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Case report

A case of AL amyloidosis presenting with refractory ventricular fibrillation

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ABSTRACT

A 66-year-old male with recent diagnosis of heart failure with reduced ejection fraction was referred to our institution for management of cardiogenic/vasodilatory shock. During his evaluation, he suffered a sudden cardiac arrest from refractory ventricular tachycardia/fibrillation (VT/VF) despite normal electrolytes and no evidence of prior ventricular arrhythmias. He was placed on rescue peripheral veno-arterial extracorporeal membrane oxygenation support (VA-ECMO) for 4 days and was decannulated without end-organ damage. Continued workup revealed Mayo stage IV immunoglobulin light chain (AL) amyloidosis. Unfortunately, he developed acute cerebellar hemorrhage several days later. Autopsy findings were consistent with AL amyloidosis, with extensive cardiac fibrosis and amyloid deposition in the myocardium and vasculature.

While the most common cause of cardiac death in patients with amyloidosis is severe bradycardia and pulseless electrical activity, sustained ventricular arrhythmias have been reported. The use of implantable cardioverter defibrillators (ICD) is highly debated in this population given the lack of survival benefit. Our patient also developed refractory VT/VF arrest, and ICD shocks would not have rescued him while causing significant distress. Emergent VA-ECMO cannulation allowed us to make a diagnosis, yet this intervention cannot be routinely recommended given the limited survival of patients with AL amyloidosis.

1. Introduction

Sustained episodes of ventricular arrhythmias are relatively uncommon in heart failure (HF) occurring in less than 5% of all patients [1]. They are often precipitated by myocardial ischemia, inflammation, underlying structural heart disease, electrolyte abnormalities, excessive neurohormonal activation, or certain medications. Sustained ventricular tachycardia (VT) and ventricular fibrillation (VF) are even rarer in non-ischemic cardiomyopathy, including amyloidosis [2]. Here we present a case of primary immunoglobulin light chain (AL) amyloidosis where patient developed refractory VF ultimately requiring rescue veno-arterial extracorporeal membrane oxygenation (VA-ECMO) cannulation.

2. Case presentation

Our patient is a 66-year-old male with hypertension and heterozygous factor V Leiden mutation who was admitted to an outside facility with new Stage C HF, NYHA Class 3 symptoms in December 2019. He was diagnosed with HF with reduced ejection fraction (LVEF: 30%) in the setting of new-onset atrial fibrillation with rapid ventricular response. Non-invasive ischemic evaluation at the time was negative, his volume status was optimized, and heart rate was controlled with oral amiodarone. Guideline-directed medical therapy was initiated and titrated subsequently as outpatient. He was readmitted in June 2020 with 2 weeks of worsening cough, weight gain, and progressive shortness of breath. Treatment was started for community-acquired pneumonia and HF exacerbation; however, the patient became increasingly hypotensive, and renal function continued to worsen. Invasive hemodynamic evaluation revealed significantly elevated filling pressures (pulmonary capillary wedge pressure: 27 mmHg) and reduced cardiac index of 1.8 L/min/m^2 in the setting of low systemic vascular resistance. Patient was initiated on milrinone and norepinephrine for suspected mixed cardiogenic/septic shock physiology and transferred to our institution for further management. Physical examination on arrival was notable for elevated jugular venous pressure and bilateral lower extremity edema. N-terminal pro–B-type natriuretic peptide was 3194 pg/

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Abbreviations

AL amyloidosis	immunoglobulin light chain amyloidosis
ATTR cardiac amyloidosis	transthyretin cardiac amyloidosis
AV	atrioventricular
HF	heart failure
ICD	implantable cardioverter defibrillator
LV	left ventricular
LVH	left ventricular hypertrophy
TTE	Transthoracic echocardiography
VA-ECMO	veno-arterial extracorporeal membrane oxygenation
VF	ventricular fibrillation
VT	ventricular tachycardia

mL, troponin I was 0.17 ıg/L, and blood cultures were repeatedly negative. ECG showed normal sinus rhythm, first-degree atrioventricular (AV) block, and pseudo-infarct pattern in multiple coronary territories (Fig. 1). Transthoracic echocardiography (TTE) revealed an improved left ventricular (LV) ejection fraction at 45%, LV concentric remodeling, grade III diastolic dysfunction, bi-atrial enlargement, and no significant valvular abnormalities (Fig. 2). Patient responded well to aggressive diuresis with medical optimization, and vasoactive medications were titrated off. Cardiac magnetic resonance imaging was planned but delayed due to low glomerular filtration rate. Despite normal electrolytes and no history of ventricular ectopy on telemetry, patient developed cardiac arrest due to VF on day 3. Repeat attempts at defibrillation were unsuccessful, and the decision was made to proceed with peripheral VA-ECMO cannulation for refractory VF. While on full hemodynamic support, patient remained in VF/polymorphic VT for an additional 75 minutes despite defibrillations, amiodarone drip, lidocaine boluses, and deep sedation, before successfully converting to sinus rhythm. Coronary angiogram revealed no obstructive coronary artery disease. He was supported on VA-ECMO for 4 days with no arrhythmia recurrence before uneventful decannulation. Given the constellation of vasoplegia, renal dysfunction, ECG findings, and TTE results, a workup for amyloidosis was initiated. Laboratory evaluation showed significantly elevated serum lambda free light chain at 49.54 mg/dL with free light chain difference of 44.32 mg/dL. While these results were pending, a Technetium 99m Pyrophosphate scan was performed and returned negative, essentially excluding transthyretin (ATTR) cardiac amyloidosis. Endomyocardial biopsy was deemed too high risk in the setting of recent refractory VF arrest. Therefore, abdominal fat pad biopsy was performed, and samples stained with Congo red demonstrated amyloid deposition (Fig. 3). Further typing by liquid chromatography tandem mass spectrometry detected a peptide profile consistent with AL (lambda)-type amyloidosis. Despite our efforts, the patient's renal function continued to worsen, ultimately requiring continuous renal replacement therapy in the setting of borderline hypotension. His hospital course was further complicated by acute right cerebellar hemorrhage on day 16. Due to his multi-organ failure in the setting of AL amyloidosis, the decision was made with the family to transition to comfort care measures. Despite only mild LV hypertrophy (LVH) on TTE, autopsy revealed marked cardiomegaly at 760g with minimal focal coronary artery disease. Significant myocardial fibrosis was noted on histology with amyloid deposition within the myocardium and the walls

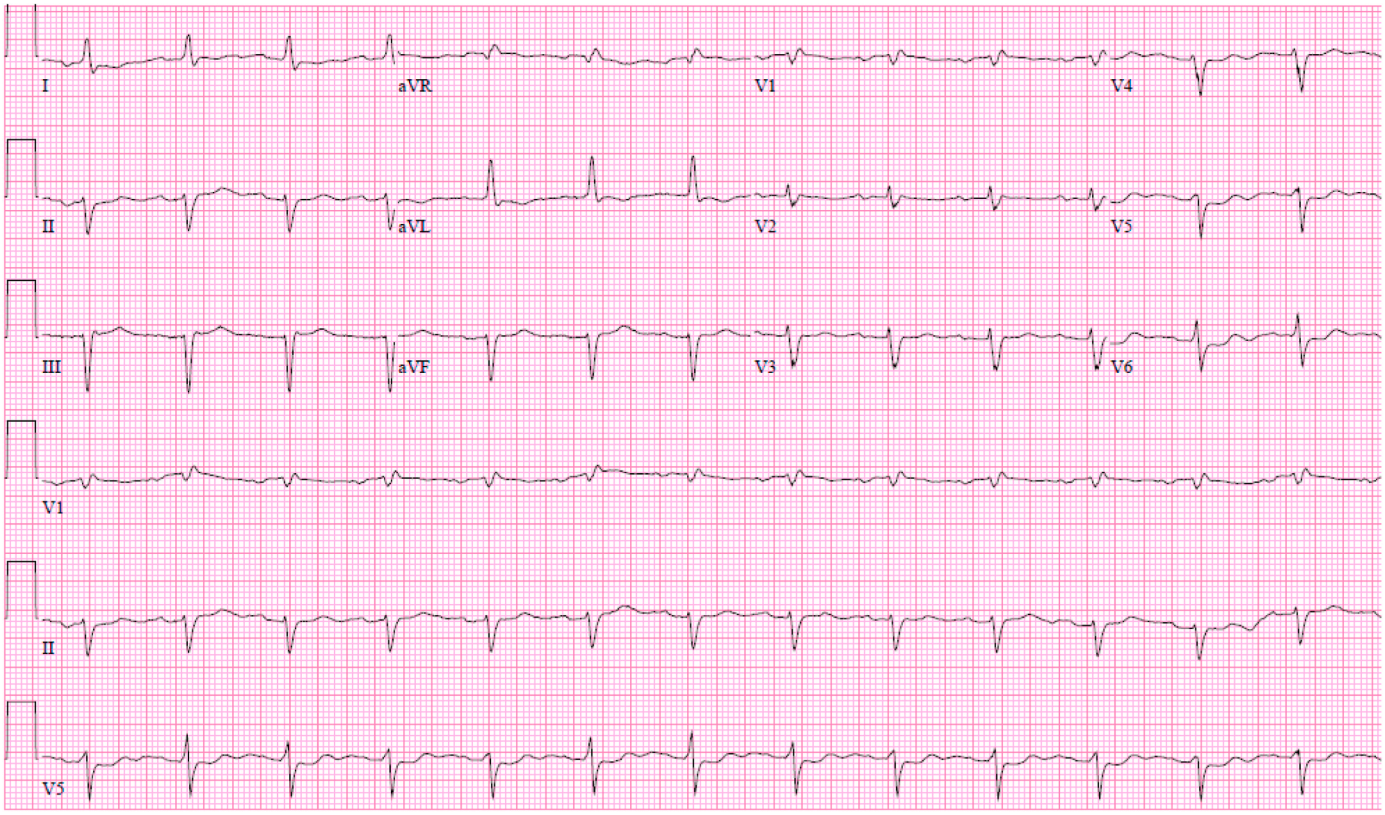

Fig. 1. The 12-lead electrocardiographic tracing obtained at presentation. The tracing shows sinus rhythm with first-degree AV block (240 msec), normal QT interval, and pseudo-infarct pattern in multiple coronary territories.

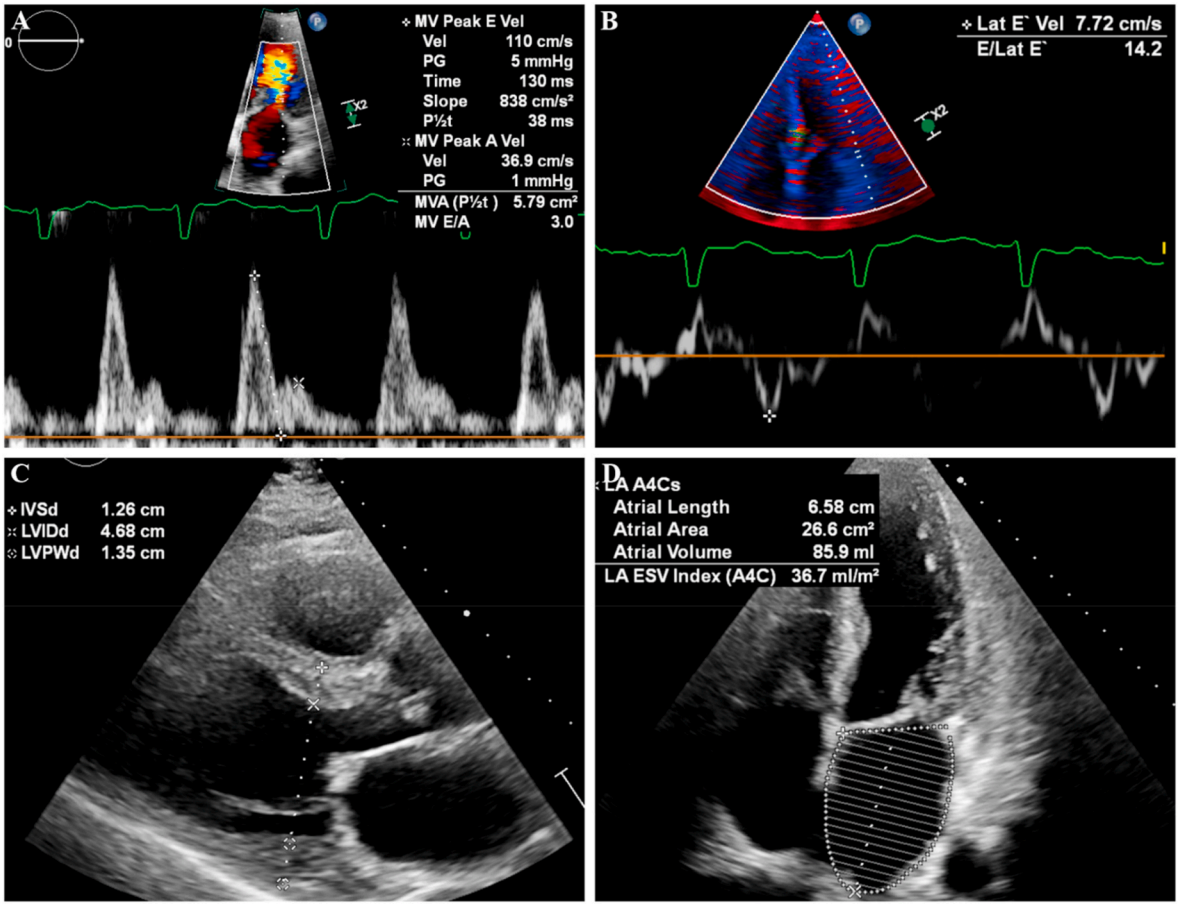

Fig. 2. Transthoracic echocardiographic findings. Pulsed-wave Doppler interrogation of the mitral inflow velocities showing restrictive filling pattern with elevated early diastolic to late diastolic peak velocity ratio (E/A) and short deceleration time (A). Lateral mitral annulus tissue Doppler demonstrating reduced early diastolic velocity (e') and elevated E/e' ratio (B). Increased left ventricular wall thickness is demonstrated in the parasternal long-axis view (C). Atrial enlargement is evident in the apical 4-chamber view (D).

of small intramural coronary vessels (Fig. 4). This finding demonstrates that AL cardiomyopathy is both a toxic and infiltrative disease where severe fibrosis may occur despite only mild LVH. While amyloid deposition was present in the heart, lungs, and kidneys, it was not apparent in the brain.

3. Discussion

Amyloidosis refers to a family of diseases characterized by the extracellular deposition of insoluble, misfolded fibrillar proteins. The most commonly affected organs are the heart, kidneys, intestines, nervous system, and the skin [3]. Of the multiple subtypes, AL and ATTR amyloidosis involve the heart most commonly. AL amyloidosis is an overall rare but increasingly recognized cause of HF in developed countries with an estimated incidence of 8–12 per million individuals [4]. It is caused by a clonal plasma cell disorder where misfolded immunoglobulin light chains aggregate into insoluble fibrils and deposit in the extracellular matrix of various organs. The average age at the time of diagnosis is 70 years, and males are affected more frequently [5,6]. The cause of tissue injury and organ dysfunction is usually multifactorial and includes mass effect by the amyloid fibrils and direct cellular toxicity [7]. Amyloid deposition within the myocardium leads to thickening of the atrial and ventricular walls and progressive restrictive cardiomyopathy. Systolic dysfunction typically develops as the disease progresses. This process is due to worsening microvascular ischemia, local myocyte necrosis, and fibrosis [8]. The conduction system involvement often leads to electrophysiological abnormalities [9], such as AV node dysfunction, atrial fibrillation, atrial flutter, premature ventricular contractions, and non-sustained VT [10,11]. On the other hand, sustained and refractory VT and VF are rare, with only a limited number of published case reports in the literature [12]. As for the terminal arrhythmias in patients with AL amyloidosis, pulseless electrical activity and severe bradycardia are recorded most frequently [13–15]. While appropriate shocks delivered by implantable cardioverter defibrillators (ICD) are not uncommon in this population, the intervention yields no significant survival benefit [16–19]. Therefore, the use of ICD remains controversial in patients with amyloidosis, and the ACC/AHA/HRS guidelines emphasize individualized decision making [20].

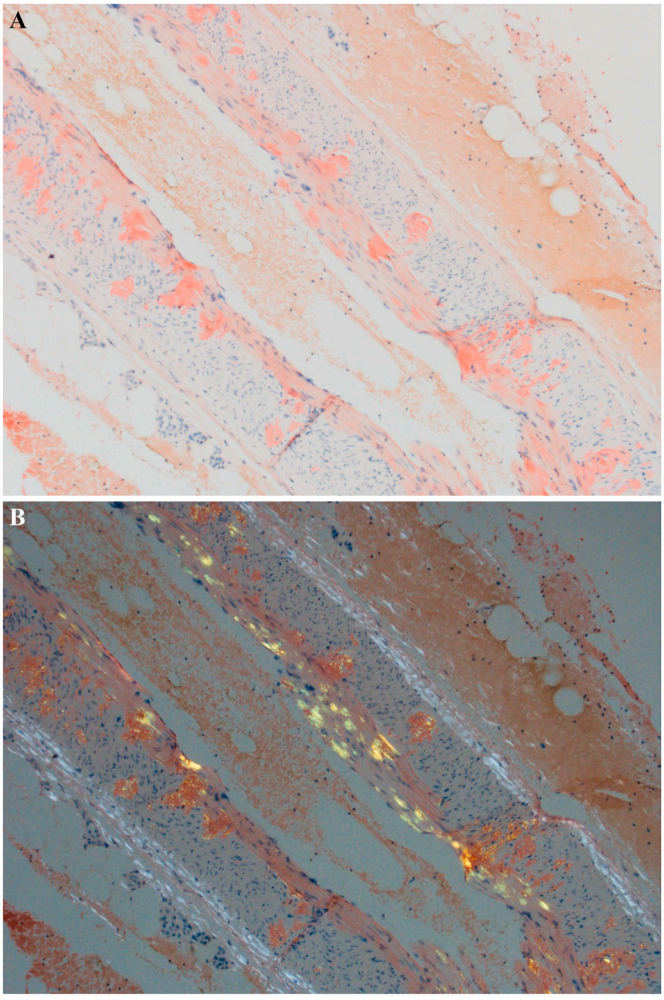

Fig. 3. Abdominal fat pad biopsy. Low-magnification (10x) Congo red staining of the abdominal wall fat pad biopsy showing multifocal pink amorphous deposits within the wall of an artery (A). The deposits show apple-green birefringence under polarized light, confirming these to be amyloid (B). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Our patient initially presented with HF and reduced ejection fraction in the setting of rapid atrial fibrillation. He responded to medical therapy, and tachycardia-induced cardiomyopathy was the working diagnosis. While the possibility of amyloidosis was entertained upon his transfer to our institution, the need for hemodynamic stabilization precluded immediate workup. Ultimately, Mayo stage IV disease was confirmed by fat pad biopsy and serum biomarkers [21]. He developed VT/VF arrest despite normal electrolytes and no prior ventricular arrhythmias that was refractory to repeat external defibrillations. This is consistent with prior reports that ICD therapy would not have rescued our patient or prolonged his survival. Uniquely, we utilized VA-ECMO to stabilize his hemodynamics while a perfusing rhythm was restored. Our case demonstrates that the rapid initiation of mechanical circulatory support may be life-saving, despite an underlying systemic disease. Ultimately, the patient was weaned from VA-ECMO without end-organ damage but developed unexpected right cerebellar hemorrhage several days later. Although special stain with Congo red showed no clear evidence for amyloid deposition within the brain, we suspect that amyloid angiopathy may have contributed to the acute intracranial hemorrhage.

Our case highlights the fact that diagnosing amyloidosis may be challenging, especially at early stages, and a high index of suspicion is needed. It may masquerade as hypertensive heart disease or tachyarrhythmia-induced cardiomyopathy. On the other hand, these "hits" can contribute to worsened systolic function in patients with AL cardiomyopathy. While controlling blood pressure and atrial arrhythmias may lead to a temporary improvement in LV function, these interventions do not change the underlying disease trajectory. Although rare, refractory VT/VF does occur in this population, prompting repeat ICD shocks. This may cause significant distress to patients and families while not necessarily prolonging survival. Although we utilized VA-ECMO successfully to temporarily stabilize our patient, its routine use cannot be recommended given the limited survival with advanced AL amyloidosis.

Declaration of competing interest

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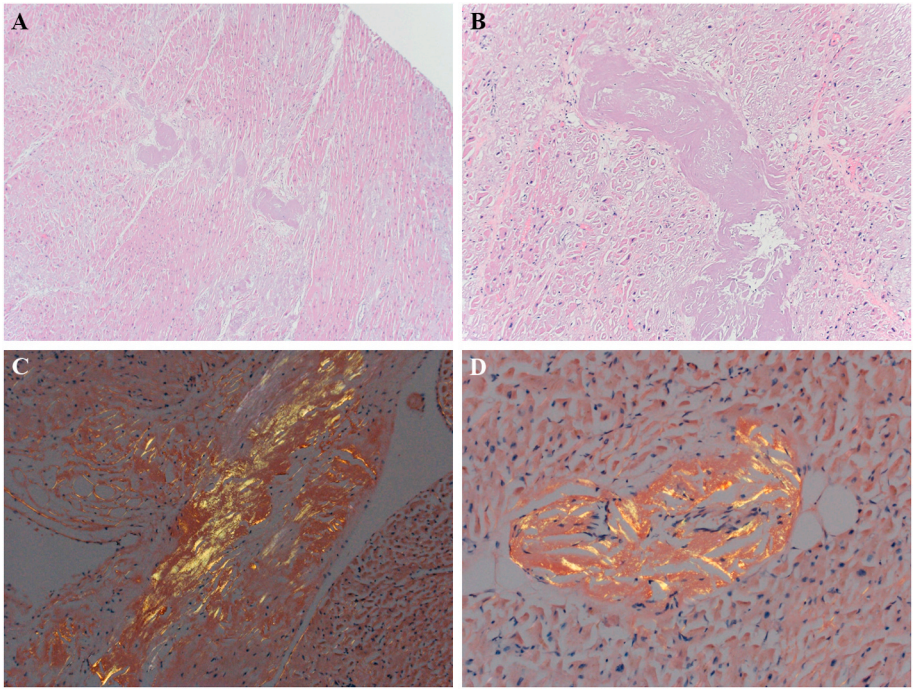

Fig. 4. Myocardial tissue obtained during autopsy. Low- (4x) and high-magnification (20x) H&E stain showing extensive fibrosis and pink amorphous deposits disrupting the myocardial structure (A, B). Deposits show typical apple-green birefringence with Congo red staining under polarized light within the myocardium (C, 10x) and the wall of a small intramural coronary vessel (D, 20x). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

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References

[1] J.R. Teerlink, M. Jalaluddin, S. Anderson, M.L. Kukin, E.J. Eichhorn, G. Francis, M. Packer, B.M. Massie, Ambulatory ventricular arrhythmias in patients with heart failure do not specifically predict an increased risk of sudden death, Circulation 101 (2000) 40–46.
[2] R.M. John, U.B. Tedrow, B.A. Koplan, C.M. Albert, L.M. Epstein, M.O. Sweeney, A. L. Miller, G.F. Michaud, W.G. Stevenson, Ventricular arrhythmias and sudden cardiac death, Lancet 380 (2012) 1520–1529.
[3] R.H. Falk, K.M. Alexander, R. Liao, S. Dorbala, AL, (light-chain) cardiac amyloidosis: a review of diagnosis and therapy, J. Am. Coll. Cardiol. 68 (2016) 1323–1341.
[4] M.I. Oerlemans, K.H. Rutten, M.C. Minnema, R.A. Raymakers, F.W. Asselbergs, N. de Jonge, Cardiac amyloidosis: the need for early diagnosis, Neth. Heart J. 27 (2019) 525–536.
[5] E. Desport, F. Bridoux, C. Sirac, S. Delbes, S. Bender, B. Fernandez, N. Quellard, C. Lacombe, J.M. Goujon, D. Lavergne, J. Abraham, Al amyloidosis, Orphanet J. Rare Dis. 7 (2012) 54.
[6] S. Duhamel, D. Mohty, J. Magne, D. Lavergne, D. Bordessoule, V. Aboyans, A. Jaccard, Incidence and prevalence of light chain amyloidosis: a population-based study, Blood 130 (2017) 5577.
[7] G. Merlini, AL amyloidosis: from molecular mechanisms to targeted therapies, Hematology Am Soc Hematol Educ Program 2017 (2017) 1–12.
[8] K.B. Shah, Y. Inoue, M.R. Mehra, Amyloidosis and the heart: a comprehensive review, Arch. Intern. Med. 166 (2006) 1805–1813.
[9] J. Reisinger, S.W. Dubrey, M. Lavalley, M. Skinner, R.H. Falk, Electrophysiologic abnormalities in AL (primary) amyloidosis with cardiac involvement, J. Am. Coll. Cardiol. 30 (1997) 1046–1051.
[10] S.W. Dubrey, K. Cha, J. Anderson, B. Chamarthi, J. Reisinger, M. Skinner, R. H. Falk, The clinical features of immunoglobulin light-chain (AL) amyloidosis with heart involvement, Q. J. Med. 91 (1998) 141–157.
[11] G. Palladini, G. Malamani, F. Co, A. Pistorio, F. Recusani, E. Anesi, P. Garini, G. Merlini, Holter monitoring in AL amyloidosis: prognostic implications, Pacing Clin. Electrophysiol. 24 (2001) 1228–1233.
[12] E.P. Hess, R.D. White, Out-of-hospital cardiac arrest in patients with cardiac amyloidosis: presenting rhythms, management and outcomes in four patients, Resuscitation 60 (2004) 105–111.
[13] P. Chung, S. Wheeler, A. Fong, H. Kyle, B. Yaghmour, Fatal refractory cardiac arrest as presentation of systemic amyloidosis, Respir Med Case Rep 30 (2020) 101042.
[14] R.M. John, Arrhythmias in cardiac amyloidosis, J Innov Card Rhythm Manag 9 (2018) 3051.
[15] R.H. Sayed, D. Rogers, F. Khan, A.D. Wechalekar, H.J. Lachmann, M. Fontana, S. Mahmood, S. Sachchithanantham, K. Patel, P.N. Hawkins, C.J. Whelan, A study of implanted cardiac rhythm recorders in advanced cardiac AL amyloidosis, Eur. Heart J. 36 (2015) 1098–1105.
[16] D. Hamon, V. Algalarrondo, E. Gandjbakhch, F. Extramiana, E. Marijon, N. Elbaz, D. Selhane, J.L. Dubois-Rande, E. Teiger, V. Plante-Bordeneuve, T. Damy, Outcome and incidence of appropriate implantable cardioverter-defibrillator therapy in patients with cardiac amyloidosis, Int. J. Cardiol. 222 (2016) 562–568.
[17] A.V. Kristen, T.J. Dengler, U. Hegenbart, S.O. Schonland, H. Goldschmidt, F. U. Sack, F. Voss, R. Becker, H.A. Katus, A. Bauer, Prophylactic implantation of cardioverter-defibrillator in patients with severe cardiac amyloidosis and high risk for sudden cardiac death, Heart Rhythm 5 (2008) 235–240.
[18] G. Lin, A. Dispenzieri, R. Kyle, M. Grogan, P.A. Brady, Implantable cardioverter defibrillators in patients with cardiac amyloidosis, J. Cardiovasc. Electrophysiol. 24 (2013) 793–798.
[19] B.C. Varr, S. Zarafshar, T. Coakley, M. Liedtke, R.A. Lafayette, S. Arai, S.L. Schrier, R.M. Witteles, Implantable cardioverter-defibrillator placement in patients with cardiac amyloidosis, Heart Rhythm 11 (2014) 158–162.
[20] S.M. Al-Khatib, W.G. Stevenson, M.J. Ackerman, W.J. Bryant, D.J. Callans, A. B. Curtis, B.J. Deal, T. Dickfeld, M.E. Field, G.C. Fonarow, A.M. Gillis, AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American college of cardiology/American heart association task force on clinical practice guidelines and the heart rhythm society, J. Am. Coll. Cardiol. 72 (2017) e91–220.
[21] S. Kumar, A. Dispenzieri, M.Q. Lacy, S.R. Hayman, F.K. Buadi, C. Colby, K. Laumann, S.R. Zeldenrust, N. Leung, D. Dingli, P.R. Greipp, Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements, J. Clin. Oncol. 30 (2012) 989–995.