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CASE REPORT
Heart failure

Critical heart failure associated with beta-blocker-induced cardiac phospholipidosis: a case report

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Background Drug-induced phospholipidosis (DIPL) is an acquired lysosomal storage disorder characterized by the accumulation of lamellar bodies and phospholipids, typically associated with the use of cationic amphiphilic drugs (CADs). Over 200 marketed CADs, including widely prescribed β-blockers, have the potential to induce phospholipid deposition in various organs. In rare cases, DIPL may lead to secondary cardiomyopathy.

Case summary We report the case of a 70-year-old man with a history of hypertension, permanent atrial fibrillation, and Stanford type B aortic dissection. The patient presented with a 2-week history of worsening dyspnoea. Examination revealed cardiomegaly, elevated B-type natriuretic peptide, and left ventricular dysfunction with an ejection fraction of 24%. Despite intensive medical treatment, the patient developed severe pulmonary congestion and died on Day 35. Post-mortem examination revealed vacuolar degeneration and lamellar body accumulation in the myocardium, consistent with DIPL. The most likely causal agent was bisoprolol, one of the patient's prescribed CADs.

Discussion While β-blockers are commonly used for the treatment of hypertension and heart failure, their potential to induce phospholipid deposition in the heart is rare but significant. This case underscores the need for awareness of DIPL as a potential adverse effect, especially in patients receiving CADs.

Keywords Drug-induced phospholipidosis • Cardiomyopathy • Heart failure • Cationic amphiphilic drugs • β-Blockers • Bisoprolol • Myocardial degeneration • Case report

ESC curriculum 6.2 Heart failure with reduced ejection fraction • 6.5 Cardiomyopathy

Learning points

- Drug-induced phospholipidosis (DIPL) should be considered as a potential cause of unexplained cardiomyopathy in patients on long-term therapy with cationic amphiphilic drugs.
- While β-blockers are widely used for treating hypertension and heart failure, they can, in rare cases, lead to secondary cardiomyopathy through DIPL, potentially resulting in severe cardiac dysfunction and fatal outcomes.

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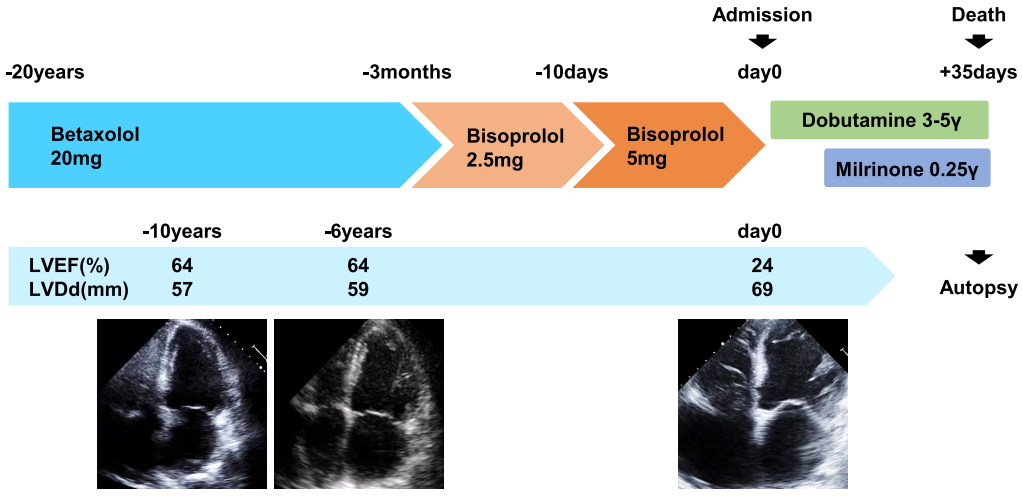
Introduction

Drug-induced phospholipidosis (DIPL) is an acquired lysosomal storage disorder characterized by the accumulation of lamellar bodies and phospholipids, typically associated with the use of cationic amphiphilic drugs (CADs).[1–5] Over 200 marketed drugs classified as CADs have the potential to induce phospholipid deposition in various organs. We report the case of a 70-year-old man who was admitted with worsening heart failure symptoms. Despite intensive medical therapy, the patient succumbed to complications. A post-mortem examination revealed DIPL, likely induced by bisoprolol, a CAD he was taking. This report highlights the clinical course and pathological findings, emphasizing the rare but serious risk of CAD-induced cardiomyopathy.

Summary figure



Case presentation

A 70-year-old man was admitted to our hospital with a 2-week history of worsening dyspnoea. The patient had a history of hypertension, permanent atrial fibrillation, and Stanford type B aortic dissection. He had been prescribed antihypertensive medications (bisoprolol, nifedipine CR, trasemide, and sacubitril valsartan) as well as an anticoagulant dabigatran. Prior to this admission, he had no history of heart failure, and previous echocardiography showed no significant abnormalities, with normal left ventricular wall thickness and preserved systolic function (see Supplementary material online, *Videos S1* and *S2*).

On examination, the patient was alert and breathless at rest; his temperature was 36.5 °C, pulse was 100 beats per minute, blood pressure was 108/63 mmHg, oxygen saturation was 97% (with 2 L of oxygen per minute), and respiratory rate was 34 breaths per minute. On auscultation, heart and breath sounds were normal except for irregular heart rhythm, and there was no peripheral pipping oedema.

An electrocardiogram showed atrial fibrillation and a right bundle branch block, with no signs of ischaemia, infarction, or ventricular hypertrophy. Laboratory investigations showed cardiac overload with a B-type natriuretic peptide level of 2936 pg per mL (normal range 0–18.4) and impaired renal function with a creatinine level of 1.4 mg per dL (normal range 0.6–1.11). Arterial blood gases showed hypoxia with a pO2 of 62.2 mmHg (normal range 83.0–108.0) on room air.

A chest X-ray showed cardiomegaly with a cardiothoracic ratio of 71%, without pulmonary congestion or pleural effusion. Transthoracic echocardiography showed left ventricular dilatation with a diastolic dimension of 69 mm and systolic dysfunction with an ejection fraction of 24% (see Supplementary material online, *Video S3*). Mild regurgitations in both mitral and aortic valves were observed, with no significant changes from previous findings. Coronary angiography by computed tomography showed no severe coronary stenosis or obstruction.

The patient received intensive medical treatment with diuretic agents, dobutamine, noradrenaline, a PDE-III inhibitor, and carperitide in the cardiac care unit. However, he developed cardiogenic shock and pulmonary congestion unresponsive to treatment. On Day 18 after admission, he developed aspiration pneumonia and ultimately died on Day 35. Subsequently, a pathological autopsy was performed with the family's consent.

The coronary arteries showed no stenosis. Myocardial sections of the left ventricle showed vacuolar degeneration and prominent periodic acid-Schiff (PAS) deposition (*Figure 1A* and *B*). Electron microscopy showed scattered lipids near mitochondria with abnormal cristae and numerous lamellar bodies (*Figure 1C* and *D*). Immunostaining to rule out secondary cardiomyopathies showed no evidence of Fabry's disease, Danon's disease, AGTL deficiency, or inflammatory dilated cardiomyopathy. Based on these pathological findings and his medication history, a diagnosis of DIPL caused by CADs was made, with bisoprolol being the most likely causal agent in this case, as it was the only medication the patient was taking at the onset of heart failure that belonged to CADs.

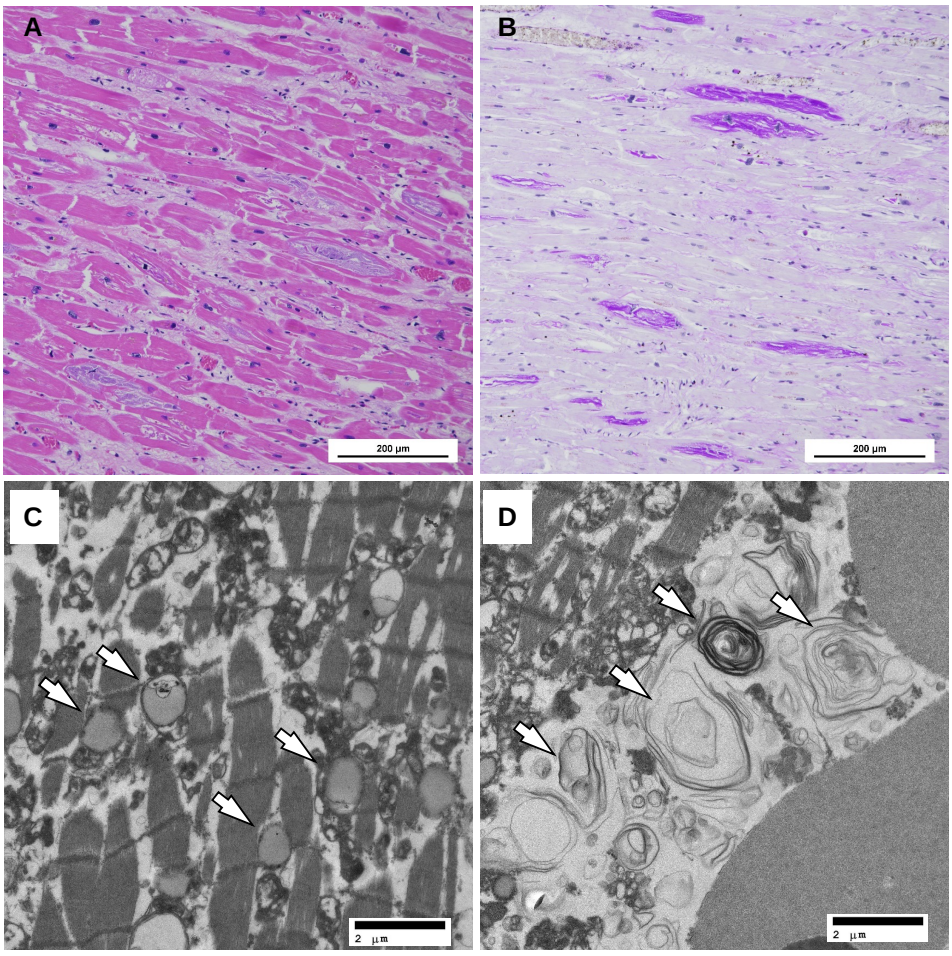


Figure 1 Histopathological analysis of the patient's cardiac left ventricular tissue section. (*A*) Haematoxylin and eosin staining shows vacuolar degeneration. (*B*) Periodic acid-Schiff (PAS) staining is positive. Electron microscopy shows scattered lipids near mitochondria with abnormal cristae (*C*) and numerous lamellar bodies (*D*).

Discussion

Drug-induced phospholipidosis is an acquired lysosomal storage disorder characterized by the accumulation of lamellar bodies and phospholipidosis.[1–5] Cationic amphiphilic drugs, including bisoprolol among more than 200 marketed drugs, have the potential to induce phospholipid deposition. Some reports have documented DIPL in the heart, with flecainide and carvedilol suspected as the causative CADs.[6,7] Mechanistically, CADs accumulate in acidic cellular compartments such as lysosomes, where they become protonated and trapped. This accumulation disrupts the central role of intraluminal vesicles in lipid catabolism by neutralizing their negative surface charge and releasing lysosomal hydrolases and sphingolipid-activating proteins. As a result, CADs inhibit the catabolic degradation of phospholipids, sphingolipids, and cholesterol, transforming lysosomes into dysfunctional storage granules, known as lamellar bodies, and ultimately contributing to the pathogenesis of DIPL.[5]

Conclusion

β-Blockers are widely prescribed for the treatment of hypertension and heart failure; however, in rare cases, they can lead to secondary cardiomyopathy caused by DIPL in the heart, which may result in fatal outcomes.

Lead author biography

Mitsunobu Kaneko, MD, graduated from the University of Kyorin, College of Medicine, in 2001. He completed his residency at Kyorin University Hospital, and he currently works at Tokyo Metropolitan Police Hospital.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

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Consent: The authors confirm that written consent for submission and publication of this case report has been obtained from the patient's family in line with COPE guidelines.

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Data availability

The data underlying this article are available in the article and in its online Supplementary material.

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