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Case Report

Prolonged complete atrioventricular block due to neostigmine and amiodarone interaction in an amyloidosis patient with left main dissection and postoperative intestinal pseudo-obstruction

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Abstract

Cardiac amyloidosis has been strongly associated with postoperative intractable circulatory failure, and intestinal amyloidosis could lead to intestinal pseudo-obstruction. The latter can be treated with neostigmine, which is notorious for its brief bradyarrhythmic complications. The amyloidosis patient presented herein, suffered an iatrogenic left main dissection, failure of bailout stenting and finally underwent urgent surgery. Meticulous fluid and drug management was key to keeping this patient stable. Postoperative atrial fibrillation was treated with amiodarone. The postoperative course was complicated with intestinal pseudo-obstruction, which was ultimately resolved with neostigmine. This short-lived cholinesterase inhibitor interacted with amiodarone and caused a previously undocumented prolonged complete atrioventricular block that resolved 48 hours after both drugs' discontinuation. The neostigmine amiodarone interaction warrants clinical vigilance and is speculated to be due to their partially shared second messenger pathway involving cyclic adenosine monophosphate. Patients with cardiac amyloidosis could maintain hemodynamic stability perioperatively.

INTRODUCTION

Timely diagnosis of amyloidosis can be a challenge. The first manifestations, such as carpal tunnel syndrome, should raise suspicion as they may occur many years before cardiac involvement which is very common and associated with increased mortality. Cardiac amyloidosis has multiple manifestations, including restrictive cardiomyopathy, angina and conduction abnormalities. Often, suspicion arises from the granular appearance of the myocardium in cardiac ultrasound. The cardiac walls are thick while the QRS voltages are low. Ischemia in these patients frequently results from small vessel disease, whereas the epicardial vessels are typically spared. When the latter are involved, coronary artery bypass grafting (CABG) has been associated with intractable circulatory failure [1, 2] and percutaneous coronary intervention (PCI) is preferred [3].

Amyloidosis of the gastrointestinal tract has multiple manifestations as well. They include abdominal pain and distention, tenderness, malabsorption, bowel dilatation, mesenteric adenopathy, gastrointestinal bleeding and intestinal pseudo-obstruction (IPO). Surgery has been suggested as the last resort for the latter [4], which is a potentially life-threatening condition associated with poor outcomes in critically ill patients [5]. Neostigmine has been proven invaluable for the treatment of intestinal pseudo-obstruction [6], yet it has been inculpated for several side-effects [7], such as arrhythmia, while some of its interactions may remain unknown.

We, hereby, present an amyloidosis patient with iatrogenic left main stem dissection who survived urgent CABG. Postoperative management with amiodarone for atrial fibrillation (AF), and neostigmine for IPO led to a previously undocumented, prolonged complete atrioventricular block with potentially grave consequences, had it not been for the pacemaker.

CASE REPORT

A 74-year-old male presented with exertional angina. He was a well-built farmer in no distress, complaining of intermittent substernal pain and peripheral edema.

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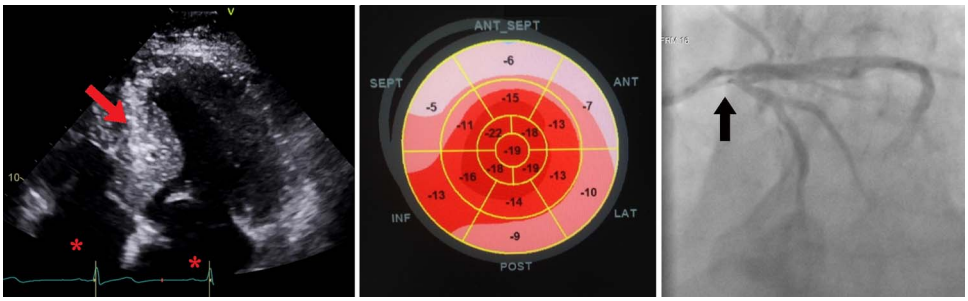

Figure 1. Preoperative imaging. At the left, the cardiac ultrasound demonstrated the sparkling pattern of the thickened myocardial walls, especially the intraventricular septum (red arrow) (video online). The atria were enlarged (asterisks). In the middle, the global longitudinal strain was measured −13.2% against a normal range of −15.9% to −22.1%. Regional strain values were greatly reduced in the basal and mid LV, yet preserved at the LV apex. At the right, the coronary angiography was complicated with dissection of the left main stem (black arrow).

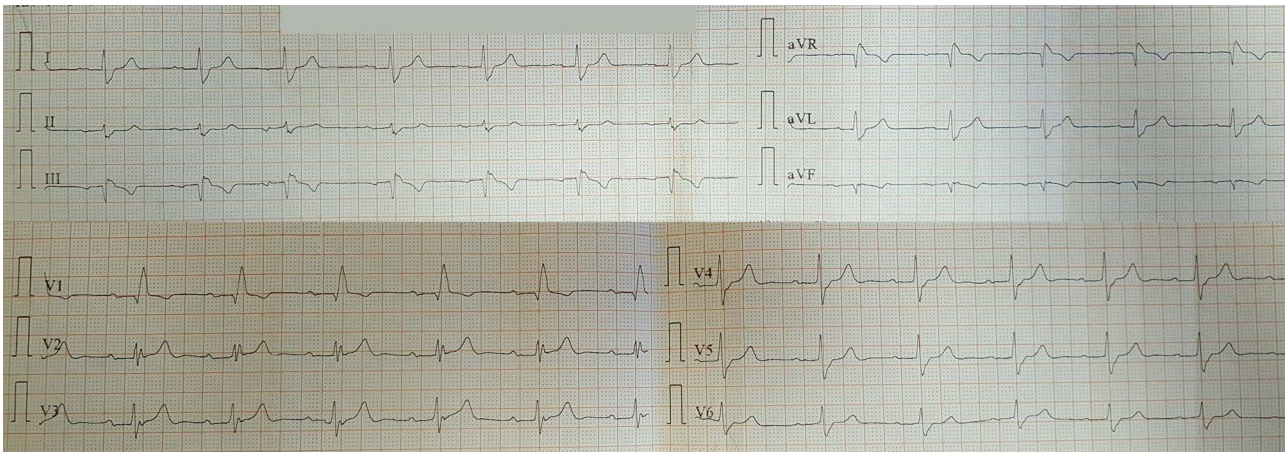

Figure 2. Preoperative electrocardiogram showing trifascicular block.

His medical history was significant for constipation and prostatic hyperplasia treated with silodosin. The clinical and laboratory tests were within normal limits but imaging was revealing (Fig. 1). The electrocardiogram showed trifascicular block (Fig. 2). The ultrasonography revealed thickened cardiac walls, small pericardial effusion and biatrial enlargement. Thus, suspicion of amyloidosis was raised. The ejection fraction by Simpson's biplane method was estimated to 50%, with no regional wall motion abnormality. However, longitudinal myocardial systolic strain by 2D speckle tracking showed far more significant left ventricular (LV) dysfunction. Global longitudinal strain measured −13.2% (normal −15.9% to −22.1%) and regional strain values were greatly reduced in the basal and mid LV, yet preserved at the LV apex. The coronary angiogram, using 6Fr Judkins right 4, and Judkins left 4 catheters, demonstrated two vessel disease, but it was complicated with dissection of the left main stem. The initial attempts for bailout stenting failed, thus urgent surgery was indicated despite the unfavorable results in amyloidosis patients.

The patient underwent urgent grafting of the left anterior descending and the obtuse marginal arteries, while temporary epicardial pacing wires were placed as part of the standard surgical procedure. Biopsy specimens were collected (Fig. 3) and confirmed light chain amyloidosis. The patient was extubated on the first postoperative day (POD). The perioperative fluid management was meticulous to prevent hemodynamic deterioration, bet- blockers were not administered, and silodosin was withheld to avoid hypotensive vasodilation. Mild positive fluid balance was the mainstay of early postoperative management, and electrolyte control was tight.

Early postoperative mild abdominal distension with absence of gas and stool passage was managed expectantly until POD 3. There were decreased bowel sounds and no tenderness on palpation. The abdominal x-rays revealed small bowel ileus (Fig. 4) and the computerized tomography showed no evidence of mechanical obstruction, suggesting IPO. Bowel rest, intravenous (IV) fluids, avoidance of opioids, administration of IV metoclopramide, nasogastric tube placement and low enemas were unsuccessful. Gastrografin per os and repeat colonic evacuation provided only partial relief. The distressed patient lapsed into atrial fibrillation on POD 5 and was managed with IV amiodarone. The loading dose was 5 mg/min (300 mg in 1 hour), and the maintenance dose was 0.65 mg/min (900 mg in 23 hours) to 0.83 mg/min (1200 mg in 24 hours). These rates of IV infusion did not affect the pre-existing heart block. On POD 7, sinus rhythm was restored and amiodarone was changed to per os.

On POD 7, IV neostigmine was administered, despite the concern of complete heart block. The loading dose was 2.5 mg over a few minutes, followed by a maintenance dose of 10 mg per day. If block occurred,

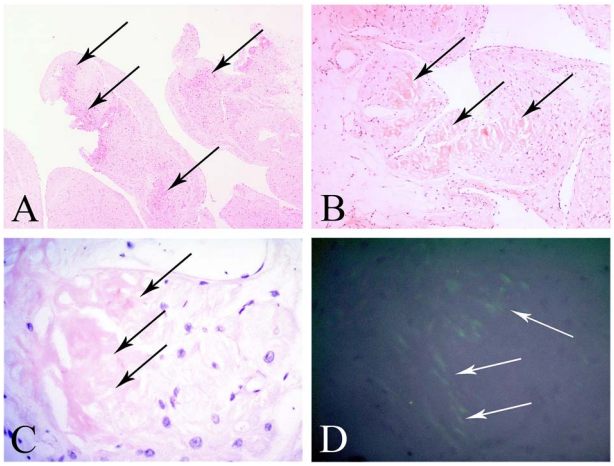

Figure 3. Amyloid deposits were found in atrial and ventricular walls. Panel A: Tissue section of atrial myocardium demonstrating deposits of eosinophilic material (arrows). Hematoxylin and eosin stain, magnification ×40. Panel B: Congo red stain highlighting amyloid deposits with pink–red color (arrows). Magnification ×100. Panel C: Higher magnification of an amyloid deposition site (arrows). Congo red stain, magnification ×400. Panel D: Same area as C observed by polarizing microscope. Note the green-apple birefringence of the deposits. Magnification ×400).

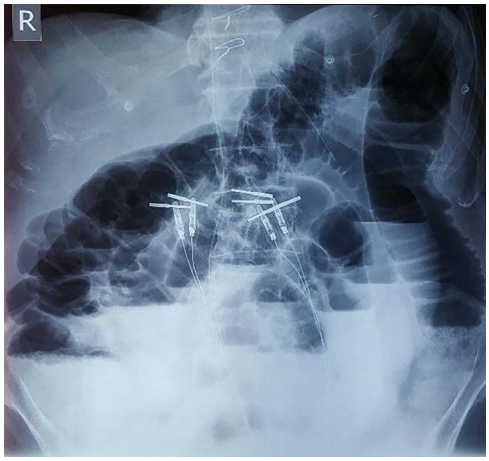

Figure 4. Dilated bowel loops with fluid levels on the fifth POD. The intestinal pseudo-obstruction was resolved with acetylcholinesterase blockage.

it was anticipated to be brief.This calculated risk evolved into a sustained threat attributed to a yet unknown interaction between amiodarone and neostigmine. On POD 9, the IPO resolved at the expense of a complete heart block. Neostigmine and amiodarone were discontinued and the pacemaker kept the heart beating. Despite expectations, return to sinus rhythm was significantly delayed. Even though neostigmine has a half-life of up to 2 hours, its interaction with amiodarone caused a prolonged complete heart block that persisted ~2 days after the discontinuation of both. The rest of the course was uneventful and the patient was discharged on aspirin 160 mg/day, furosemide 20 mg/day and esomeprazole 40 mg/day. He was referred for hematologic evaluation and further management. At 1 month follow-up, he was still in good general condition. Given the significant cardiac involvement and advanced age, the patient was deemed ineligible for autologous stem cell transplantation. He was treated with cyclophosphamide, bortezomib and dexamethasone (CyBorD). Diuretic therapy was maintained.

DISCUSSION

PCI is strongly preferred for patients with cardiac amyloidosis that require coronary revascularization [3]. Nevertheless, CABG is inevitable under certain conditions, as the case presented herein. It was demonstrated that circulatory failure can be evaded with meticulous perioperative fluid and drug management. Beta-blockers were withheld. Amiodarone monotherapy was event free with IV infusion rates that are much lower than the recommended dose for life-threatening arrhythmias (15 mg/min for 10 minutes). Silodosin, a selective a1A adrenoceptor antagonist, was also withheld to avoid its hypotensive side-effect and the recognized detrimental interaction with amiodarone [8].

Early postoperatively, the patient developed IPO. This acute, life threatening condition is typically associated with gastrointestinal amyloidosis and poor outcomes in critically ill patients [5]. Neostigmine was administered, as the last resort before urgent bowel surgery, and it was proven effective. The conversion of the preoperative trifascicular block to a complete heart block by neostigmine was anticipated. However, coadministrating amiodarone led to the significant prolongation of the block, which was not anticipated, and to an extended dependence on the external pacemaker.

Coadministrating neostigmine and amiodarone appears to have a previously unreported, prolonged drug–drug effect on the cardiac conduction system. Neostigmine inhibits acetylcholinesterase, thus the parasympathetic output to the atrioventricular nodal cells is enhanced by increased acetylcholine concentration. Acetylcholine acts on the muscarinic-2 receptors which mediate, via Gi proteins, a strong inhibition of adenylyl cyclase which leads to decreased cyclic adenosine monophosphate (cAMP), decreased intracellular calcium, and blunted excitability. This effect on atrioventricular nodal cells is further exacerbated by amiodarone. This drug's inhibition of the delayed rectifier outward potassium current at phase 3 of the action potential describes its chronic effect [9]. The acute effect is mediated by decreasing the activity of the L-type calcium channels and blocking the beta 1 adrenergic receptors [10], thus inhibiting adenylyl cyclase and decreasing cAMP, as neostigmine does, though via Gs proteins.

The take home messages include avoidance of amiodarone and neostigmine coadministration in patients without a pacemaker, especially those with conduction disease. Should this prolonged bradyarrhythmia be triggered, its prognosis depends on the hemodynamic impact and the prompt implantation of a pacemaker. In the presence of a temporary pacemaker, amiodarone and neostigmine management might be considered

as the prognosis of this bradyarrhythmia appeared good. A permanent pacemaker would render this drug–drug interaction clinically irrelevant. It was also shown that post-CABG prognosis of patients with cardiac amyloidosis might be good if perioperative fluid and drug management is meticulous.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST STATEMENT

None declared.

ETHICAL APPROVAL

No ethical approval was required.

CONSENT

Written informed consent has been obtained from the patient.

GUARANTOR

G.L. is the guarantor of this study.

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