CASE REPORT

Sudden cardiac arrest secondary to cardiac amyloidosis in a young woman with cryopyrin-associated periodic syndrome

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SUMMARY

Cryopyrin-associated periodic syndrome (CAPS) is caused by NLRP3 mutations, which result in dysregulated interleukin 1 β (IL-1 β) production and inflammation. Some patients with CAPS develop systemic amyloidosis via an inflammatory reaction. We describe a case of a 39-year-old woman who experienced cardiopulmonary arrest secondary to ventricular fibrillation complicated by cardiac amyloidosis as well as by CAPS. She was diagnosed with renal amyloidosis at 32 years of age. At 34 years of age, genetic sequencing of the NLRP3 gene demonstrated that she was heterozygous for the p.E304 K mutation, and she was subsequently diagnosed with CAPS. After treatment with canakinumab (human anti-IL-1 β monoclonal antibody) for CAPS, the inflammatory reaction was improved. However, she eventually developed cardiac arrest with ventricular fibrillation and was successfully resuscitated. Echocardiography demonstrated mildly reduced left ventricular systolic function (left ventricular ejection fraction of 48%). Coronary angiography revealed no stenosis, but a cardiac biopsy demonstrated cardiac amyloidosis. She received an implantable cardioverter defibrillator.

BACKGROUND

Cryopyrin-associated periodic syndrome (CAPS) is a group of chronic inflammatory diseases caused by an NLRP3 mutation, which results in dysregulated IL-1 β production and inflammation. CAPS presents with sustained fever and organ dysfunction; the courses of several patients' diseases have been complicated by amyloidosis in conjunction with elevated serum amyloid A (SAA) levels. Systemic amyloidosis, including secondary renal amyloidosis, has been reported in patients with CAPS; however, there have been no reports regarding complicated cardiac amyloidosis.

CASE PRESENTATION

The patient was a 39-year-old woman who presented with sudden cardiac arrest with ventricular fibrillation. She had suffered from fever and arthralgia since birth, and no improvement of her symptoms was elicited by various treatments. She was diagnosed with renal amyloidosis secondary to renal dysfunction at 32 years of age. In 2008 (at 34 years of age), genetic sequencing of the NLRP3 gene demonstrated that she was heterozygous for the p.E304K mutation. She was subsequently diagnosed with CAPS. In 2009, she was hospitalised due to heart failure. Her SAA level was 750 μ g/mL.

Her ECG demonstrated sinus rhythm with a normal axis and a normal QRS duration (94 ms; [figure 1](#)). Echocardiography demonstrated slightly reduced left ventricular (LV) contraction (LV ejection fraction of 51%), and a right ventricular endomyocardial biopsy yielded a diagnosis of cardiac amyloidosis. Histopathological examination demonstrated diffuse amyloid deposition. In February 2010, treatment with anakinra (IL-1 receptor antagonist, 100 mg subcutaneously every other day) was initiated, but the patient's renal function worsened. In April 2012, treatment with canakinumab (human anti-IL-1 β monoclonal antibody, 150 mg subcutaneously every 8 weeks) was initiated for CAPS; the inflammatory reaction subsequently improved. 99m Tc-aprotinin scintigraphy demonstrated aprotinin uptake in the heart, which was suspected of having amyloid deposits, and revealed decreased aprotinin levels both before and during therapy ([figure 2](#)).

In February 2013, the patient returned to our hospital owing to sudden cardiac arrest during canakinumab treatment, which she had been undergoing for 10 months. She developed cardiac arrest with ventricular fibrillation, as detected via an Automatic External Defibrillator, and she was electrically shocked. She was subsequently resuscitated

Figure 1 Twelve-lead ECG performed in 2009.

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Figure 2 ^{99m}Tc -aprotinin scintigraphy, which was performed before (A) and during (B) canakinumab (anti-interleukin 1 β monoclonal antibody) treatment.

and hospitalised in our facility. A 12-lead ECG demonstrated sinus rhythm, left axis deviation, poor R wave progression in V2–4, a relatively wide QRS duration (120 ms) and low electric potentials (figure 3). Echocardiography revealed mildly reduced LV systolic function (LV ejection fraction of 48%) (figure 4). The patient was classified as New York Heart Association (NYHA) functional class II, her plasma B-type natriuretic peptide (BNP) level was 514 pg/mL and her SAA level was 15.5 $\mu\text{g/mL}$.

INVESTIGATIONS

Cardiac catheterisation was performed. Coronary angiography revealed no significant stenosis; however, left ventriculography revealed slight LV enlargement (LV end-diastolic volume index 101 mL/m²) and impaired LV contraction (LV ejection fraction of 50%). A right ventricular endomyocardial biopsy was also performed. Histopathological examination demonstrated diffuse myocardial amyloid deposition but no inflammatory cell infiltration (figure 5). Cardiac MR (CMR) showed myocardial hypertrophy of the interventricular septum with no remarkable myocardial hyperintensity on T2-weighted short-tau inversion recovery (STIR) imaging (figure 6). Dual single photon emission CT (SPECT) of ^{123}I iodine β -methyl-iodophenyl pentadecanoic acid (^{123}I -BMIPP) and ^{201}Tl also showed no Tl-BMIPP mismatch or abnormal BMIPP uptake, with no interval change from 2009 to 2013.

Figure 3 Twelve-lead ECG performed in 2013.

However, the parameters of ventricular late potentials (LPs), determined using signal averaged ECG findings (Predictor BSM-32, Arrhythmia Research Technology, CORAZONIX, USA), were found to have changed between 2008 (before treatment) and 2010. The filtered QRS duration (fQRS) increased from 129.5 to 132.5 ms; the root mean square voltage of the last 40 ms of the QRS complex (RMS40) decreased from 5.28 to 4.27 μV ; and the duration of low amplitude signal <40 μV (LAS40) increased from 54.5 to 59.5 ms (figure 7). The heterogeneity of repolarisation, which was obtained by mapping of the body surface, was characterised by an abnormal distribution.

TREATMENT

The patient underwent cardioverter defibrillator implantation for the secondary prevention of sudden cardiac death. She was treated with canakinumab (300 mg subcutaneously every 4 weeks) for CAPS, amiodarone 200 mg daily for non-sustained ventricular tachycardia, and carvedilol 5 mg daily and losartan 12.5 mg daily for heart failure.

OUTCOME AND FOLLOW-UP

The patient has experienced no recurrence of ventricular fibrillation 2 years after discharge. Her cardiac status is NYHA functional class II; her plasma BNP level is 332.1 pg/mL and her SSA level is 5.4 $\mu\text{g/mL}$.

DISCUSSION

CAPS comprises a group of inherited inflammatory disorders, including familial cold autoinflammatory syndrome, Muckle-Wells syndrome and neonatal-onset multisystem inflammatory disorder.^{1–3} Systemic AA amyloidosis is reported to be a relatively late-onset complication; it presents in up to 10% of affected individuals, according to a previous report.⁴ Systemic AA amyloidosis is a severe complication of CAPS, which causes renal failure and results in death in approximately one-quarter of affected patients.^{1–4} However, there have been no reports regarding cardiac amyloidosis, lethal ventricular arrhythmia or sudden cardiac death associated with CAPS. CAPS is associated with mutations in the NLRP3 gene, which encodes cryopyrin, a component of the interleukin 1 inflammasome that regulates the production of interleukin 1 β .^{5 6} Treatment with subcutaneous canakinumab once every 8 weeks has been reported to reduce the symptoms associated with inflammatory disorders among patients with CAPS.⁷ In this study, however, no cases of organ dysfunction were evaluated either during treatment with canakinumab or after treatment with canakinumab. Kortus-Götze and Hoyer⁸ described a case involving a patient with Muckle-Wells syndrome and end-stage renal disease who was successfully treated with both canakinumab and renal transplantation. In our

Figure 4 Echocardiography after resuscitation. IVS, interventricular septum; LV, left ventricle; LVEF, left ventricular ejection fraction; LVDD, LV internal dimension during diastole; LVDS, LV internal dimension during systole; PW, posterior wall.

Figure 5 Endomyocardial biopsy specimens obtained in 2013, as viewed after H&E (A) and direct fast scarlet stain (B); the samples were obtained after resuscitation. These samples indicated the presence of diffuse amyloid deposition in the myocardial tissue.

Figure 6 Cardiac MR: cine imaging and T2-weighted short tau inversion recovery (STIR) imaging.

Figure 7 Changes in the signal averaged ECG, before (A) and after (B) treatment with canakinumab. fQRS, filtered QRS duration; RMS40, root mean square voltage of the last 40 ms of the QRS complex; LAS40, duration of the low amplitude signal <40 µV.

case, after having begun treatment with canakinumab for CAPS, the patient's inflammatory reaction improved. Her fever and arthralgia, which had been present since birth, were both relieved during treatment with canakinumab; her CRP level decreased from 10.27 to 0.71 mg/dL, and her SAA level decreased from 750 to 15.5 µg/mL.

After 10 months of treatment with canakinumab, our patient has entered remission and is free of the symptoms of her inflammatory disorder. However, a recent histopathological examination demonstrated diffuse amyloid deposition in her myocardial tissue. Left ventriculography revealed slight LV enlargement and impaired contraction of the LV, but CMR and dual SPECT of ^{123}I -BMIPP and ^{201}Tl showed no remarkable myocardial damage. Ventricular arrhythmia may arise from the progress of myocardial conduction disturbances caused by amyloid deposition complicated by CAPS. On a recent 12-lead ECG, low electrical potential demonstrated gradual progression, and the QRS duration was characterised by a gradual widening. Signal-averaged ECG also demonstrated a prolonged fQRS duration, a decreased RMS40 and an increased LAS40 after treatment with canakinumab. Body surface mapping indicated an abnormal distribution of ventricular depolarisation. Among patients with amyloidotic cardiomyopathy, the management of ventricular arrhythmias is challenging, and there is a lack of evidence-based guidelines for management.⁹ In the setting of structural heart disease, LP has been used for risk assessment of lethal arrhythmia. Hörnsten *et al* reported that the occurrence

of LP was associated with non-sustained ventricular arrhythmia in the setting of familial amyloidotic polyneuropathy (FAP) among patients older than 60 years of age. Older patients with both FAP and LP exhibited increased ventricular septal thickness and left posterior wall thickness compared with patients without LP.¹⁰ Cardiac amyloidosis complicated by CAPS is characterised by the development of ECG in ventricular fibrillation despite the effectiveness of canakinumab.

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Contributors KE was the doctor in charge of this patient during her hospitalisation and undertook a literature search to evaluate the pathophysiology of CAPS. AS was the attending physician who instructed KE. KS was the doctor in charge of this patient during her outpatient cardiology clinic visits and provided us with helpful suggestions regarding the pathophysiology of CAPS and amyloidosis. AS and TS wrote the paper.

Competing interests None declared.

Patient consent Obtained.

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Learning points

- ▶ Although rare, cardiac amyloidosis causes ventricular fibrillation in patients with cryopyrin-associated periodic syndrome (CAPS).
- ▶ During the anti-interleukin 1β monoclonal antibody treatment, there was a discrepancy between the improvement of the patient's systemic inflammatory disorders and the progression of her cardiac conduction disturbance.
- ▶ ECG should be carefully followed during the treatment and management of CAPS.

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