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CASE REPORT
Medical management of arrhythmias

Case report of progressive renal dysfunction as a consequence of amiodarone-induced phospholipidosis

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Background Amiodarone is associated with a range of unwanted effects on pulmonary, thyroid, and liver function. However, the nephrotoxic side effect caused by renal phospholipidosis has hardly received any attention up to now.

Case summary This is a case of an 86-year-old Caucasian male with an acute on chronic kidney disease 4 months after the initiation of amiodarone. A renal biopsy demonstrated the intracellular accumulation of phospholipids that have previously been demonstrated in association with organ dysfunction because of amiodarone use. Serum creatinine levels subsequently improved from 388 to 314 µmol/L after stopping amiodarone over the course of 2 months.

Discussion In this case, a diagnosis of partially reversible acute on chronic kidney disease caused by lysosomal phospholipidosis due to amiodarone use was deemed highly likely. Lysosomal dysfunction leads to the accumulation of intra-lysosomal phospholipids (phospholipidosis). This accumulation is accompanied by progressive organ damage and dysfunction, including renal dysfunction, in rare instances. Guidelines advise regular surveillance for liver, lung, and thyroid toxicity during amiodarone treatment but do not mention the potential for renal toxicity. This case suggests that it might be prudent to include screening for renal toxicity in this surveillance.

Keywords Amiodarone • Renal toxicity • Drug-related renal dysfunction • Phospholipidosis • Case report

ESC curriculum 5.6 Ventricular arrhythmia • 5.10 Implantable cardioverter defibrillators • 5.11 Cardiac resynchronization therapy devices • 6.2 Heart failure with reduced ejection fraction

Learning points

- Renal insufficiency is a potential side effect of amiodarone caused by renal phospholipidosis.
- It might be prudent to include screening for renal toxicity in the regular surveillance of side effects during treatment with amiodarone.
- Renal insufficiency due to amiodarone can be reversible.

Introduction

Amiodarone is used extensively in the treatment of ventricular and supraventricular arrhythmias and is the most effective pharmacologic agent for achieving and maintaining sinus rhythm in patients with atrial fibrillation and the treatment of (recurrent) ventricular arrhythmias.[1] Amiodarone is associated with a range of unwanted effects, including the well-documented adverse effects on pulmonary, thyroid, and liver function.[1] However, it is largely unknown that amiodarone can also cause nephrotoxicity with the documentation of an association

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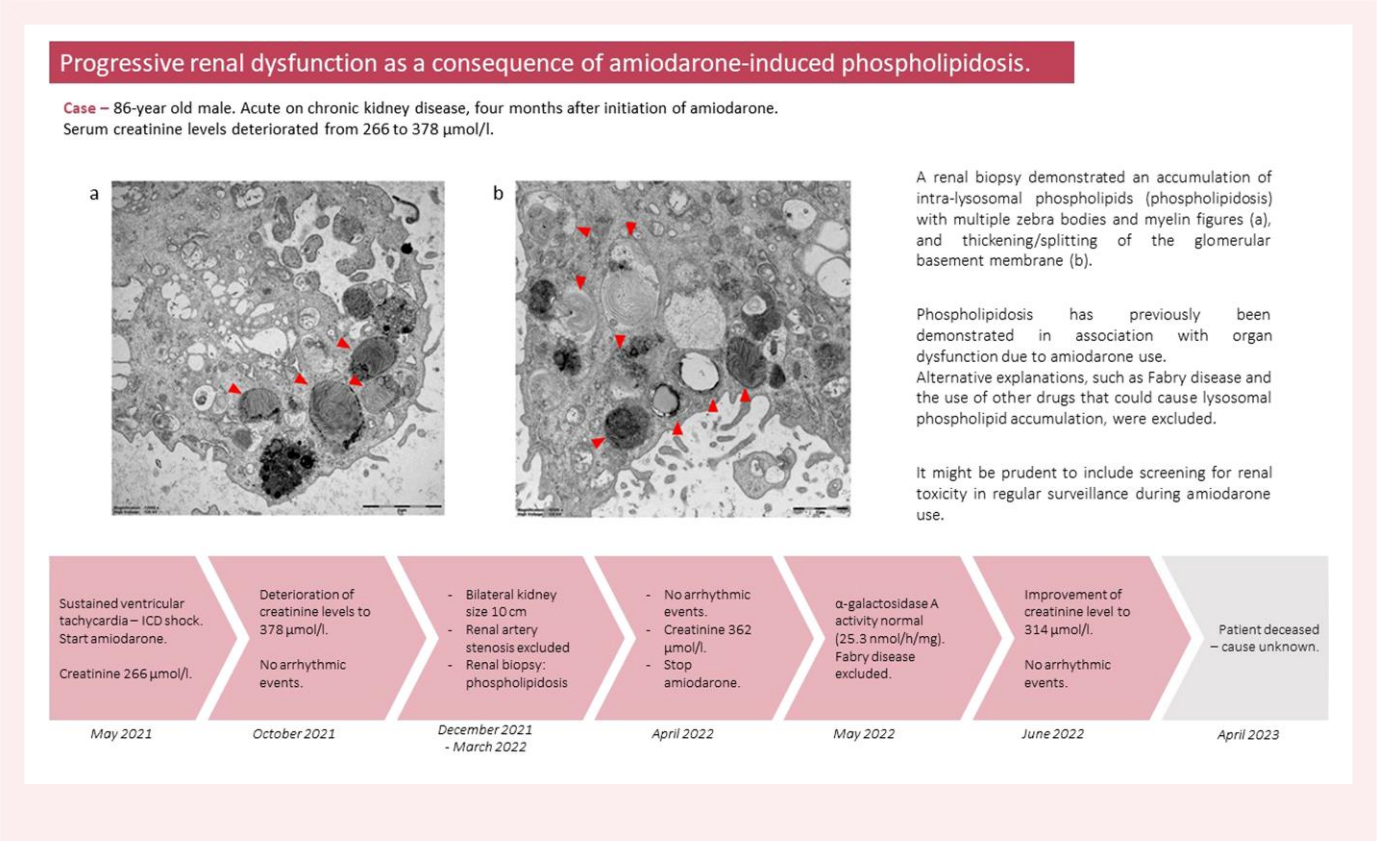
between amiodarone use and the occurrence of renal dysfunction limited to only a few case reports.[2–4]

Here, we present an additional case of progressive renal insufficiency caused by a histologically documented renal phospholipidosis, which manifested after the initiation of amiodarone treatment and regressed after stopping the drug. The putative pathogenesis of this rare complication of amiodarone treatment is addressed after the presentation of the case.

Summary figure



Case summary

We present the case of an 86-year-old Caucasian male with an acute on chronic kidney disease, which was observed during a routine outpatient visit. The patient was asymptomatic. His medical history included chronic kidney disease stage 4 with a relatively stable serum creatinine level of around 280 µmol/L (reference range 65–115 µmol/L) with a serum urea level of 26 mmol/L (reference range 2.5–7.5 mmol/L), gout, hypertension, and an ischaemic cardiomyopathy with a left ventricular ejection fraction of 25–30%, ventricular dyssynchrony, and a third-degree atrioventricular block for which he had received a cardiac resynchronization therapy defibrillator (CRT-D) device. His cardiomyopathy was caused by an inferoposterolateral myocardial infarction in 1996. Details about the treatment of this event are lacking. A coronary angiography done in 2015 showed chronic total occlusions of the right coronary artery and the circumflex artery. An elective percutaneous coronary intervention of these lesions was not successful because of the inability to pass the occlusion. Cardiac magnetic resonance imaging had corroborated the supposed aetiology by demonstrating inferior and posterolateral late gadolinium enhancement. Prior to CRT-D implantation, no episodes of sustained ventricular tachycardia had been reported. However, after implantation, there had been several events of ventricular tachycardia terminated by anti-tachycardia pacing and once a CRT-D shock. Preventive treatment with metoprolol had not been successful, and therefore, amiodarone with a once daily dose of 200 mg had been started after an initial loading dose regiment (1 week 200 mg t.i.d.; 1 week 200 mg b.i.d.). Further work-up to exclude the progression of coronary artery disease was not performed in response to these episodes of ventricular tachycardia.

A kidney biopsy had been performed 7 years earlier, when his serum creatinine level was 230 µmol/L, serum urea level was 23 mmol/L, and proteinuria was 2.2 g/24 h in the absence of microscopic haematuria. This biopsy demonstrated focal global glomerulosclerosis in 4/9 glomeruli and mesangial expansion with nodular sclerotic lesions, arteriolar hyalinosis, and focal tubulointersitial atrophy and fibrosis in the remainder. These biopsy findings were compatible with the histological picture of diabetic nephropathy. However, the patient did not have diabetes mellitus [HbA1c 37 mmol/mol (reference range 20–42 mmol/mol) at the time of biopsy], nor did he have diabetic retinopathy as a microvascular complication in another diabetic end organ. A diagnosis of idiopathic nodular sclerosis was, therefore, made. To reduce proteinuria, a mineralocorticoid receptor antagonist (eplerenone) and an angiotensin-converting enzyme inhibitor (quinapril) was started, which, over time, reduced proteinuria to <1 g/24 h.

Four months after the introduction of amiodarone, renal function appeared to have deteriorated at a routine outpatient visit with a serum creatinine level that had increased from 266 to 378 µmol/L, accompanied by the development of a renal metabolic acidosis and an increase in parathyroid hormone levels. Serum urea levels had slightly increased

Table 1 Laboratory results

	Value (reference range)	Value prior to amiodarone initiation
Serum/blood		
Urea (mmol/L)	30.4 (2.5–7.5)	25.8
Creatinine (μmol/L)	378 (65–115)	266
Sodium (mmol/L)	140 (135–145)	141
Potassium (mmol/L)	5.0 (3.2–4.7)	5.1
Bicarbonate (mmol/L)	19 (22–26)	23
Parathyroid hormone (pmol/L)	26.2 (1.0–7.0)	20.3
Haemoglobin (mmol/L)	7.1 (8.0–10.5)	7.5
Thrombocytes	141×10^9/L	146
Leucocytes	7.0×10^9/L	6.3
Eosinophils	0.07×10^9/L	—
Albumin (g/L)	43.3 (39.0–52.0)	44
Alpha1-globuline (g/L)	3.5 (2.0–4.0)	—
Alpha2-globuline (g/L)	7.1 (5.0–10.0)	—
Beta-globuline (g/L)	7.6 (6.0–12.0)	—
Gamma-globuline (g/L)	8.1 (6.0–13.0)	—
Myeloma protein	Absent	—
Cholesterol (mmol/L)	4.3	4.0
Triglycerides (mmol/L)	0.8	0.7
LDL cholesterol (mmol/L)	2.2	2.2
HDL cholesterol (mmol/L)	2.0	1.8
Urine		
Urinalysis	pH 6.0, erythrocytes negative	pH 7.0, erythrocytes negative
Urine volume (mL)	1800	1200
Protein (mg/24 h)	400 (<150)	310
Creatinine (mmol/24 h)	9.9 (6.0–18.0)	8.3
Urea (mmol/24 h)	297.5 (200.0–600.0)	262.1

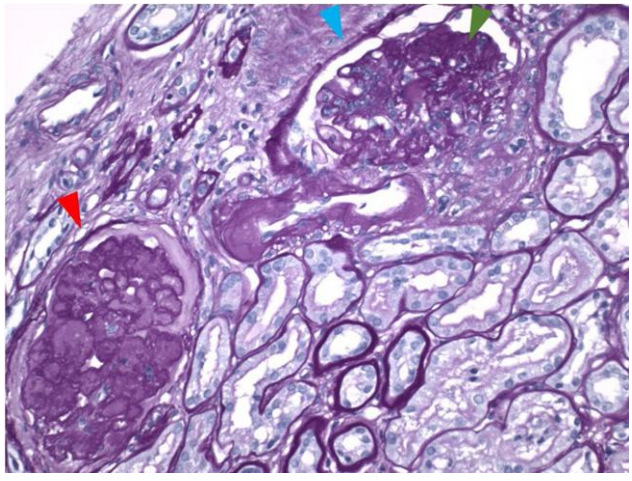


Figure 1 Sclerotic glomerulus showing extensive global hyalinized glomerulosclerosis (red arrow). The other glomerulus (blue arrow) shows segmental sclerosis (green arrow) and a hyalinized hilar arteriolae (periodic acid-schiff stain with diastase, 200x magnification).

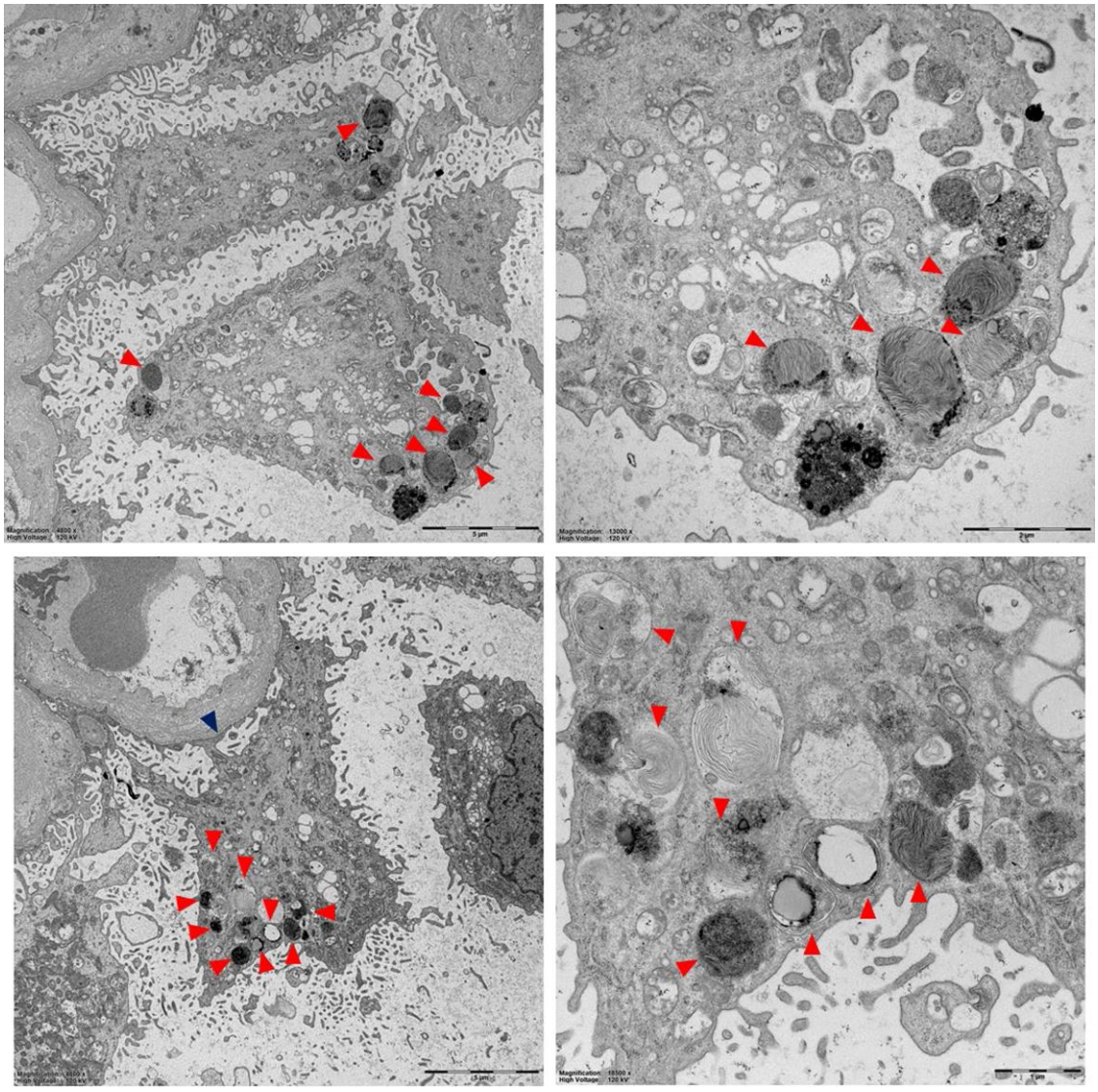


Figure 2 Electron microscopy images showing multiple zebra bodies and myelin figures and also a thickening/splitting of the glomerular basement membrane.

from 25.8 to 30.4 mmol/L. The patient was asymptomatic. Microscopic haematuria was absent and 24 h proteinuria was unchanged at 400 mg/24 h (see *Table 1*). HbA1c was 39 mmol/mol. There was no history of vomiting and diarrhoea, nor was there any change in any prescribed or over-the-counter medication other than the addition of amiodarone. Other prescribed drugs that could influence kidney function in use at the time of biopsy included an angiotensin-converting enzyme inhibitor (perindopril), mineralocorticoid receptor antagonist (eplerenone), and a loop diuretic (bumetanide). However, the patient had already been using these drugs for at least a year and the dosage was not adjusted recently. Lower urinary tract symptoms were also absent. His blood pressure was comparable to previous measurements (110/45 mmHg), and there were no signs of cardiac decompensation, uraemia, or neurological deterioration. A cardiac device check-up demonstrated optimal biventricular pacing and the absence of any relevant arrhythmia after the addition of amiodarone. On sonography, kidney size was 10 cm bilaterally with a cortical diameter of 1.2 cm in the absence of obstruction. Renal artery stenosis was excluded after performing magnetic resonance angiography (a right-sided stenosis of 50%).

The hypothesis that remained was the one in which the deterioration of his renal function was caused by the recent introduction of amiodarone. However, his cardiologist was reluctant to stop amiodarone in the absence of sufficient proof for a causal association. Therefore, the patient underwent a diagnostic renal biopsy to either support or refute this diagnosis.

Renal biopsy showed extensive glomerular damage consisting of nodular mesangial sclerosis, glomerulomegaly, thickened glomerular basement membranes, and segmental and global glomerulosclerosis,

Table 2 Examples of cationic amphiphilic drugs

Name	Therapeutic category
Amiodarone	Anti-arrythmic
Amitriptyline	Anti-depressant
Chlorcyclizine	Anti-histaminic
Chloroquine	Anti-malarial
Clozapine	Anti-psychotic
Erythromycin	Anti-bacterial
Fluoxetine	Anti-depressant
Gentamicin	Anti-bacterial
Haloperidol	Anti-psychotic
Hydroxychloroquine	Anti-malarial
Ketoconazole	Anti-fungal
Promethazine	Anti-histamine
Sertraline	Anti-depressant
Tamoxifen	Anti-oestrogenic

as well as advanced interstitial fibrosis and tubular atrophy. The severity of these lesions had progressed since the previous biopsy. There were no signs of acute tubular necrosis. Immunofluorescence result was negative. As before, the histological picture was entirely compatible with the findings in patients with diabetic nephropathy. Electron microscopy on the biopsy after initiation of amiodarone treatment showed a thickening/splitting of the glomerular basement membrane (average diameter of 652 nm, range 350–927 nm), endothelial activation, and podocyte damage with microvillus transformation and foot process effacement. Multiple zebra bodies and myelin figures, which are the result of intracellular accumulation of phospholipids, were present in the cytoplasm of damaged podocytes. This has previously been demonstrated in association with amiodarone use. These lesions were not observed in the electron microscopy of the previous biopsy. Light and electron microscopy results are shown in *Figures 1* and *2*, respectively.

After subsequently stopping amiodarone, serum creatinine levels improved spontaneously from 388 to 314 μmol/L with a decrease in the serum urea level from 30.7 to 21.9 mmol/L over the course of 2 months. A normal α-galactosidase A activity (25.3 nmol/h/mg) excluded a diagnosis of Fabry disease. The patient was also referred to the ophthalmologist, who discovered the presence of cornea verticillata, which is a well-known symptom of systemic phospholipidosis, and which has also been found in patients using amiodarone.[2] Amiodarone was stopped and metoprolol was resumed with the intention of considering catheter ablation in the event of recurrence of ventricular tachycardia. He was admitted to the hospital 11 months later after experiencing multiple appropriate implantable cardioverter defibrillator shocks in a state of severe cardiac failure with dyspnoea and peripheral oedema. He was treated by conservative means with intravenous loop diuretics. Four weeks after discharge, he died. A post-mortem examination or CRT-D device interrogation was not performed.

Discussion

Lysosomes are cytoplasmic organelles that are important for the catabolism of phospholipids through numerous phospholipase enzymes. Inhibition of these enzymes leads to the accumulation of intra-lysosomal phospholipids (phospholipidosis), which can be identified as lamellar bodies (zebra bodies or myelin figures) on electron microscopy. This accumulation is accompanied by progressive organ damage and dysfunction.[2,4–6] More than 50 drugs have been identified, which can induce phospholipidosis by inhibiting lysosomal phospholipase activity. Cationic amphiphilic drugs that contain a hydrophobic aromatic and/or aliphatic ring and a hydrophilic domain with an ionizable nitrogen group are more likely to induce the inhibition of lysosomal activity.[5] The interaction of these specific drugs with phospholipids on the cellular membrane leads to alterations of several biological processes. These alterations lead to a change in the distribution of lysosomal enzymes and inhibition of enzymatic activities such as the activity of lysosomal phospholipase.[5–7] Amiodarone inhibits the activities of phospholipase A1, phospholipase C, and calcium-dependent phospholipase A2 in a dose-dependent fashion.[8] *Table 2* contains a list of amiodarone and other cationic amphiphilic drugs.[5–7,9]

Phospholipidosis can also be caused by Fabry disease.[2] Fabry disease is an X-linked recessive lysosomal storage disorder, caused by a deficiency of α-galactosidase A, a lysosomal enzyme. This deficiency leads to the accumulation of lipids in the lysosomes in numerous tissues and organs, including the renal glomeruli and tubules. Renal manifestations, including the ultrastructural finding of lamellar bodies, are identical to those that occur due to acquired causes of phospholipidosis.[10,11] It is important to mention that a measurement of α-galactosidase A activity is an appropriate evaluation in men but cannot reliably exclude Fabry disease in women because of random X inactivation, which can lead to α-galactosidase A activities ranging from low to normal values. A GLA gene test can be performed to exclude Fabry disease in women.[12]

With the exclusion of Fabry disease, the absence of other drugs that could cause lysosomal phospholipid accumulation, the presence of cornea verticillata, and the improvement in kidney function after stopping amiodarone, a diagnosis of partially reversible acute on chronic kidney disease caused by lysosomal phospholipidosis due to amiodarone use was deemed highly likely.

The suspected causality between amiodarone treatment and the deterioration of renal function to stage 5 chronic renal insufficiency created the clinical dilemma of whether to continue treatment with amiodarone, despite progressive renal insufficiency, or discontinue treatment with the associated risk of a recurrence of ventricular arrhythmias. In patients with structural heart disease, the choice of antiarrhythmic agents in the prevention of ventricular arrhythmias is limited to amiodarone and beta blockers.[13] In our patient, previous preventive treatment with metoprolol had not been successful. Alternative pharmacological treatments were, therefore, not available. The patient preferred the risk of recurrence of arrhythmia to the prospect of dialysis treatment. Amiodarone was, therefore, discontinued. Catheter ablation, which has become increasingly important in the treatment of ventricular arrhythmias, especially scar-related ventricular tachycardia, would be considered in the case of recurrence of ventricular arrhythmia.[13]

Conclusions

The well-documented spectrum of side effects of amiodarone include its pulmonary and hepatic toxicity. These side effects are also caused by phospholipidosis.[4] However, the nephrotoxic side effect caused by renal phospholipidosis has hardly received any attention up to now. Guidelines advise regular surveillance for liver, lung, and thyroid toxicity during amiodarone treatment but do not mention the potential for renal toxicity.[14] This case suggests that it might be prudent to include screening for renal toxicity in this surveillance.

Lead author biography

Dr Mirjam D. Duineveld graduated in 2019 from the Faculty of Medicine of the University of Amsterdam, The Netherlands. She is currently a Cardiology resident at Haga Teaching Hospital in The Hague, The Netherlands. Her main areas of interest are cardiovascular imaging and heart failure.

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Data availability

The data underlying this article are available in the article. All data are incorporated into the article.

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