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Atrial standstill associated with lamin A/C mutation: A case report

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Abstract

The case report shares evidence for a better understanding of atrial standstill. This being a rare arrhythmogenic condition. This is a 46-year-old woman presented with multiple sites of arterial embolism, including lower extremity arteries, coronary artery, and cerebral artery. Unexpectedly, multiple arterial embolization in the patient was due to atrial standstill by transthoracic echocardiography and cardiac electrophysiological study. An additional family investigation revealed that the patient's brother and sister also suffered from this disease. In search of further understanding the case, we carried out the genetic testing of the family and a frame shift double-G insertion mutation at c.1567 in the *LMNA* gene was found in all the three individuals. The patient recovered well after anticoagulation therapy and left bundle branch area pacing. This report remarks on the importance of multiple sites of arterial embolism which should be wary of family atrial standstill.

Keywords

Arterial embolism, left bundle branch area pacing, cardiology, atrial standstill, lamin A/C mutation

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Introduction

Atrial standstill (AS), being a rare cardiac arrhythmia, is known to generate junctional rhythm or ventricular rhythm associated with sinus arrest and atrial arrest without retrograde atrial conduction. The diagnostic is set by guiding criteria, namely: (1) right atrial (RA) pressure tracings and the absence of A-waves in jugular venous pulse; (2) presence of a supraventricular type QRS complex; (3) the absence of P-waves specifically in surface and intracavitary electrocardiograms (ECGs); (4) immobility of the atria on fluoroscopy; and (5) the inability to stimulate the atria electrically.[1] A diversity of etiologies has been identified. These include drug intoxication, amyloidosis, ischemia, muscular dystrophies, and metabolic derangements.[2]

Several studies have shown that homozygosity of the genes for the cardiac sodium channel (SCN5A) mutation and polymorphism of the atrial gap junction protein (Connexin 40) likely result in AS and sudden death due to suppression of the initiation of action potential.[3,4] Here, we present a unique family of AS cases, possibly due to novel lamin A/C (LMNA) mutations, through preliminary genetic studies on their relationship.

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LMNA gene maps to chromosome 1q21.1-21.2. Evidence has shown its composition being 12 exons spanning around 25 kb. This gene has been proven to encode the A- and C-type lamin proteins in the nuclear membranes of vertebrates. In addition, it is known that mutations in the *LMNA* gene cause laminopathies and Emery-Dreifuss muscular dystrophy (EDMD). A form of laminopathy connected with a mutation of the LMNA expressed by dilated cardiomyopathy and partial AS was reported.[5] Additional more recent research on cardiac disease associated EDMD has predominantly shown cardiac conduction defects, atrial fibrillation/flutter, and AS.[6]

Currently, 562 pathogenis and likely pathogenic LMNA variants have been described. These include 68.5% missense and nonsense mutations, 13.0% splice mutations, 10.7% small deletions, 4.6% small insertions,1.2% small indels, 0.9% gross deletions, 0.9% gross insertions, and 0.2% complex rearrangements from the HGMD database. A study published 2020 by Silvia Crasto et al.[7] indicated that a total of 498 LMNA mutations had been described in the literature and were associated with more than 15 different phenotypes. In the article, the authors also indicate that the laminopathies could either specifically affect distinct tissues, including the peripheral nerves, that striated muscles and the adipose tissue. In addition, comparable to premature aging syndromes, the authors also indicate these as a systemic disease which may affect several organs.[7]

This case report describes the case of a family with clinical features of AS. However, this case is without a known pathogenic mutation in LMNA. Thus, this led the authors to evaluate the possibility of a novel variant in c.1567dupG. Following that process, the identification of a new variant is assumed to potentially contribute to a better understanding of the function of LMNA in AS, specifically.

Case report

A 46-year-old female patient was admitted to the hospital complaining of "sudden weakness of both legs for 2 days." The right leg was markedly swollen and painful. Physical examination showed that the myodynamia of the distal muscle strength of the right lower limb was level 3, and the distal muscle strength of the right lower limb was level 1 by Lovett's scale.[8,9] The patient had a previous history of old cerebral infarction for 6 years, old myocardial infarction for 4 years, but did not have hypertension nor diabetes mellitus.

The ECG showed a regular junctional rhythm of 43 beats/min (Figure 1(a)). The laboratory test results, including liver function, D-dimer, brain natriuretic peptide (BNP), and white blood cell count, were obviously elevated. Surprisingly, the results of double lower-limb arterial computed tomography (CT) angiography showed diffuse embolus and stenosis of both the left iliac artery and right femoral artery, and occlusion of the left popliteal artery. Why did the patient have multiple embolism in the lower-limb arteries? To answer this question, we tried to clarify if arterial embolism was caused by atherosclerosis or by the shedding of cardiac emboli.

Further evaluation with transthoracic echocardiography (TTE) showed 49 mm for the left ventricular end-diastolic diameter. In addition, the same exam showed 40 mm for the left atrial diameter, 44 mm for the RA diameter, 37 mm for the right ventricular diameter, left ventricular ejection fraction (LVEF) 33%, and no atrial mechanical contraction (Figure 1(b)). Atrial and ventricular systolic spectra and tissue Doppler imaging (TDI) at the mitral valve annulus showed the absence of a' at the annulus (Figure 1(c) and (d)). Coronary artery–enhanced CT revealed no stenosis in the coronary artery. However, thrombosis was seen in the left atrial appendage unexpected (Figure 1(e)). We considered the reason of arterial embolism was not the atherosclerosis. So far, we found the answer that the patient's multiple arterial embolism was due to an atrial embolus.

The patient was prescribed, for 7 days, intravenous injection of urokinase and subcutaneous injection of low molecular weight heparin. This was followed by oral administration of rivaroxaban. Fifty days later, the muscle myodynamia of the lower limbs returned to grade 5 without edema.

To continue to clarify the diagnosis, the patient was prepared for electrophysiological examination (EPS). The basal rhythm was a slow junctional rhythm, approximately 43 times/min. No A-wave appeared in the high RA, the middle RA, the Koch triangular, or all CS domain (Figure 2(a)). Electrical stimulation (10 V) at a frequency of 60 times/min was performed on the high RA, the middle RA, the Koch triangular domain, and the CS, but the right and left atria were not captured (Figure 2(b)). On fluoroscopy, no atrial contraction was observed. So, the diagnosis of AS was clear. A single-chamber ventricular pacemaker in left bundle branch pacing (LBBP) mode was implanted because of the patient's high percentage of ventricular pacing.

On account of AS, it was identified a family predisposition, and all the members of the patient's family were subjected to disease history analysis, routine physical examination, ECG, and other examinations to draw a genealogical map. The authors found that the patient's father died of a slow heart rate at 36 years old, meanwhile her elder sister and younger brother were diagnosed with AS, 48-year-old and 41-year-old, respectively, and pacemakers were implanted. The patient's younger sister and son do not have the disease currently.

Because of the unique clinical characteristics of the family, the proband underwent genetic testing with whole-exon sequencing of arrhythmia disorders, which analyzed 721 genes associated with 1475 diseases (NovaCardio, Beijing, China). Of those 721 genes, 1 locus (c.1567dupG) revealed a frameshift mutation in LMNA. The amino acid frameshift insert mutation of asparagine to glutamic acid

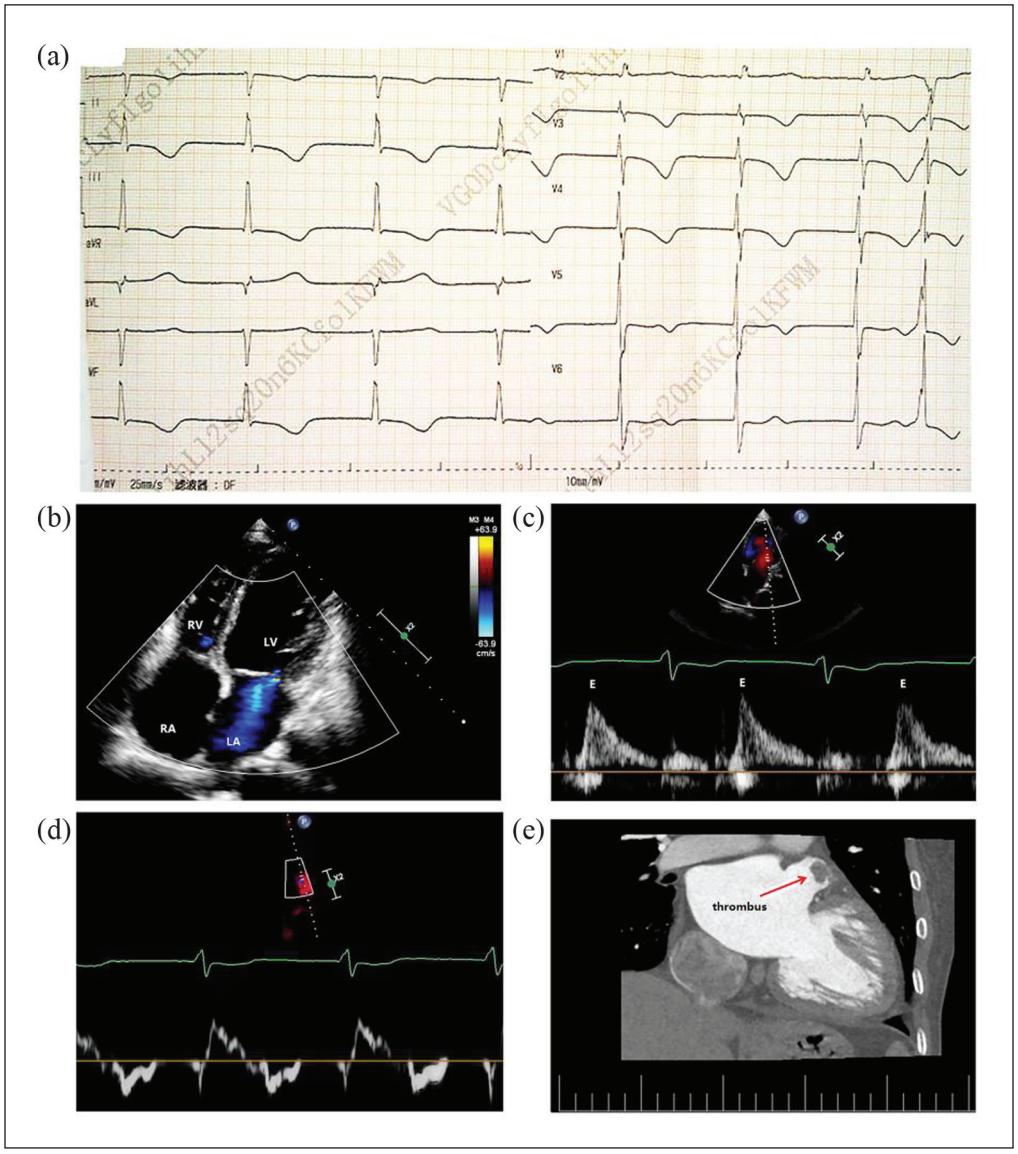

Figure 1. (a) ECG of the proband; (b) TTE showed left and right atria; (c) TTE showed the presence of peak E-wave and the loss of A-wave; (d) TDI at the MV annulus further supported left AS; (e) coronary artery CT showed thrombosis of left atrial appendage.
TEE: transthoracic echocardiography; TDI: tissue Doppler imaging; MV: mitral valve.

at the 524 locus and early termination after the latter 28 amino acids (p.Asn524Glufs*28) was due to a double-G insertion c.1567 within the *LMNA* gene (Figure 3(a)). The heterozygous mutation of the *LMNA* gene was also detected in the patient's younger brother and her older sister (Figure 3(b) and (c)). The patient's younger sister and son did not carry the gene mutation (Figure 3(d) and (e)). The family tree was showed as Figure 3(f). According to the interpretation standard of ACMG gene variation and the patient characteristics of this family, the mutation at this site has very strong pathogenic evidence, but its pathogenicity has not yet been determined accurately. The current domestic and foreign databases were searched in HGMD and ClinVar database, but we did not find the same variation in this locus of LMNA.

Discussion

AS is a very rare arrhythmia, and the clinical data of this family fully conformed to the diagnostic criteria. The proband was first manifested as multiple arterial embolism. Combined with ECG, echocardiography, EPS, and X-ray fluoroscopy, AS was diagnosed. Finally, the subsequent genetic investigation revealed that the patients' family members had a heterozygous frameshift insert mutation with a double-G insertion at locus 1567 in the *LMNA* gene. The treatment of left bundle branch area pacing and anticoagulation was very effective.

Clinically, AS is hard to differentiate from sinus arrest. Evidence suggests that both share similarities between ECG forms with loss of P-waves, absent atrial fibrillatory waves,

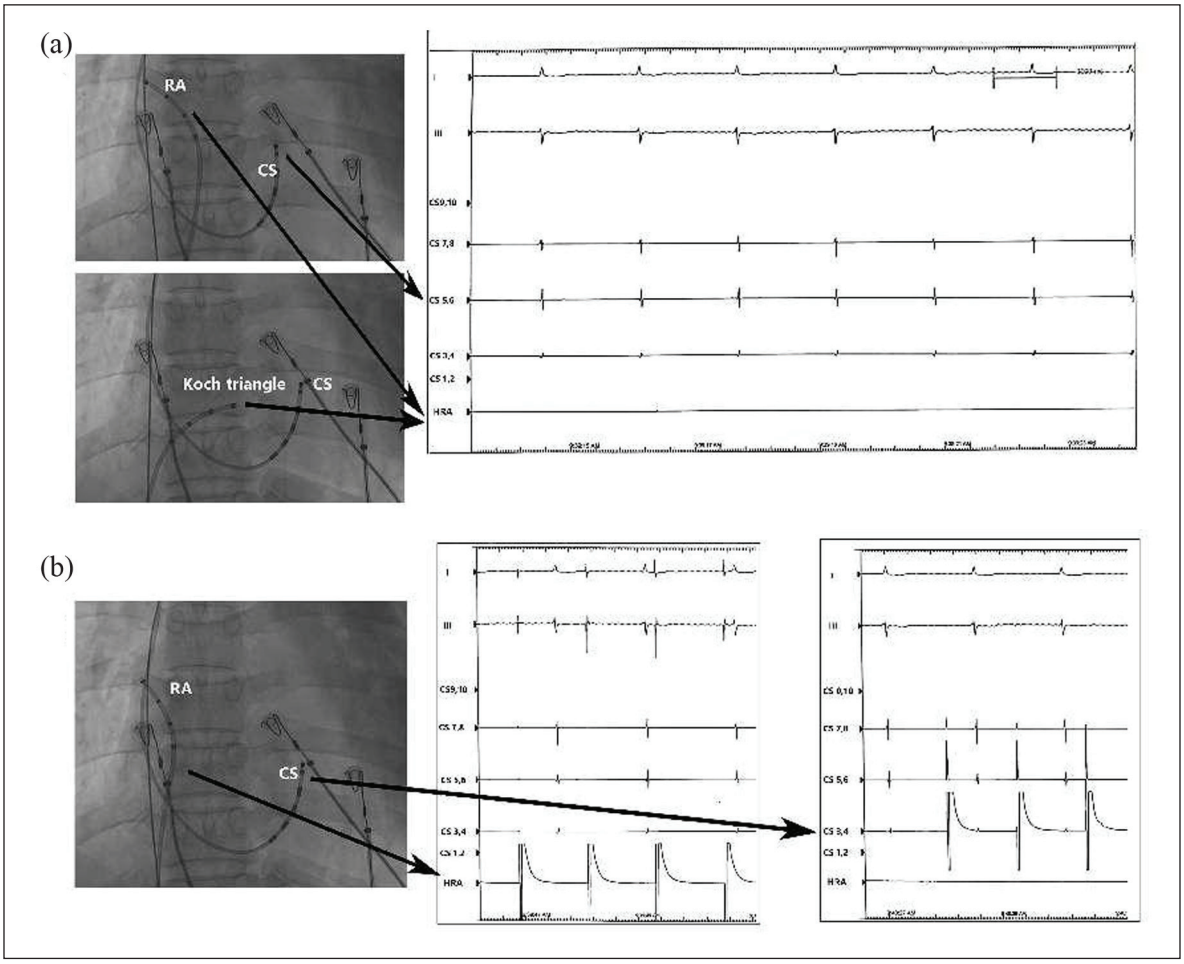

Figure 2. (a) Electrocardiogram of RA, Koch triangle and CS were recorded without waves, HRA in the intracavitary electrogram showed the potential of RA and Koch triangle and (b) 10 V electrical stimulation in RA and CS could not capture the atrium. The intracavitary electrogram showed that CS 3,4 was stimulated.

and irregular slow escape rhythm.[10] AS can be divided into three types: (1) temporary AS, usually associated with digitalis quinidine poisoning, hyperkalemia, and hypoxemia; (2) AS before death, which is a predeath arrhythmia; and (3) persistent AS, which is the result of long-term atrial muscle damage and fibrosis, which is often preceded by atrial arrhythmia and temporary AS.[1]

An electrophysiological mapping on the RA and CS and no P-wave in the RA and CS was performed. This was performed to identify whether it was possible to prioritize the patient's own synchronous atrioventricular conduction through the implant a dual-chamber pacemaker. In addition, it is recognized that synchronous AV conduction can help avoid right ventricular apical pacing with a left bundle branch block ECG morphology, pacemaker syndrome, or heart failure. Therefore, a VVI pacemaker was implanted with the LBBP mode considering the high pacing frequency and no P-wave in the RA and CS. LBBP is a feasible and effective method for achieving electric resynchronization of left bundle branch block (LBBB), with resultant improvements in left ventricular structure and function.[11] Therefore, LBBP appears to be a reliable method for physiological pacing for patients with either a bradycardia or heart failure pacing indication.

In terms of genetic mutation, the heterozygous double-G mutation in the *LMNA* gene may be the pathogenic gene in the family associated with AS. Mutations in LMNA have been associated with being the cause of a variety of clinical phenotypes. These include cardiac disorders, especially dilated cardiomyopathy, atrioventricular conduction defect, atrial fibrillation, and Emery-Dreifuss muscular dystrophy.[12–14] The mutations identified have been associated with manifestations of cardiac phenotypes in LMNA-related cardiomyopathy. This has consequently suggested that genetic analysis of LMNA generates very relevant insights into diagnosis and risk stratification. Evidence suggests that middle-aged adult carriers of rare missense or loss-of-function LMNA variants are at increased risk for arrhythmia and cardiomyopathy.[15] Disease-associated variants were more often associated with inherited cardiomyopathy syndromes and the most common genes were *TTN, MYH7, MYH6, LMNA*, and *KCNQ1*.[16] Reports showed

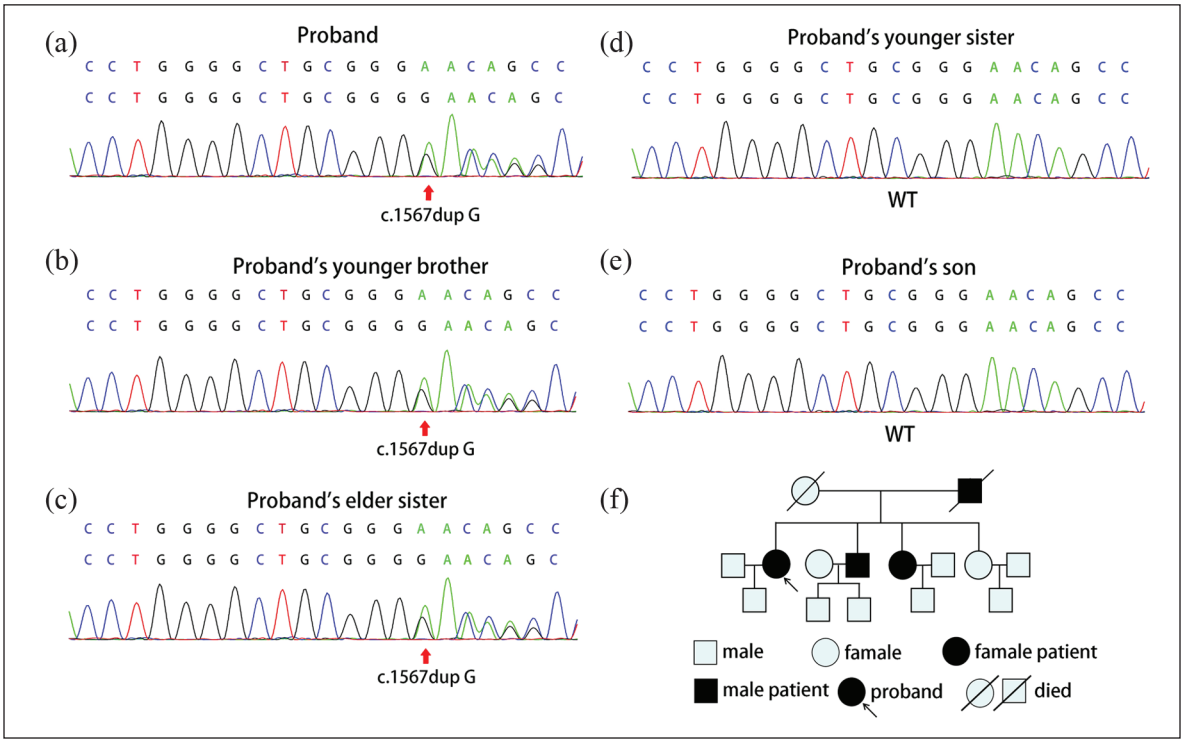

Figure 3. (a)–(e) Sanger sequencing showing the c.1567dupG pathogenic heterozygous variant in the proband, the proband's younger brother, elder sister, younger sister, and her son. (f) Family tree. Pedigree showing the pathogenic people with black box and the nonpathogenic person in blue box.

that LMNA cardiomyopathy is associated with early atrial myopathy reflected by high AF prevalence and reduced LA contractile strain.[17] There are findings suggesting that rare variants in cardiomyopathy and arrhythmia genes, including LMNA, may be associated with increased risk of mortality among patients with early onset AF, especially those diagnosed at a younger age.[18] Our report in this case shows a novel mutation in LMNA which caused the familial AS, further suggesting that patients with arrhythmia and cardiomyopathy caused by mutations in *LMNA* genes may be at great risk.

Other published cases have also demonstrated that point mutations in c.1567 have been reported, including c.1567G > A (p.Gly523Arg) and c.1567G > C (p.Gly523Arg), which associated with left ventricular noncompaction, Charcot-Marie-Tooth disease type 2, lethal tight skin contracture syndrome, and dilated cardiomyopathy. Up to now, there have been few relevant reports about the mutation of c.1567dupG of LMNA in the database and literature. So, this is among the first reported cases that show a heterozygous double-G mutation at c.1567 of the *LMNA* gene in familial AS.

AS is classified as a rare disease. As such, the international community is still expecting sustained international treatment guidelines directed toward potential outcomes. It can be assumed that patients with AS should be put under long-term oral anticoagulation. In addition, permanent pacemaker implantation is accepted to avoid the decline of heart function or other cardiovascular events, in which physiological pacing may the preferred option. This case report is also in line with recent trends in international healthcare research.[19,20]

Conclusion

This is a rare and unusual case of AS. The patient's family has been diagnosed with a novel mutation in *LMNA* gene. The applied treatment of AS involved pacemaker implantation, especially left bundle branch area pacing and long-term oral anticoagulation to reduce the risk of further embolism.

As the scarce available evidence suggests, this is a rare and unusual case of AS. Our main conclusion from our case is that, having the patient and the patient's family been diagnosed with a novel mutation in *LMNA* gene, the applied treatment of AS which involved pacemaker implantation, especially left bundle branch area pacing and long-term oral anticoagulation, seems to be an option to reduce the risk of further embolism. This is the main finding from our case and a contribution to the international debate and evidence-based decisions on other similar cases.

Author contributions

The first author identified and lead the research process with all authors contributing equally for the writing, revision an discussion of the case, reference to related literature and the article drafting process.

Declaration of conflicting interests

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Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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