56. Atrial Appendages Thrombi and Stroke in a Patient With Light-Chain Cardiac Amyloidosis

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Body

Background: Light-chain cardiac amyloidosis is characterized by extracellular deposition of abnormal misfolded immunoglobulin light chain in the myocardium. Increased intracardiac thrombus formation in this disease has been linked to thrombotic events such as stroke and high rates of mortality and morbidity.

Case: A 51-year-old man was admitted to our emergency department with a sudden change in consciousness. His wife informed that he had lost the ability to identify his family members precisely several hours ago and started to produce obscure speech without any other significant symptoms. On examination, his vital signs were noted with a moderately low blood pressure of 85/57 millimeter of mercury, a regular pulse rate of 85 beats per minute, a temperature of 36.8 degrees Celsius and a SpO2 of 100% on breathing ambient air. No paralysis was found and other signs were unremarkable. However, his emergency brain magnetic resonance imaging showed two foci of cerebral infarction on bilateral temporal lobes. He was then transferred to the neurologic department for further management. When asking for his detailed medical history, his wife notified that he had been told to have a thickened heart with a diagnosis of hypertrophic cardiomyopathy by a doctor in another hospital 5 months ago, so we decided to carry out a fully thorough cardiac examination. His echocardiogram displayed a normal sinus rhythm with some atrial premature beats, along with low QRS voltages at the limb leads and his 24-hour-ECG also didn't capture any atrial fibrillation. N-terminal pro B-type natriuretic peptide level (971.58 picomoles per liter) was markedly elevated, while Troponin I level (0.58 nanograms/milliliter) was slightly increased. Serum free immunoglobulin analysis showed increased lambda free light chains (295.59 milligrams/liter) with a reduced kappa/lambda ratio (0.08). Other testing parameters were consistent with a nephrotic syndrome with a total protein level of 12 grams on a 24 hour-urine collection. Table 1 displayed his comprehensive biochemical test results.

Transthoracic echocardiography showed concentric thickened left and right ventricles, dilatation of both atria, a left ventricular ejection fraction of 53% and a grade-three diastolic dysfunction with an E wave to A wave ratio of 3.11 and an average E/e' of 18.1. The bull-eye plot on speckle tracking echocardiography displayed a distinct apical sparing or "cherry on the top" pattern, which was highly suggestive of cardiac amyloidosis. On transesophageal echocardiography (TEE), we found an elongated static thrombus on the left atrial appendage (LAA), which was highly likely to constitute the source of his embolic stroke and a mobile bouncing oval thrombus on the right atrial appendage (RAA), along with spontaneous echo contrast on both atria and low velocities in the LAA and RAA. Light-chain amyloidosis was confirmed by examining histology of the abdominal fat-pad tissue. His bone marrow biopsy later reached a conclusion of multiple myeloma with a 15q22 deletion on G-band staining.

After consulting with a hematologist, a regimen with melphalan, dexamethasone and thalidomide was initiated for specific treatment of light-chain amyloidosis and atrial appendages thrombi were managed with a full dose of dabigatran of 150 milligrams twice daily. He was discharged with a minor improvement in his neurologic condition. Two months later, another TEE was performed for evaluating

his thrombus status, which showed no residual thrombi in both atria and atrial appendages. Image displayed thrombi (white arrows) in the left atrial appendages with spontaneous contrast (A1) and in the right atrial appendages (B1); resolution of thrombi (asterisks) in the left (A2) and right (B2) atrial appendages after two months of coagulation therapy. However, due to the persistent low velocities and spontaneous contrast in the atrial appendages on TEE, we decided to continue his anticoagulation therapy for further prevention of thrombus reformation. He reported that his symptoms ameliorated and he didn't suffer from any second stroke on follow-up examinations.

Discussion: Cardiac amyloidosis (CA) is a disease characterized by extracellular deposition of insoluble protein called amyloid which mostly derived from the breakdown of light chains from plasma cells in the bone marrow (light-chain cardiac amyloidosis, AL-CA), or from the misfolded thyroxine and retinol-transporting protein called transthyretin, in which the latter may be linked with a genetic mutation (mutant transthyretin cardiac amyloidosis) or not (wild-type transthyretin cardiac amyloidosis). With the introduction and advancement of cardiac imaging methods and specific diagnostic protocols from current guidelines, cardiac amyloidosis once underdiagnosed has been increasing recognized and identified. However, high mortality and poor prognosis remained significant although there has been profound effort with novel regimens to prolong survival and ameliorate quality of life in such debilitating population, especially in AL-CA with a median survival of 6 months in those reaching the last stage of the disease.

Complicating intracardiac thrombosis, which is not an uncommon finding, has been considered one of the major contributions of death in this scenario. In a study examining 116 autopsy of cardiac amyloidosis including 55 AL-CA, the authors found that intracardiac thrombosis was present in up to 33% of the cases, with a higher incidence of 51% in the light-chain type, in which multiple thrombi were not rare. In those with occurrence of embolic events, 82.6% were fatal, primarily having the light-chain type and involving the pulmonary artery. By multivariate analyses, the two clinical independent factors associated with thrombus formation were atrial fibrillation and AL-CA, while left ventricular diastolic function, higher heart rate at TTE and right ventricular wall thickness were the exclusive echocardiographic parameters related to thromboembolism. However, limitations of this study were the lack of including transesophageal echocardiography parameters in analysis due to the limited number of cases performed and evaluating the effect of anticoagulation therapy [1].

Following report by Dali Feng surpassed the limitations of the previous one, which included 156 patients with cardiac amyloidosis undergoing both TTE and TEE. In 27% of the patients with intracardiac thrombi, 58 clots were detected by TEE, decreasing to only three clots by TTE. Interestingly, such as in our case, 16.7% of the patients who were in sinus rhythm developed atrial thrombosis, supporting the hypothesis of contribution of more than one mechanism of atrial rhythm disturbance to thrombosis formation [2]. The combination of different factors such as hypercoagulable state, endomyocardial injury due to amyloid infiltration and altered atrial blood stasis could lead to atrial thrombosis even in the presence of sinus rhythm or even anticoagulation treatment [3].

A recent retrospective study evaluated 58 patients with cardiac amyloidosis undergoing direct current electrical cardioversion for atrial arrythmia. Compared with the control patients, those with CA had a higher rate of cancellation due to intracardiac thrombosis identified on TEE (81% versus 22%, $p = 0.02$) despite high rates (31%) of adequate anticoagulated for 3 weeks [4]. The results of this study were

consistent with others in that low atrial appendage emptying velocity and spontaneous contrast were highly present in those with AL-CA and significantly related to formation of atrial thrombus [2], [4]

According to previous literature, majority of CA patients with thrombosis were managed with warfarin (81%) with a lesser number were controlled with other oral anticoagulated agents. However, the effectiveness of each therapy has not been fully examined yet, with a tendency of switching among regimens in those with persistence of thrombus [5]. The resolution rate was reported to be low (43%) after 50 days of the first follow-up based on a recent report [5] and guidance on anticoagulation for primary and secondary prevention of stroke has been lacking.

Our case highlighted a growing need to detect and manage atrial thromboembolism in AL-CA patients. In that, transesophageal echocardiography is fundamental in identifying and evaluating resolution of atrial thrombus. Taking into account that although no specific guideline has been given and there is enough evidence to support the close relationship between a low atrial appendage emptying velocity, spontaneous contrast on TEE and the formation of atrial thrombus, we decided to sustain coagulation regimen following resolution of thrombus in our patient. The fact that there was no recurrent attack of stroke in our case supports the concept of maintaining the patient on coagulation in such a high-risk condition; however, further investigation is warranted.

References:

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[2] Feng D, Syed IS, Martinez M, et al. Intracardiac thrombosis and anticoagulation therapy in cardiac amyloidosis. Circulation. 2009;119(18):2490-2497.

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[4] El-Am EA, Dispenzieri A, Melduni RM, et al. Direct Current Cardioversion of Atrial Arrhythmias in Adults With Cardiac Amyloidosis. J Am Coll Cardiol. 2019;73(5):589-597.

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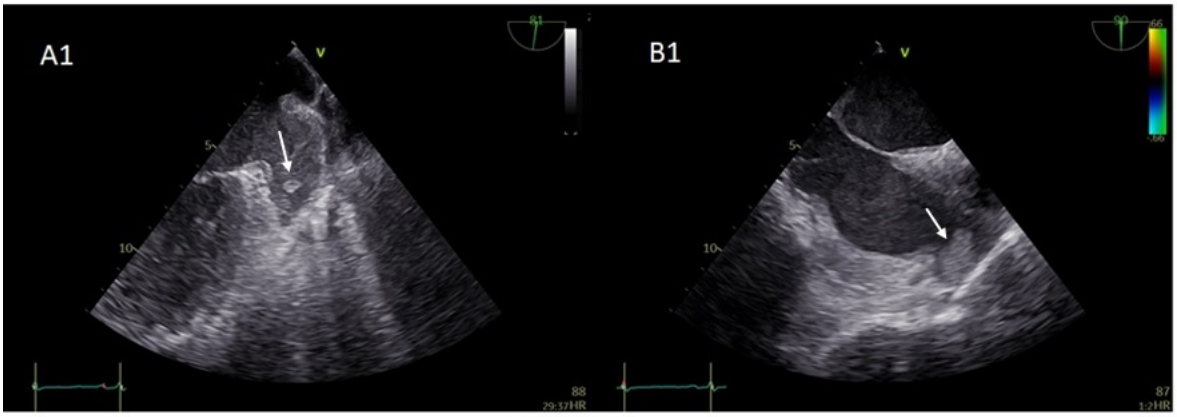
On admission



After 2 months

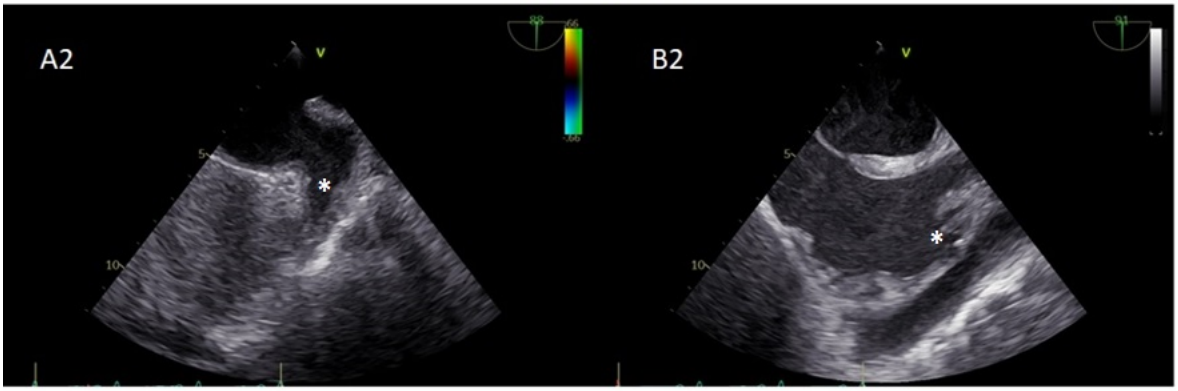


Table 1. Laboratory data

Variable	Value	Reference normal range
Serum		
Free Lambda (mg/l)	**295.59**	3.3 – 19.4
Free Kappa (mg/l)	25.77	5.71 – 26.3
Ratio of free Kappa/free Lambda	**0.08**	0.3 – 1.7
IgA (mg/dl)	107	70 – 400
IgG (mg/dl)	293	700 – 1600
IgM (mg/dl)	110	40 – 230
β2-microglobulin (µg/l)	**6232**	780 – 1600
N-terminal pro-B-type natriuretic peptide (pmol/l)	**971.58**	< 14.75
Troponin I (ng/ml)	**0.579**	< 0.2
Urea (mg/dl)	**32**	7 – 20
Creatinine (mg/dl)	1.2	0.7 – 1.5
Estimated glomerular filtration rate (ml/min/1.73m^2)	69.6	
Sodium (mmol/l)	139	135 – 150
Potassium (mmol/l)	4.1	3.5 – 5.5
Chloride (mmol/l)	107	98 – 106
Aspartate transaminase (U/L)	**49**	9 – 48
Alanine transaminase (U/L)	30	5 – 49
Gamma glutamyl transferase (U/L)	**447**	4 – 38
Cholesterol (mg/dl)	231	140 – 239
Low density lipoprotein-cholesterol (mg/dl)	**160**	90 – 150
High density lipoprotein-cholesterol (mg/dl)	**34**	>45
Triglyceride (mg/dl)	**282**	35 – 160
Glucose (mg/dl)	94	70 – 110
Free thyroxine (pg/ml)	9.82	8 – 20
Thyroid-stimulating hormone (mIU/l)	2.22	0.4 – 5
Urine		
24-hour protein (grams/24 hours)	**12**	0

dl: deciliter; l: liter; mg: milligram; mIU/l: milli-international units per liter; ml: milliliter; mmol: millimole; pg: picogram; pmol: picomole; U/L: units per liter; µg: microgram