Case Report: Syncopal atrioventricular block complicating primary hyperoxaluria type 1 [version 1; peer review: 1 approved]

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Abstract
Primary hyperoxaluria (PH) type 1 is a rare hereditary metabolic disorder resulting in accumulation of calcium oxalate in several organs, including the heart. Cardiac oxalosis in PH is poorly described in the medical literature. We report the case of a 42-year-old woman diagnosed with primary hyperoxaluria type 1 and end-stage renal failure who presented with syncope related to a paroxysmal third-degree atrioventricular block. The patient benefited from the implantation of a dual chamber pacemaker with a good outcome. Conduction blocks in case of primary hyperoxaluria type 1 are exceptional; in fact, less than five reports have previously been published in the medical literature. With this case, we would like to highlight the need for regular and careful monitoring of cardiac status in patients treated for primary oxalosis, especially when renal function is impaired.

Keywords
atrioventricular block, primary hyperoxaluria, syncope, end-stage renal failure, heart block
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Introduction
Primary hyperoxaluria (PH) type 1 is a scarce hereditary metabolic malady in which an increased production of oxalic acid results in hyperoxalemia and an accumulation of calcium oxalate in different body organs, including the heart.1 Oxalosis involving the myocardium can lead to congestive heart failure, arrhythmias and conduction disturbances.2 We report the case of a 42-year-old-woman followed for PH over 15 years who was admitted to our cardiology department for a paroxysmal syncopal atrioventricular block (AVB). Heart block in patients with primary oxalosis is exceptional, indeed less than eight reports have been previously reported in the medical literature.

Case report
A 42-year-old Tunisian housewife was referred eighteen months ago to our cardiology department for repetitive episodes of syncope over two weeks. The patient had PH1 diagnosed at the age of 27 by a genetic study that revealed a c.33-34insC mutation; she had a grandfather with the same disease. Over time, she developed progressive renal failure, and five years earlier, she had undergone a left partial nephrectomy for nephrocalcinosis. Nevertheless, she developed total chronic renal failure and had recently begun hemodialysis via a left humerocephalic fistula.

Upon admission in March 2020, physical examination showed a mucocutaneous pallor. Blood pressure was 100/60mmHg, and heart rate was 70/min. Cardiac auscultation found a 2/6-degree systolic aortic murmur. She had no signs of heart failure. Electrocardiogram (EKG) performed in the emergency room showed a regular sinus rhythm at 75 beats per minute (bpm), a complete left bundle branch block (LBBB), and a first-degree AVB (Figure 1). Laboratory tests showed a normochromic normocytic anemia at 5.9 g/dl, urea level at 37.7 mmol/l, creatinine level at 1771 micromol/l, a normal potassium serum level at 4.3 mEq/l, and a low calcium serum level at 2.08 mmol/l.

The patient’s plasma oxalate level was 98.5 umol/L. Urinary crystallographic exam showed the presence of calcium oxalate crystals in the urine of characteristic icosahedral shape (Figure 2). Plain abdominal X-ray showed images of nephrocalcinosis of the left kidney (Figure 3).

During monitoring in the intensive care unit, the patient presented a further episode of syncope with an EKG (Figure 4) showing a prolonged ventricular asystole (Figure 4A) with second degree AVB 2/1 (Figure 4B) and a ventricular rate of 55 bpm followed by a complete AVB (Figure 4C) with a ventricular rate of 50 bpm. First, the patient received an isoprenaline infusion (1 mL/hour =0.5 microgram/kg/minute) under EKG control, but the heart rate did not accelerate. Within minutes, repeated episodes of syncope imposed the urgent placement of a temporary cardiac pacing lead. Transthoracic echocardiography showed increased left ventricular mass index and diastolic dysfunction. The patient was implanted with a dual-chamber pacemaker (Figure 5) with a good outcome. The patient was discharged three days later.

After one-year follow-up in April 2020, no episodes of syncope were reported. The patient is still waiting for a kidney transplant.
Discussion

Primary hyperoxaluria type 1 (PH1) is an autosomal recessive inherited metabolic disorder related to the deficiency of alanine glyoxylate aminotransferase, a peroxisomal liver enzyme that allows the transformation of glyoxylate into glycine.\(^1\) This deficiency leads to oxalate overproduction by the liver, followed by urine filtration and complexation with calcium to form massive calcium-oxalate nephrolithiasis potentially leading to chronic renal failure (nephrocalcinosis).\(^1\)

Once end-stage renal failure develops, calcium oxalate is deposited in other organs because of high plasma oxalate concentrations, which exceed the saturation threshold for calcium oxalate.\(^2\)

Cardiac involvement in PH is rarely described; medical literature is limited to case reports and small case series. Mookadam and colleagues, from the team of the Mayo Clinic Rochester, published in 2010, is the first and only systematic study describing cardiac abnormalities in PH. They reviewed a dataset of 33 patients with primary hyperoxaluria.\(^2\) The mean age at the time of cardiac manifestation was 40 years.\(^2\) Cardiac anomalies are associated with an alteration in renal function and appear to correlate with the plasma oxalate level.\(^2\) Of the patients with cardiac findings, 78% had a history of end-stage renal failure.\(^2\) In our case, the oxalate plasma level was much higher. Mookadam also describes this finding in his study.\(^2\) The plasma oxalate level was 79.4 \(\mu\)mol/L in those with cardiac findings, compared to 7.3 \(\mu\)mol/L in those without.\(^2\)

![Figure 2](image1.png)

**Figure 2.** Urinary crystallographic exam showing the presence of calcium oxalate crystals (red arrow).

![Figure 3](image2.png)

**Figure 3.** Plain abdominal X-ray showed images of nephrocalcinosis of the left kidney (red arrow).
Conduction deficits and heart block have previously been reported in patients with primary oxalosis.3–7 Massie et al.,4 reported the first case of cardiac electrophysiological abnormalities due to oxalate infiltration in a 27-year-old man. In that case, oxalate was described to infiltrate the sinoatrial node and to approach the atrioventricular node leading to numerous electrophysiological abnormalities. This finding is also shared by other authors.3–7 Conduction blocks are reported in 13.2% of patients in the Mayo Clinic study.2

Figure 4. Electrocardiogram showing prolonged ventricular asystole (A) Second degree AVB 2/1 with ventricular rate of 55bpm (B) Atrioventricular dissociation with ventricular rate of 50 bpm (C).

Figure 5. Chest X-ray showing the emplacement of the dual-chamber pacemaker.
Myocardial invasive transjugular biopsy remains the gold standard for the diagnosis of cardiac involvement; but it is not routinely used and does pose a definable risk.2

Two reports in the literature have performed a histologic study of the conduction system, they showed extensive crystal deposits all around the sinoatrial node, atrial myocardium, atrial preferential pathways, common bundle, and both bundle branches associated to secondary degenerative and fibrotic changes.3,4 In addition, the arteries of the atrioventricular and sino-atrial nodes exhibited mural crystals with a narrowing of the lumens.3

Although ventricular pacing may avoid death from complete heart block, it is improbable to prolong life expectancy in oxalosis patients once visceral involvement becomes important.4 Dialysis is supposed to temporarily remove oxalate, but it cannot compensate for the excessive oxalate production rate, thus making it difficult to excrete calcium oxalate in the urine and eventually increasing the blood oxalate level.5

Large left ventricular mass index, impaired left ventricular and right ventricular function, left atrium enlargement, diastolic dysfunction, increased wall thickness suggestive of myocardial dissemination, and rhythm abnormalities are probably due to calcium oxalate deposits in cardiac tissue.2

While kidney transplantation corrects kidney failure, liver transplantation is the only solution for definitive correction of the metabolic defect in PH 1. Combined hepatorenal transplantation is the only therapeutic alternative to dialysis,1 which, unfortunately, is not yet practiced in Tunisia. Cardiac manifestations can be fatal; however, they are reversed after successful liver transplantation.9

The case, which we have presented here, has been limited by the short follow up of the patient. However, it demonstrates that in front of any syncopal signs, particularly in patients with primary hyperoxaluria, monitoring in a cardiological resuscitation unit can be lifesaving.

Conclusion
Oxalate deposits in cardiac tissue compromise prognoses as they can lead to potentially fatal complications. This case demonstrates the need for regular and careful monitoring of cardiac status in patients treated for primary oxalosis, especially when renal function is impaired. Because oxalate cannot be sufficiently removed by hemodialysis, early hepato-renal transplantation is required to improve the chances of survival in these patients.

Data availability
All data underlying the results are available as part of the article and no additional source data are required.

Consent
Written informed consent for publication of the patient’s clinical details and clinical images was obtained.

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This is an interesting, well-written manuscript. The article highlights the importance of cardiac monitoring in patients treated for primary oxalosis, especially when renal function is impaired. The manuscript respects the CARE case reports guidelines. The patient's case is well reported with good quality figures. The discussion part of the article is very well done and is exhaustive. The conclusion is consistent with the case presented.

Is the background of the case's history and progression described in sufficient detail?  
Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?  
Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?  
Yes

Is the case presented with sufficient detail to be useful for other practitioners?  
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: General cardiology, rhythmology

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