

Clinical Report

Renal phospholipidosis possibly induced by ranolazine

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Abstract

A 76-year-old male Caucasian patient was treated in our hospital for acutely decompensated heart failure due to restrictive cardiomyopathy. Acute-on-chronic kidney failure developed with serum creatinine rising from 160 to 345 $\mu\text{mol/L}$ (1.8–3.9 mg/dL); therefore, a kidney biopsy was performed. Besides secondary focal-segmental glomerulosclerosis and minimal amyloidosis, histological analysis showed zebra bodies in the cytoplasm of some podocytes, suggesting renal phospholipidosis (PL). Possible causes for this storage disorder encompass Fabry's disease, in rare cases silicosis, and an iatrogenic drug-induced aetiology. The main suspects are cationic amphiphilic drugs, such as amiodarone and chloroquine. The only cationic amphiphilic drug our patient had taken was the anti-anginal ranolazine, a compound not yet associated with PL. The patient had taken ranolazine for diastolic dysfunction over a period of 9 months until 6 weeks before renal biopsy. In the absence of a hereditary disorder, silicosis and well-known pharmaceutical triggers, a causative role of ranolazine seems likely, and this drug should be considered in the differential diagnosis of drug-induced PL.

Keywords: cationic amphiphilic drugs; myelin bodies; ranolazine; renal phospholipidosis; zebra bodies

Case report

A 76-year-old male Caucasian patient was treated in our hospital for acutely decompensated heart failure due to restrictive cardiomyopathy. A diagnosis of smouldering myeloma (IgG λ) had been made 2 months earlier (serum-IgG 30.8 g/L [normal range 7.5–15.6 g/L], serum-free light chain ratio κ/λ : 0.6 [normal range in renal insufficiency 0.37–3.1]). Because of the restrictive cardiomyopathy, systemic amyloidosis with cardiac involvement was suspected.

The patient had chronic kidney disease stage G3bA1 with stable renal function during the previous 12 months (MDRD-eGFR \sim 40 mL/min per 1.73 m², albuminuria 279 mg/24 h); his blood pressure was hypo- to normotensive (between 90/60 and 120/70 mmHg) and remained so during his stay in hospital.

A few days after hospital admission, the patient developed acute-on-chronic kidney failure with serum creatinine rising to 345 $\mu\text{mol/L}$ (3.9 mg/dL) and progressive proteinuria (465 mg/g creatinine, mostly Bence Jones protein). Urinalysis did not show any casts or haematuria.

As renal involvement of the known gammopathy and the suspected amyloidosis was assumed, a kidney biopsy was performed.

The major light microscopic findings were secondary focal and segmental glomerulosclerosis not otherwise specified (according to the classification proposed by D'Agati *et al.* [1]), affecting 2 of 31 glomeruli, moderate

benign nephrosclerosis with moderate arteriolar hyalinosis, fibrosis and kinking and \sim 20% cortical tubular atrophy and interstitial fibrosis and minimal acute tubuloepithelial damage; Congo-red stains were negative. On ultra structural examination, podocyte foot process effacement of only 5% indicated secondary FSGS. Also, a few mesangial fibrils were found—suspicious, but not diagnostic for minimal glomerular amyloidosis.

Surprisingly, the cytoplasm of a few podocytes was laden with zebra and myelin bodies (see Figure 1); as described, these bodies are considered to represent an excessive accumulation of phospholipids in the lysosome, and typically found in phospholipidosis (PL) [2, 3].

During the next few days after renal biopsy, the patient's decompensated heart failure got worse in spite of intensive diuretic therapy, and renal replacement therapy had to be initiated. After some weeks of dialysis, cardio-renal function recovered sufficiently to stop extracorporeal therapy.

Discussion

Renal PL is an intracellular storage disease characterized by accumulation of phospholipids within several types of renal cells, ranging from mesangial and glomerular endothelial cells and podocytes to tubuloepithelial and interstitial cells [2].

Electron microscopic analysis shows intra-lysosomal membranous lamellar inclusions, termed myelin or Zebra

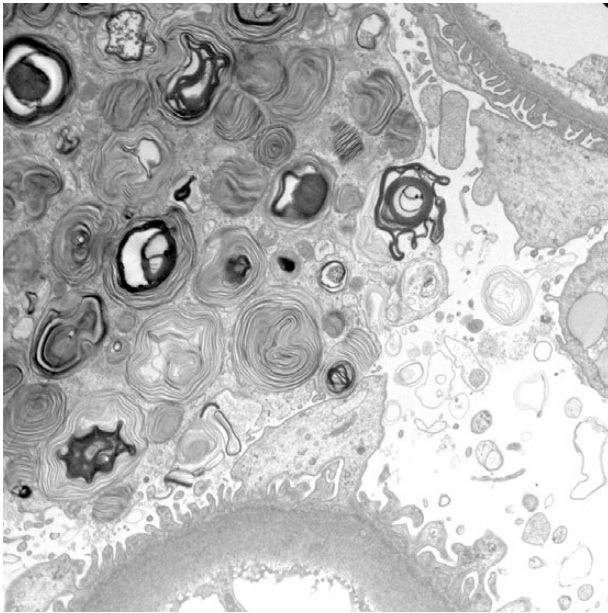


Fig. 1. Transmission electron micrograph of a podocyte with massive accumulation of zebra bodies and myelin bodies (round structures) within the cytoplasm. The glomerular basement membrane (top right corner and bottom edge) appears unremarkable, foot processes and glomerular endothelium on either side of the glomerular basement membrane are well preserved. Original magnification $\times 6300$.

bodies, as the ultra-structural correlate of the accumulated phospholipids [4, 5].

A decreased activity of lysosomal phospholipase leads to an impaired elimination and hence accumulation of phospholipids in the lysosomes. Several organs besides the kidney may be involved, i.e. lung, liver and heart [6].

Hereditary as well as acquired causes of reduced phospholipase activity have been described [2].

Fabry's syndrome is an X-linked disease. An inborn mutation results in a reduced activity of α -galactosidase A and consecutively in systemic PL [7]. Renal symptoms usually include a progressive loss of renal function and proteinuria; Fanconi syndrome has been described in some cases [8]. Angiokeratomas and neuropathic pain are typical extra-renal manifestations [7]. Cardiac involvement (such as left ventricular hypertrophy, coronary artery disease, conduction abnormalities) is common and prognostically important [9].

Acquired PL is mostly iatrogenic and caused by a variety of drugs. Typically, cationic amphiphilic substances, such as amiodarone, chloroquine and aminoglycosides, induce PL [2, 4, 6, 10], probably all except the latter without any detrimental effect on renal function [5].

In rare instances, exposure to silica may lead to similar histological changes and mimic Fabry's disease [11].

Therefore, the histological finding of renal PL should lead to an extensive search for possible causes of this storage disorder.

Since it is virtually impossible to distinguish an iatrogenic drug-induced PL from Fabry's disease on ultra-structural analysis of kidney tissue, the clinician has to use the patient's family history, extra-renal symptoms, and biochemical features, such as a reduced α -galactosidase A activity, to differentiate these two entities.

In our case, the patient's negative family history, the absence of typical signs or symptoms (i.e. angiokeratoma

or burning pain), and a normal α -galactosidase A activity ruled out Fabry's disease.

Even though the patient had been exposed to silica over several years, we did not find any signs of silicosis in a high-resolution CAT scan of the chest.

Finally, a drug-induced PL had to be considered [2]. As cationic amphiphilic drugs (i.e. amiodarone, chloroquine, aminoglycosides) are the main reasons for PL, we strongly suspected such a drug as the cause. However, the patient had never taken any of the drugs classically described to cause PL.

The only cationic amphiphilic drug the patient had taken was the anti-anginal ranolazine, a compound never previously linked to PL. The patient had taken 375 mg ranolazine twice daily for diastolic dysfunction over a period of 9 months until 6 weeks before renal biopsy. His general physician had discontinued it in order to cut down on the extensive medication the patient had been prescribed.

Even though some cases of acute kidney injury have been attributed to PL induced by cationic amphiphilic drugs [12], PL is generally not believed to have any negative consequences for renal function [5].

In our patient, GFR had remained stable while he was taking ranolazine, and only worsened 6 weeks after ranolazine had been discontinued; therefore, the drug did not seem to have any impact on kidney function; neither did the other histological pathologies described above—except for the acute tubular damage.

Retrospectively, cardio-renal syndrome due to restrictive cardiomyopathy was the cause of the patient's acute-on-chronic renal failure.

One can only speculate as to the reason why ranolazine caused PL in this patient. The patient had been prescribed a rather low dose of the drug, and had not taken a larger dose than he was supposed to.

A dosage adjustment is recommended only when creatinine clearance falls below 30 mL/min and therefore did not seem necessary in our patient (initial MDRD-eGFR of 40 mL/min per 1.73 m²).

However, our patient had low muscle mass, so the real GFR may lie well under the creatinine-based estimated GFR.

Considering the (minimal) amyloidosis, it is tempting to draw an analogy to digitalis toxicity in this disease. As early as 1981, Rubinow *et al.* [13] described that isolated amyloid fibrils bind digoxin and suggested this phenomenon as the reason for increased digitalis toxicity in amyloidosis. It is beyond the scope of this report to test this hypothesis, but one may well conjecture that a similar mechanism concerning ranolazine might play a role in this case of renal PL. To the best of our knowledge, no association between monoclonal gammopathy or amyloidosis and PL has ever been described in the literature.

Thus, in the absence of any other likely causative factors, ranolazine should be considered in the differential diagnosis of drug-induced PL.

Conflict of interest statement. None declared.

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