-stage kidney disease (ESKD) [1]. As kidney function deteriorates, crystals accumulate in other organs (bones, retina, heart, vessels, skin, etc.), highlighting the importance of early diagnosis and treatment.

In ESKD, none of the dialysis methods are effective enough in eliminating the excess oxalate, therefore, liver and kidney transplantation should be planned before advanced kidney failure to prevent systemic oxalosis in order to limit systemic damage [5]. This study aims to describe and analyze the cases of 11 patients with PH1.

2. Patients and Methods

This is a retrospective and descriptive study, conducted over 9 years, between 2014 and 2023, in the Nephrology-Dialysis-Transplant Department at Ibn Sina University Hospital in Rabat. We included all patients with primary hyperoxaluria diagnosed in adulthood who were hospitalized or seen in consultation during the study period.

The diagnosis of primary hyperoxaluria was confirmed by genetic study or guided by the results of complementary biological and radiological explorations. The clinical, biological and radiological data of the patients were collected from their medical records.

The data collected was based on patients' medical records, and are listed below:

- Circumstances of discovery
- Personal and family medical history
- Consanguinity
- The results of the paraclinical assessments such as complete blood count hemoglobin, leukocytes, leukocyte formula [Polymorphonuclear neutrophils, lymphocytes, platelet], crystalluria, bone marrow biopsy, renal graft biopsy, morphological and infrared spectrophotometric analysis of stones, radiological assessment: Kidney, Ureter, and Bladder X-ray (KUB x-ray), abdominal-pelvic CT scan, Transthoracic Echocardiogram (TTE), lumbar Magnetic resonance imaging (MRI) scan.
- Genetic study
- Treatment modalities
- Evolution

Data were analyzed using Jamovi 2.3.9 software. Quantitative variables were expressed as means ± standard deviation and qualitative variables were expressed as percentages.

3. Results

Over the nine-year period of study, we identified 11 cases of PH1 with an aver-

age age of 27 ± 8.5 years and a M/F ratio of 1.5. These patients were from various regions of Morocco. Seven patients were consanguineous and two patients had a family history of PH1. The time interval between the first urinary stone and positive diagnosis ranged from 1 to 20 years. Clinically, eight patients experienced bone pain and deterioration in general condition. Ascites occurred in three patients, hepatosplenomegaly in two, splenomegaly in one. Two patients had subcutaneous calcifications.

Biologically, four chronic hemodialysis patients, *i.e.* 36% of cases, had normocytic normochromic anemia, of whom two had pancytopenia, while one patient had a normal hemoglobin level. Crystalluria showed type 1C whewellite calcium oxalate crystals in two patients. Bone marrow biopsy (BMB) in four patients with pancytopenia revealed marrow invasion by oxalate crystals. Spectrophotometric analysis revealed pathognomonic type 1C oxalocalcic calculi in two patients. KUB x-radiography was performed in four patients, revealing nephrocalcinosis (**Figure 1**, **Figure 2**). Renal biopsy of the graft, showed calcium oxalate deposits in the tubules in favour of PH1 (**Figure 3**).

Abdominal CT scan showed bone lesions in two patients, hepatosplenomegaly in two and splenomegaly in one patient. In another patient, TTE showed a scintillating appearance of the myocardium due to oxalate crystal deposits, while lumbar MRI showed diffuse vertebral compression of D12, L2, and L5.

Genetic study revealed the recurrent moroccan mutation c.731T>C in exon 7

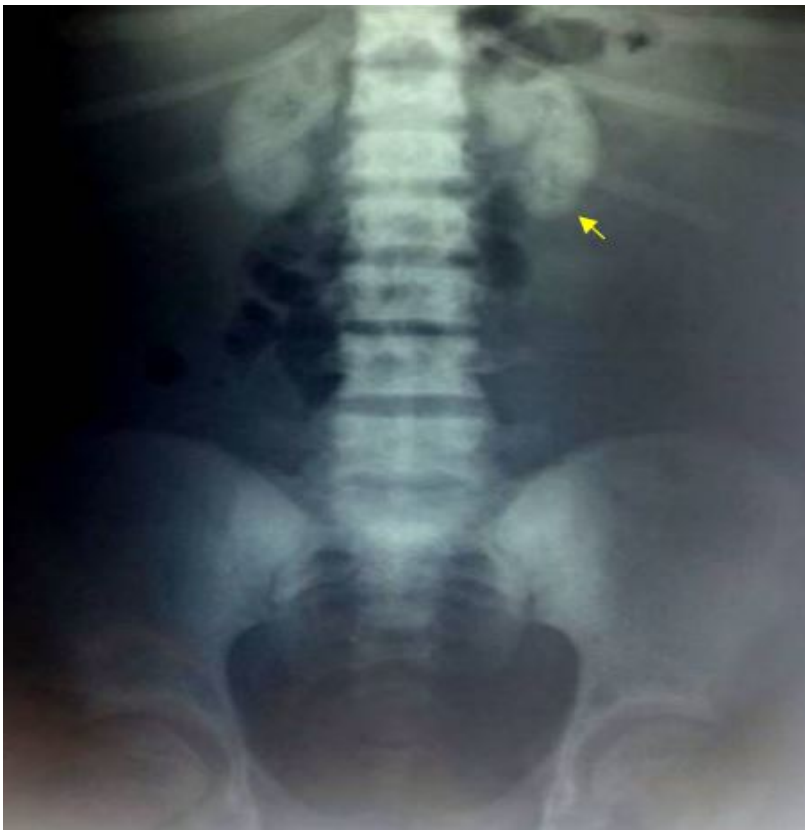


Figure 1. KUB X-ray: Bilateral nephrocalcinosis (case I.F).

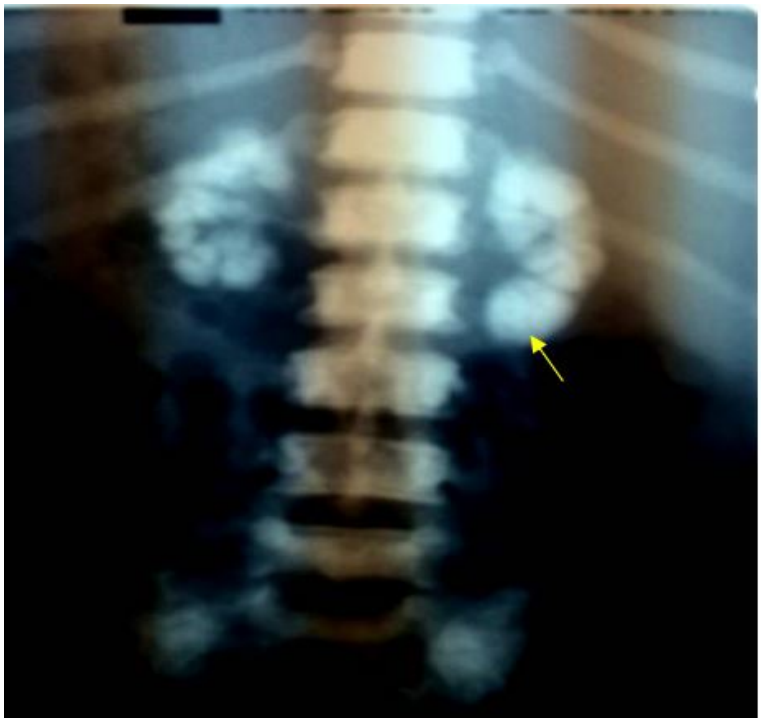
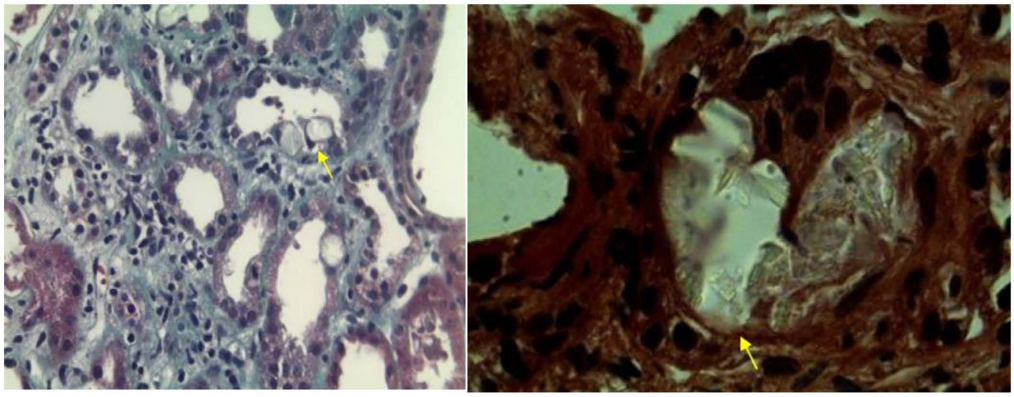


Figure 2. KUB X-ray: Bilateral nephrocalcinosis (case Y.G).



(a) (b)

Figure 3. Graft biopsy puncture: the majority of tubes (70%) are occupied by calcium oxalate crystals. (a) Masson's trichrome staining (High magnification); (b) Oxalate crystals with silver coloring.

of the AGXT gene in the homozygous state within eight patients, confirming the diagnosis of PH1.

Based on clinical and paraclinical examinations, the diagnosis of PH1 was confirmed in eight cases through genetic study. In the other cases, the diagnosis was based on clinical, biological, radiological outcomes.

The majority of our patients with primary hyperoxaluria diagnosed in adulthood were already at the dialysis stage, *i.e.* 90% of cases.

Two patients died at the age of 19 and 35 respectively, due to pericarditis in one and acute lung oedema in the other. Seven patients are currently on haemodialysis (HD), and one patient is on peritoneal dialysis (PD), with systemic

damage. Only one patient received conservative treatment and maintained a stable eGFR of 60 ml/min according to the MDRD formula. The conservative treatment was based on:

A water intake of 3 l/day distributed over the entire nycthemera, monosodium citrate at a dose of 100 - 150 mg/kg/day in 3 to 4 doses, vitamin B6: 300 mg/day and diet low in oxalate.

None of our patients has benefited from liver transplantation (Table 1).

Table 1. Summary of the 11 PH1 cases.

Case	Age (Years)	Sex	Origin	Consanguinity	Clinical signs	Diagnostic guidance	Genetic study (PH1)	Interval between 1st stone and diagnosis	Evolution
T.A	22	M	Salé	No	Repeated stone emission Repeated pyelonephritis	**Infrared spectrophotometry** of renal calculi: oxalocalcic calculi of an oxalo-dependent type	Done	14 years	In HD (3 sessions/week)
B.T	43	M	Salé	1st degree	Repeated stone emission Bone pain	**BMB** performed to identify EPO-resistant anemia cause: a marrow invaded by oxalate crystals	Done	4 years	In peritoneal dialysis
L.I	31	F	Salé	2nd degree	Repeated stone emission Widespread bone pain Diffuse joint stiffness General condition deterioration	**KUB x-ray:** bilateral nephrocalcinosis	Done	10 years	In HD (3 sessions/week)
S.N	22	F	Salé	2nd degree	Repeated stone emission Diffuse bone pain	**KUB x-ray:** bilateral nephrocalcinosis	Done	-	In HD (3 sessions/week)
Y.G	18	M	Jrada	2nd degree	Diffuse bone pain General condition deterioration Hepato-splenomegaly and ascitis	**BMB** performed to identify pancytopenia cause: a marrow invaded by oxalate crystals + myelosclerosis	Done	7 years	In HD (3 sessions/week)
A.G	22	F	Jrada	2nd degree	Stone emission Episodes of pyelonephritis (left kidney nephroctomy)	**Crystalluria:** Type 1C calcium oxalate monohydrate (whewellite) crystals	Not done (sister of case T.A)	9 years	GFR = 60 ml/min MDRD
I.F.	19	M	Agadir	1st degree	General condition deterioration Diffuse bone pain Hepatosplenomegaly and ascitis	**KUB x-ray:** bilateral nephrocalcinosis	Done	1 years	Died/ Pericarditis

Continued

M.S	35	M	Marrakech	No	Repeated stone emission Diffuse bone pain	**Infrared spectrophotometry:** oxalocalcic calculi of an oxalo-dependent type	Done	20 years	In HD (5 sessions of 4 hours per week)
L.E.	23	F	Tiflet	1st degree	Diffuse bone pain Metatarsal fractures	**Graft biopsy** showed calcium oxalate deposits in tubes	Not done	2 years	Return to hemodialysis (3 sessions/ week)
R.E.	35	M	Salé	No	General condition deterioration Diffuse bone pain Splenomegaly and ascitis	**BMB:** massive marrow infiltration by oxalate crystals	Not done	6 years	Died from acute lung oedema
E.A	39	M	Rabat	No	General condition deterioration Repeated stone emission Diffuse bone pain	**KUB x-ray:** bilateral nephrocalcinosis **Crystalluria:** Type 1C calcium oxalate monohydrate (whewellite) crystals **BMB:** oxalosis lesion **Uro MRI:** Right pyelo-caliceal corraliform lithiasis	Done	10 years	In HD (3 sessions/week)

-PH1: Primary hyperoxaluria type 1; -HD: haemodialysis; -KUB x-ray: Kidney, Ureter, and Bladder X-ray; -BMB: bone marrow biopsy; -URO MRI UroMagnetic resonance imaging.

4. Discussion

PH1 is a rare autosomal recessive genetic disease characterized by allelic and phenotypic heterogeneity [1].

Its prevalence is estimated at 1 to 3 cases/million inhabitants, and its incidence is 1/100,000 births in Europe and the United States [5].

In Morocco, only a limited number of studies have been published: Ait Ouamar [6] published 6 cases in 1999, and a paediatric thesis reported 19 cases in 2014 [7]. One Molecular studies of 29 unrelated Moroccan patients with PH, made it possible to estimate the prevalence of hyperoxaluria in Morocco, which was 1/7267 to 1/6264 [8].

PH1 is responsible for 0.5% of pediatric chronic kidney disease in Europe, compared with around 10% in Kuwait and 13% in Tunisia. This percentage is probably high due to the accumulation of a founder mutation and the frequency of consanguinity in these countries [9] [10]. In our study, consanguinity was found in 7 out of 11 patients.

The median age of first symptoms is 5 to 6 years, ranging from birth to over 60 years of age [2]. In our study, the time between emission of the 1st urinary calculus and positive diagnosis varied between 1 and 20 years.

PH1 affects more men than women [11], and this is in line with the findings

of our work, which shows a male predominance, with a sex ratio of 1.5. There are several types of primary hyperoxaluria. Type I accounts for around 80% of cases and is due to an AGT enzyme deficiency, as in our patients. Type II is secondary to glyoxylate and hydroxypyruvate reductase deficiency. Type III is secondary to mutation of the HOGA1 gene [7] [9].

Early diagnosis of PH1 is based on several factors: Stone analysis is the key to an early and more accurate diagnosis, only one patient has benefited from stone analysis, and this after 20 years of disease progression. Crystalluria provides diagnostic support by showing large numbers of whewellite crystals (>200/mm3), often forming aggregates [1] [12]. Crystalluria provided early diagnostic guidance in a single patient. KUB x-ray shows multiple, bilateral radiopaque kidney lithiasis or nephrocalcinosis of predominantly medullary topography. In our case, KUB x-radiography was performed on four patients, revealing nephrocalcinosis. In patients with normal or slightly impaired glomerular filtration, the most suggestive association of PH1 is hyperoxaluria (urinary oxalate > 0.5 mmol/1.73m^2/day and hyperglycolaturia (urinary glycolate > 0.5 mmol/1.73m^2/day). However, elevated glycolaturia is not always present, and its absence does not exclude the diagnosis [13].

Oxalemia measurement is difficult and does not, on its own, establish the diagnosis of PH1. The concentrations reached in PH1 are over 20 mmol/L [9] [14].

Testing of AGT activity on liver biopsy is indicated when no mutation of the AGXT, GRHPR or HOGA1 genes is identified [15].

Liver biopsy, which is an invasive procedure, is increasingly avoided in favor of molecular genetic testing [16].

When the phenotype is suggestive, it is logical to propose genotyping, targeting the most frequent mutations according to the patient's geographical and ethnic origin [17].

Genetic studies were carried out in 8 of our patients. It detected the c.731T>C (p.Ile244Thr) mutation in exon 7 of the AGXT gene in the homozygous state, which is the recurrent mutation in Morocco. This mutation is common in the north African population [18].

Although the disease is most frequently diagnosed in paediatrics, PH1 can appear in adulthood, initially with varying degrees of severity. Diagnosis is sometimes difficult. It should be systematically suspected in cases of recurrent lithiasis and/or nephrocalcinosis, especially when renal function is impaired. However, PH1 is often diagnosed only at the ESKD, and in patients already receiving dialysis or kidney transplants [19]. This was the case in 30% of patients in a survey in the USA in 2009 [5] and in 36% in a Netherlands study in 2003 [20].

In a French survey [1], 9 out of 74 patients had advanced kidney failure and 12 were on dialysis (including one after transplant rejection) at the moment of diagnosis [1].

Biochemical PH1 diagnosis is difficult in advanced CKD as oxaluria is unin-

terpretable, and hyperoxalemia is common in hemodialysis patients [16] [18]. In our study, 10 out of 11 patients were diagnosed at the HD stage based on genetic study in 8 patients, crystalluria and family history of HP1 in 1 patient, transplant biopsy in 1 patient and stone analysis in 1 patient.

Conservative treatment should be initiated as soon as possible, in order to limit systemic oxalosis [5].

This treatment is based on hydration with 2 to 3 l/m^2 per day, if kidney function is normal, though non-adherence is a challenge [10].

Moreover, sensitivity to pyridoxine, the main coenzyme of AGT, is found in a third of PH1 patients. Recommended doses range from 5 to 20 mg/kg/day, not exceeding 1 g/day for adults [5] [9].

Only one patient had a good response to pyridoxine therapy combined with hydration, with the disappearance of crystals and a 50% reduction in oxaluria.

Diuretics should be used with caution. Furosemide increases urinary output, but has a calciuretic action. Thiazide diuretics, on the other hand, have a less marked diuretic effect, but reduce calciuria [9].

Nevertheless, it is reasonable to limit dietary intake of oxalate, even if this represents only 5% - 10% of the oxalate eliminated by the kidneys.

Furthermore, vitamin C supplementation should be avoided, since ascorbic acid is a precursor of oxalate [21].

The advent of RNA-interferon (RNAi) therapy is expected to revolutionize the management and prognosis of this disease. One of the key enzymes in hepatic oxalate synthesis is glycolate oxidase (GO). Lumasiran, the only treatment currently approved in the USA and many European countries for this indication, is an RNAi that acts upstream of the trifluoroacetic acid enzyme deficiency, by targeting the hepatic GO (blocking its synthesis), thereby reducing hepatic production of glyoxylate and thus oxalate. The results of clinical trials have been spectacular, and probably indicate the end of double liver/kidney transplants in this indication in countries where the treatment is available [22] [23].

Urological treatment of calculi should avoid open surgery and percutaneous surgery whenever possible, due to the risk of associated parenchymal damage, likely to alter glomerular filtration [6] [10].

In patients suffering from recurrent kidney colic, placement of a double-J catheter helps control pain and preserve kidney parenchyma.

In ESKD, hemodialysis only removes circulating soluble oxalate. Consequently, daily hemodialysis (minimum 5 hours per session) is best suited, but cannot be applied to all patients [24].

Only one patient, allows himself 5 hemodialysis sessions per week of 4 hours each.

PD does not offer sufficient oxalate purification, but in a few patients, particularly those with infantile oxalosis, the combination of daily HD and PD allows relatively efficient clearance [9].

In our case, our patients remain in HD in the absence of any possibility of liv-

er transplantation.

Organ transplantation represents the only curative treatment for PH1, either combined liver-kidney transplantation or sequential liver-kidney transplantation. Thus a medical treatment based on lumasiran can also be offered if it is available.

The choice of strategy obviously depends on the resources available and the experience of the team, but every effort should be made to ensure that the time spent on the waiting list is as short as possible [11].

However, early diagnosis by genetic analysis is still necessary to confirm PH1, in the presence of suggestive clinical manifestations such as recurrent urinary lithiasis, urinary calculi in children or nephrocalcinosis. The aim is to initiate conservative treatment and limit the rapid decline in renal function.

Limitations of the study:

The limitations of our study are the type of study which is retrospective, the small size of the population.

5. Conclusions

PH1 is a serious condition whose diagnosis is often delayed. The clinical picture is often severe, associated with advanced kidney failure that can be observed from an early age.

In our context, early diagnosis combined with well-maintained conservative treatment is the only way to limit the worsening of this disease in the absence of liver transplantation.

Optimal management must be initiated as early as possible, and requires collaboration between nephrologists, urologists and biologists as part of a specialized team.

Analysis of the stone, whose appearance is pathognomonic, is of crucial importance.

Raising awareness of this condition among healthcare professionals and the general public is the only way to ensure early diagnosis.

The management of PH1 will undoubtedly change in the near future. With the arrival of Lumasiran, it is likely that liver-kidney transplantation will no longer be necessary to treat the metabolic defect associated with PH1, thus ensuring improved survival and quality of life for patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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