─Case Reports─

Long-Term Electrocardiographic Follow-Up of a Patient with Light-Chain Cardiac Amyloidosis

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Amyloid light-chain (AL) cardiac amyloidosis can cause restrictive cardiomyopathy, which has a poor prognosis. Although electrocardiography (ECG) is useful for its diagnosis and management, there are few reports on the long-term follow-up of electrocardiographic changes in affected patients. The present patient was a 62-year-old woman who visited our hospital for assessment of palpitations and lower leg edema. A chest radiograph showed cardiac enlargement, and ECG revealed sinus rhythm, first-degree atrioventricular block, low QRS voltage in the limb leads and a pseudo-myocardial infarction pattern in the precordial leads. Echocardiography revealed left ventricular hypertrophy with systolic and diastolic dysfunction. Immunoelectrophoresis demonstrated M-protein (IgGλ), and bone marrow biopsy suggested IgGλ-type plasmacytoma. Myocardial biopsy findings were compatible with cardiac amyloidosis. On the basis of these findings, we diagnosed AL cardiac amyloidosis. Melphalan-prednisolone (MP) therapy was started in conjunction with treatment for non-sustained ventricular tachycardia and congestive heart failure. Two years and 4 months later, the sinus rhythm converted to atrial tachycardia. At a follow-up examination at 4 years and 8 months, right branch block appeared. After that, intraventricular conduction worsened, and the low voltage in the limb leads was not observed. Seven years after diagnosis, she was hospitalized for treatment of pneumonia and heart failure with tachycardia. On the seventh day of hospitalization, heart rhythm changed to atrial stand-still with escaped ventricular rhythm and she died of cardiac arrest. These ECG changes are valuable information regarding the pathophysiological changes that occur in AL cardiac amyloidosis. (J Nippon Med Sch 2022; 89: 119−125)

Key words: AL cardiac amyloidosis, ECG, arrhythmia

Introduction

Amyloid light-chain (AL) cardiac amyloidosis is a disease that can result in restrictive cardiomyopathy due to deposition of monoclonal amyloid light-chain, mainly in the heart. Without proper diagnosis and treatment, the prognosis is extremely poor[1]. Some recent studies reported that early pharmacological interventions for plasmacytosis, which produces amyloidogenic proteins, improves outcomes and life expectancy for patients with cardiac amyloidosis[2,3]. Electrocardiography (ECG) plays a pivotal role in the timely diagnosis and treatment of this condition[4].

The characteristic electrocardiographic findings of cardiac amyloidosis include low voltage in the limb leads[5−7] and a QS pattern in leads V1-V3 (pseudo-myocardial infarction [MI] pattern), regardless of the underlying disease[5,8]. In addition, various supraventricular and ventricular extrasystoles are often observed. Many reports have described ECG findings at diagnosis; however, few reports have examined stage and ECG changes in cardiac amyloidosis. Moreover, few reports have closely tracked ECG changes associated with the clinical course of AL cardiac amyloidosis[8]. Herein, we describe a case in which we were able to follow ECG changes for 7 years after diagnosis of AL amyloidosis.

Case Presentation

A 62-year-old woman visited our hospital for evaluation of palpitations and bilateral lower leg edema. She first reported palpitation on exertion 1 year previously, and cardiomegaly and premature ventricular contractions were noted at a medical check-up. Hypothyroidism was diagnosed at that time, and she was started on levothyroxine 50 mg/day. Her family history was unremarkable.

On initial examination, her blood pressure was 122/72 mm Hg, and her heart rate was 78 beats/min and regular. No obviously abnormal lung sounds were heard, and there were no III or IV sounds. Pitting edema was found bilaterally on the lower legs. A chest radiograph showed cardiomegaly (CTR 61.5%). The ECG findings included sinus rhythm, HR 63 beats/min, first-degree atrioventricular block, low voltage on limb leads and a pseudo-MI pattern (**Fig. 1A**). Transthoracic echocardiography (TTE) (**Fig. 2A**) showed left ventricular hypertrophy (interventricular septal thickness, 14 mm; left ventricular posterior wall thickness, 14 mm), left ventricular systolic and diastolic dysfunction (left ventricular ejection fraction, 39%) and left atrial dilatation (LAD, 49 mm). $^{99\,m}$Tc-methoxy-isobutyl-isonitrile and ^{123}I-β-methyl-P-iodophenyl-pentadecanoic acid scintigraphy showed a slight decrease in left ventricular wall motion but no evidence of ischemia. Cardiac magnetic resonance imaging (MRI) was not performed. Holter monitoring revealed 118,987 total beats/day and 5,951 ventricular arrythmias/day, including 18 episodes of non-sustained ventricular tachycardia. Signal-averaged ECG (SAECG) showed no late-potentials (**Fig. 3A**); however, the high-frequency component of the initial part of the QRS was fragmented and the total value of the high-frequency component was diminished, suggesting a diffuse ventricular conduction disturbance.

Table 1 shows the laboratory findings on the patient's first visit. Total protein increased to 8.5 g/dL and IgG level was high (2,952 mg/dL), while IgA and IgM levels were low (43 mg/dL and 32 mg/dL, respectively). Brain Natriuretic Peptide (BNP) was elevated at 324 pg/mL and troponin T level was 0.11 ng/mL. These findings suggested heart failure and myocardial damage[9,10]. Immunoelectrophoretic revealed IgGλ-type M-protein. A bone marrow analysis revealed normocellular bone marrow with plasma cells in 23% of the total bone marrow cells. Plasma cells of different sizes were also observed. Immunostaining revealed that most plasma cells were IgG (+), λ (+). These findings were consistent with IgGλ-type plasmacytoma. On endomyocardial biopsy, amyloid de-

posits were confirmed by positive hematoxylin and eosin staining and Congo red staining. Fibrosis of the cardiomyocyte stroma was prominent, and amyloid deposits were observed at these sites. On the basis of these findings, we diagnosed AL cardiac amyloidosis[11].

Figure 4 shows the patient's clinical course. Melphalan-prednisolone therapy was given for AL amyloidosis, and non-sustained ventricular tachycardia was treated with sotalol instead of amiodarone because hypothyroidism was observed. The diuretics furosemide and spironolactone were administered for heart failure.

Atrial tachycardia with 2-to-1 ∼ 4-to-1 conduction was observed 2 years and 4 months later (**Fig. 1B**). Her heart rate remained within the normal range, and heart failure did not worsen. At 4 years and 8 months after diagnosis, incomplete right bundle branch block (RBBB) appeared, the pseudo-MI pattern (Q waves in V1-V2 leads) remained, and atrial tachycardia persisted (**Fig. 1C**). At a follow-up examination at 6 years and 8 months, the patient had persistent 2-to-1 atrial tachycardia and worsened intraventricular conduction. The low voltage in the limb leads was not detectable. The P wave was negative in the II, III, and aVf leads, suggesting that the origin or exit site of atrial tachycardia was near the coronary sinus (**Fig. 1D**).

At 7 years after diagnosis, she was hospitalized with pneumonia and heart failure. ECG on admission showed a fast heart rate and wide QRS atrial tachycardia (**Fig. 1 E**). TTE showed left ventricular hypertrophy and diastolic dysfunction (**Fig. 2B**). SAECG revealed prolongation of the filtered QRS duration and a fragmented high-frequency component within the QRS (**Fig. 3B**). Despite treatment for heart failure and pneumonia, her condition worsened. She suddenly developed atrial stand-still with escaped ventricular rhythm (**Fig. 1F**), resulting in hypotension and cardiac arrest. Cardiopulmonary resuscitation was ineffective, and she died. The patient's family did not consent to an autopsy.

Discussion

Cardiac amyloidosis can cause deposition of amyloid protein in the myocardium and interstitium[12] and shows characteristic electrocardiographic findings. Many patients with cardiac amyloidosis die of fatal arrhythmias[13,14] and heart failure. Although ECG is simple and widely used in screening for cardiac diseases, there is no consensus on the relationship between electrocardiographic findings and the clinical stage of cardiac amyloidosis.

Our patient had low QRS voltages in the limb leads

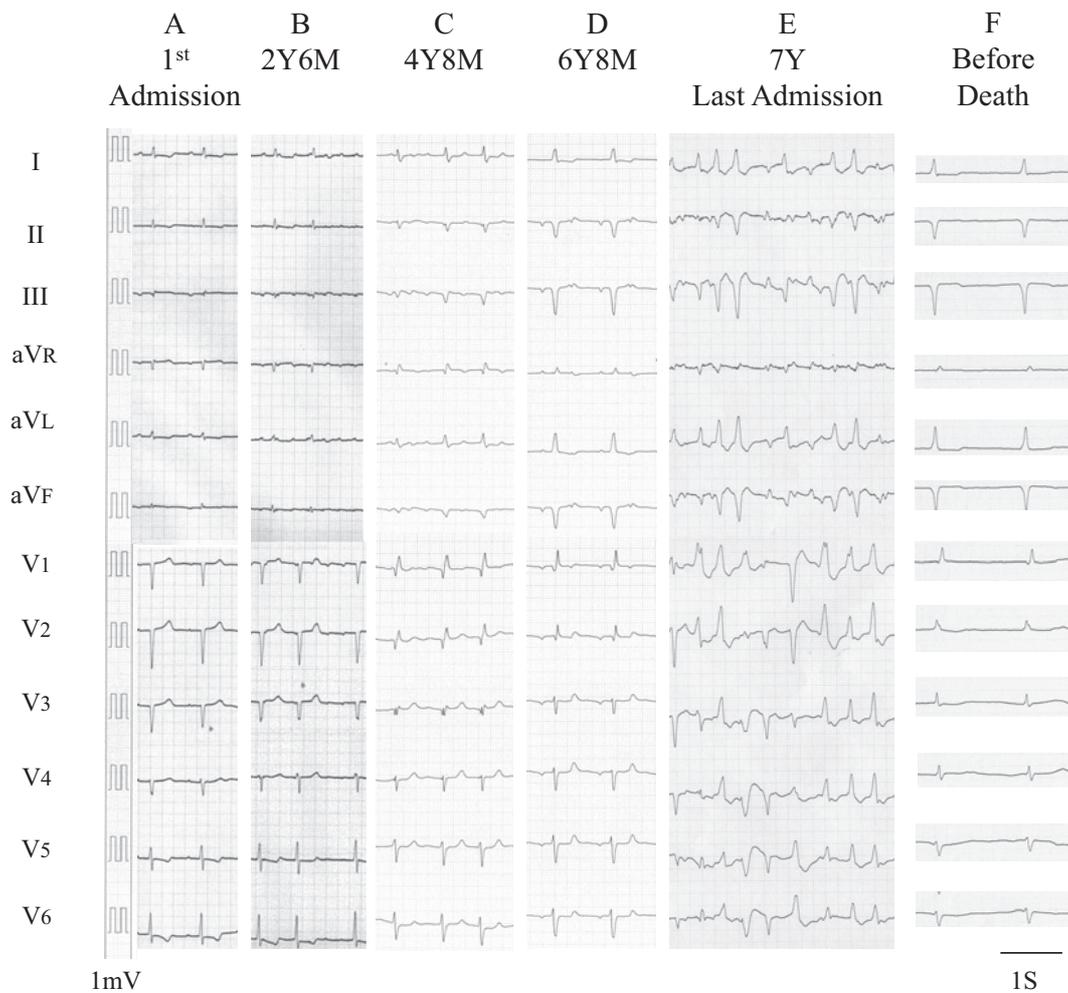| | A
1st
Admission | B
2Y6M | C
4Y8M | D
6Y8M | E
7Y
Last Admission | F
Before
Death |

Fig. 1   ECG findings

A) ECG findings at admission

ECG showed sinus rhythm, a heart rate of 63 beats/min, and first-degree atrioventricular block.

B) ECG at 2 years and 4 months after diagnosis.

ECG showed sinus rhythm, a heart rate of 63 beats/min, and first-degree atrioventricular block. Low limb lead voltages and a pseudo-MI pattern in V1-3 were observed.

C) ECG 4 at years and 8 months after diagnosis.

Atrial tachycardia (AT) with block. ICRBBB appeared and the pseudo-MI pattern (Q waves in V1-V2 lead) remained.

The limb leads continued to show low voltage.

D) ECG at 6 years and 8 months after diagnosis.

ECG showed 2: 1 atrial tachycardia (AT) and bi-fascicular block. The P wave was negative in the II, III, and aVf leads. The low voltage of the limb leads was no longer observed.

E) ECG findings at last admission (7 years after diagnosis).

Fast heart rate and wide QRS atrial tachycardia with non-sustained ventricular tachycardia.

F) ECG before death.

Atrial tachycardia terminated to atrial stand-still with escaped ventricular rhythm.

and a pseudo-MI pattern in the anterior precordial leads at the first visit. Among patients with AL cardiac amyloidosis, low QRS voltage was present in 23% to 64%[5–7], while a pseudo-MI pattern was detected in 15% to 69%[5,8]. Furthermore, the combined presence of low QRS voltages[5,8] and a pseudo-MI pattern[15,16] was associated with poor outcomes in cardiac amyloidosis.

SAECG revealed a decrease in the QRS high-frequency component, suggesting the presence of diffuse and uniform conduction disorders in the myocardium and matrix, which may be a cause of the low QRS voltage in the limb leads[17]. The rate of pseudo-MI pattern positivity was reported to increase in relation to the degree of delayed imaging in cardiac MRI, suggesting that progression of
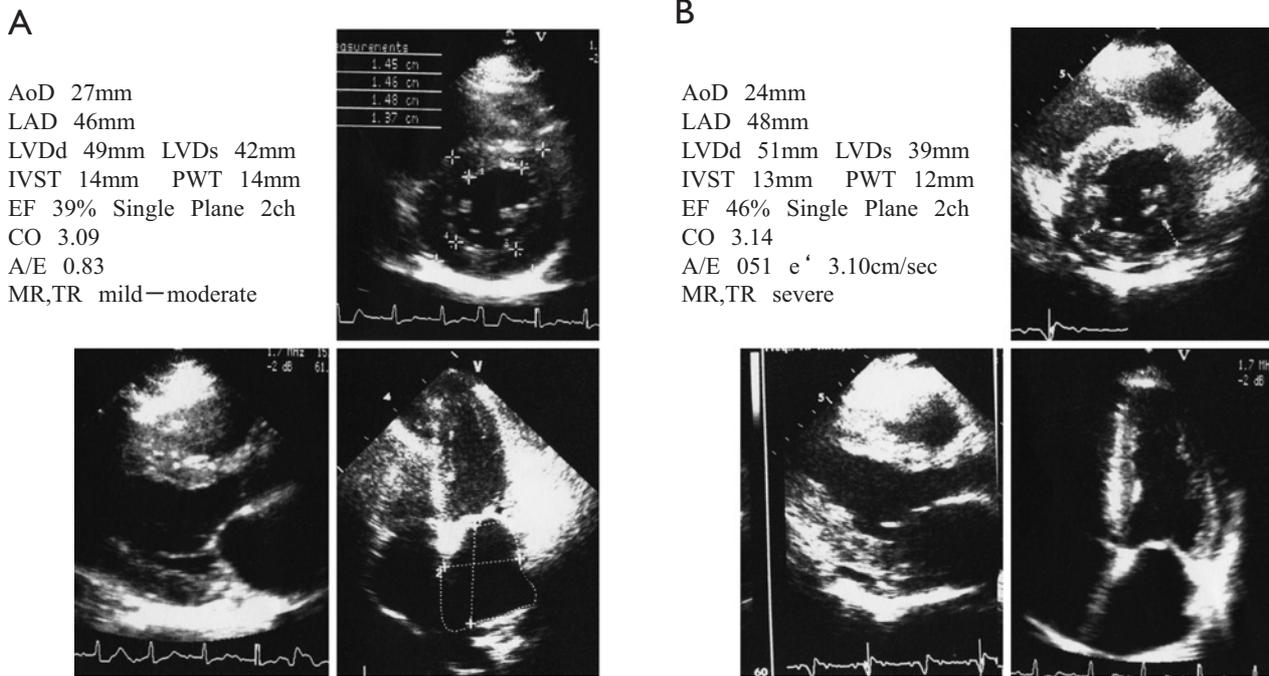
Fig. 2 Transthoracic echocardiogram at the first visit (A) and 7 years later (B). Left ventricular hypertrophy was observed at the first visit and later, and a characteristic "granular sparkling" appearance of the ventricular wall became evident later.

AOD: aortic dimension, LAD: left atrial dimension, LVDd: left ventricular diastolic dimension, LVDs: left ventricular systolic dimension, IVST: interventricular septal thickness, PWT: posterior wall thickness, EF: ejection fraction, CO: cardiac output, MR: mitral regurgitation, TR: tricuspid regurgitation.
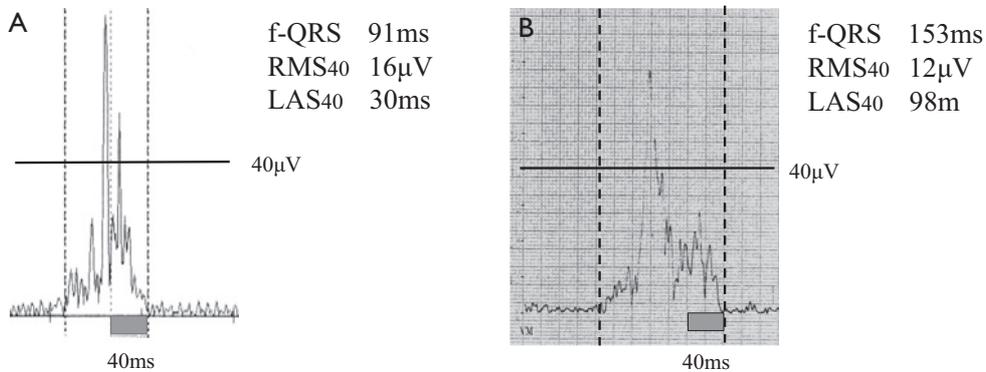

Fig. 3 SAECG

A. SAECG at the first visit

The high-frequency component was diminished. The F-QRS duration was within the normal range.

B. SAECG at 7 years aftetr diagnosis. Late potential was not observed. Prolongation of the filtered QRS duration and fragmented high-frequency component were observed.

amyloid deposition is associated with the appearance of a pseudo-MI pattern[18].

During the clinical course, we observed two major ECG changes. The first was that sinus rhythm changed to atrial tachycardia. After that, the origin of atrial tachycardia changed to a site near the coronary sinus and eventually resulted in atrial stand-still with escaped ventricular rhythm. Deposition of amyloid protein in the atrial muscles and stroma impairs conduction in the atrium. If the conduction disorder progresses, it ultimately becomes atrial stand-still. At the last admission, she showed atrial tachycardia originating near the coronary sinus. At that stage, she could only maintain electrical activity in a limited area between the focus of atrial tachycardia and

	1	2	3	4	5	6	7 years

Palpitation, SOB

CHF,Pneumonia
→Death

| Sinus Rhythm, PVC, NSVT | AT (2:1~4:1conduction) | | | | | * | ** |

*:tri-fascicular block

: AT (wide QRS, fast HR) with NSVT →Atrial Standstill + Escaped Junctional Rhythm

Low Voltage

Pseudo MI pattern

RBBB

EF 34%	48%	55%				55%	46%
LVDd 49mm	50mm	43mm				52mm	48mm
IVST 15mm	14mm	14mm				12mm	13mm

BNP 324pg/mL	231pg/mL 185pg/mL	240pg/mL		215.6pg/mL	158.3pg/mL	342.5pg/mL	758pg/mL

MP therapy 1/month

Sotalol 40mg/day

Furosemide 40mg/day   Furosemide 80mg/day

Spironolactone 25mg/day   Spironolactone 50mg/day

Warfarin 3mg/day

Levothyroxine 50μg/day

Fig. 4   Clinical course from first visit to death

SOB: shortness of breath, CHF: congestive heart failure, PVC: premature ventricular contraction, NSVT: non-sustained ventricular tachycardia, AT: atrial tachycardia, HR: heart rate, AVB: atrioventricular block, RBBB: right bundle brunch block, NSVT; non-sustained ventricular tachycardia, MP therapy: melpaharan with predonisolone therapy

Table 1   Laboratory data at the initial assessment

WBC	8,400 /μL	UA	7.8 mg/dL	TP	8.3 g/dL
RBC	400×10⁴ /μL	BUN	28.3 mg/dL	Alb	4.5 g/dL
Hb	13.3 g/dL	Cr	1.38 mg/dL	IgG	2,952 mg/dL
Ht	38.1 %	Na	144 mEq/L	IgA	43 mg/dL
Plt	26.5×10⁴ /μL	K	4.8 mEq/L	IgM	32 mg/dL
ALT	38 IU/dL	Cl	104 mEq/L		
AST	21 IU/dL				
LDH	615 IU/L	CRP	0.18 mg/dL		
ALP	148 IU/L				
γ-GTP	96 IU/L	FBS	110 mg/dL		
TC	204 mg/dL				
TG	305 mg/dL	freeT3	2.52 μU/mL		
CK	149 IU/L	freeT4	0.49 pg/mL		
CKMB	10 IU/L	TSH	1.26 ng/dL		
TropT	0.11 ng/mL				
h-FABP	9.8 ng/mL				
BNP	324 pg/mL				

atrioventricular node. Eventually, excitement or conduction in that area was lost, leading to atrial stand-still[19,20].

The second major ECG change was progression of conduction system disorders. After the initial RBBB, conduction worsened to bi-fascicular block. Because first-degree atrioventricular block was already present, the presence of tri-fascicular block may be used for diagnosis at this stage. QRS voltages changes in the limb leads were caused by alteration of the ventricular conduction pattern, which resulted from amyloid protein deposition in the conduction system.

Atrioventricular block is detected as a complication in 15% to 26% of patients with AL amyloidosis, while RBBB is reported in 3% to 19% of patients[5]. Intraventricular conduction disorder is considered to have a poor prognosis.

We did not perform direct current cardioversion because the heart rate was stable and heart failure did not

worsen before last admission. When tri-fascicular block is observed, indications for pacemaker implantation should be considered. However, although direct current cardioversion for atrial arrhythmias in patients with cardiac amyloidosis might improve cardiac function, the complication rate of bradycardic and tachyarrhythmias events is high[21]. In addition, pacemaker implantation is complicated by unsolved problems, such as the timing of implantation, pacing site, and mode[22]. So, careful assessment is required for these interventions.

The present ECG changes can be explained by progression of pathological and electrophysiological conditions of the atrial muscle and conduction system, along with deposition of amyloid protein. Thus, when managing patients with AL cardiac amyloidosis, it is important to diagnose the condition and start treatment before heart failure or myocardial damage becomes apparent. In patients with cardiac hypertrophy with low QRS voltage in the limb leads and pseudo-MI patterns in the precordial leads, cardiac amyloidosis should be suspected, even without a prolonged QRS duration.

Conclusion

We experienced a case of AL cardiac amyloidosis that we followed for 7 years. The progression of conduction disorders resulted in various ECG findings during the clinical course.

Conflict of Interest: The authors declare no conflicts of interest in association with the present study.

References

1. Kumar S, Dispenzieri A, Lacy MQ, et al. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. J Clin Oncol [Internet]. 2012 Mar 20;30(9): 989−95. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22331953

2. Finocchiaro G, Merlo M, Pinamonti B, et al. Long term survival in patients with cardiac amyloidosis. Prevalence and characterisation during follow-up. Heart Lung Circ [Internet]. 2013 Aug;22(8):647−54. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23485473

3. Macedo AVS, Schwartzmann PV, de Gusmao BM, Melo MDT, Coelho-Filho OR. Advances in the Treatment of Cardiac Amyloidosis. Curr Treat Options Oncol [Internet]. 2020 Apr 23;21(5):36. Available from: https://www.ncbi.nlm.nih.gov/pubmed/32328845

4. Piper C, Butz T, Farr M, Faber L, Oldenburg O, Horstkotte D. How to diagnose cardiac amyloidosis early: impact of ECG, tissue Doppler echocardiography, and myocardial biopsy. Amyloid [Internet]. 2010 Mar;17(1):1−9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20146643

5. Mussinelli R, Salinaro F, Alogna A, et al. Diagnostic and prognostic value of low QRS voltages in cardiac AL amyloidosis. Ann Noninvasive Electrocardiol [Internet]. 2013 May;18(3):271−80. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23714086

6. Rapezzi C, Merlini G, Quarta CC, et al. Systemic cardiac amyloidoses: disease profiles and clinical courses of the 3 main types. Circulation [Internet]. 2009 Sep 29;120(13): 1203−12. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19752327

7. Quarta CC, Solomon SD, Uraizee I, et al. Left ventricular structure and function in transthyretin-related versus light-chain cardiac amyloidosis. Circulation [Internet]. 2014 May 6;129(18):1840−9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24563469

8. Pinney JH, Whelan CJ, Petrie A, et al. Senile systemic amyloidosis: clinical features at presentation and outcome. J Am Heart Assoc [Internet]. 2013 Apr 22;2(2):e 000098. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23608605

9. Takashio S, Yamamuro M, Izumiya Y, et al. Diagnostic utility of cardiac troponin T level in patients with cardiac amyloidosis. ESC Heart Fail [Internet]. 2018 Feb;5(1):27−35. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28869340

10. Januzzi JL Jr, Mahler SA, Christenson RH, et al. Recommendations for institutions transitioning to high-sensitivity troponin testing: JACC Scientific Expert Panel. J Am Coll Cardiol [Internet]. 2019 Mar 12;73(9):1059−77. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30798981

11. Falk RH, Alexander KM, Liao R, Dorbala S. AL (Light-Chain) cardiac amyloidosis: A review of diagnosis and therapy. J Am Coll Cardiol [Internet]. 2016 Sep 20;68(12): 1323−41. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27634125

12. Binder C, Duca F, Stelzer PD, et al. Mechanisms of heart failure in transthyretin vs. light chain amyloidosis. Eur Heart J Cardiovasc Imaging [Internet]. 2019 May 1;20(5): 512−24. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30649240

13. Towbin JA, McKenna WJ, Abrams DJ, et al. 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy. Heart Rhythm [Internet]. 2019 Nov;16(11):e301−72. Available from: https://www.ncbi.nlm.nih.gov/pubmed/31078652

14. Hess EP, White RD. Out-of-hospital cardiac arrest in patients with cardiac amyloidosis: presenting rhythms, management and outcomes in four patients. Resuscitation [Internet]. 2004 Jan;60(1):105−11. Available from: https://www.ncbi.nlm.nih.gov/pubmed/14987790

15. Zhao L, Li J, Tian Z, Fang Q. Clinical correlates and prognostic values of pseudoinfarction in cardiac light-chain amyloidosis. J Cardiol [Internet]. 2016 Nov;68(5):426−30. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26685729

16. Boldrini M, Salinaro F, Mussinelli R, et al. Prevalence and prognostic value of conduction disturbances at the time of diagnosis of cardiac AL amyloidosis. Ann Noninvasive Electrocardiol [Internet]. 2013 Jul;18(4):327−35. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23879272

17. Dubrey SW, Bilazarian S, LaValley M, Reisinger J, Skinner M, Falk RH. Signal-averaged electrocardiography in patients with AL (primary) amyloidosis. Am Heart J [Internet]. 1997 Dec;134(6):994−1001. Available from: https://www.ncbi.nlm.nih.gov/pubmed/9424057

18. Syed IS, Glockner JF, Feng D, et al. Role of cardiac magnetic resonance imaging in the detection of cardiac amyloidosis. JACC Cardiovasc Imaging [Internet]. 2010 Feb;3 (2):155−64. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20159642

19. Rocken C, Peters B, Juenemann G, et al. Atrial amyloidosis: an arrhythmogenic substrate for persistent atrial fibrillation. Circulation [Internet]. 2002 Oct 15;106(16):2091−7. Available from: https://www.ncbi.nlm.nih.gov/pubmed/12379579

20. Leone O, Boriani G, Chiappini B, et al. Amyloid deposition as a cause of atrial remodelling in persistent valvular atrial fibrillation. Eur Heart J [Internet]. 2004 Jul;25(14):1237−41. Available from: https://www.ncbi.nlm.nih.gov/pubmed/15246642

21. El-Am EA, Dispenzieri A, Melduni RM, et al. Direct current cardioversion of atrial arrhythmias in adults with cardiac amyloidosis. J Am Coll Cardiol [Internet]. 2019 Feb 12;73(5):589−97. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30732713

22. Cheung CC, Roston TM, Andrade JG, Bennett MT, Davis MK. Arrhythmias in cardiac amyloidosis: Challenges in risk stratification and treatment. Can J Cardiol [Internet]. 2020 Mar;36(3):416−23. Available from: https://www.ncbi.nlm.nih.gov/pubmed/32145868