Bleeding Risk and Thrombotic Events in Cardiac Amyloidosis: A Critical Assessment

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Case Report

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Abstract

Cardiac amyloidosis (CA) is a condition in which amyloid fibres are deposited in the cardiac muscle tissue, causing tachyarrhythmias, heart failure, or sudden cardiac death. We report a case of immunoglobulin light chain cardiac amyloidosis in which the patient experienced neurological symptoms multiple times during the course of the disease, with magnetic resonance imaging showed cerebral infarction and cerebral haemorrhage. Ischemic and haemorrhagic stroke are complications in CA patients, among which ischemic stroke may be closely associated with poor prognosis and increased all-cause mortality, in diagnoses patient systematic assessment and monitoring of bleeding risk and thrombotic events should be strengthened. When CA is combined with atrial fibrillation (AF), atrial or ventricular wall thrombosis, and cardiogenic cerebral embolism, antithrombotic therapy under comprehensive bleeding risk assessment is necessary. If AF and atrial or ventricular wall thrombosis are not detected, and ischemic and haemorrhagic stroke coexist, it is important to consider how to choose anticoagulant treatment.

Introduction

Cardiac amyloidosis (CA) can affect the synthesis of coagulation factors in the liver causing fibrin polymerization disorder, hyperfibrinolysis, platelet dysfunction, local amyloid deposition damage to the blood vessel wall, and other factors that are prone to bleeding. [1] Skin bleeding (petechiae, ecchymosis, and purpura) and gastrointestinal bleeding are common. Simultaneously, myocardial injury and cardiac dysfunction caused by the deposition of amyloid fibres in the myocardium can directly increase the risk of arrhythmias and intracardiac thromboses.[1] We report a case in which a patient with a definite diagnosis of immunoglobulin light chain amyloidosis (AL-CA) combined with cerebral infarction and cerebral haemorrhage. Recurrent neurological symptoms occurred during the onset and course of treatment, but no anticoagulant therapy was administered. Transthoracic echocardiography (TTE), transoesophageal echocardiography (TEE), and cardiac magnetic resonance (CMR) imaging have been emphasized in the evaluation of intracardiac thrombosis, and aggressive anticoagulant therapy is important in improving outcomes in the context of a comprehensive assessment for bleeding risk. Despite the absence of atrial fibrillation (AF) and atrial or ventricular wall thrombosis, multiple occurrences neurological symptoms prompted us to reconsider the patient's anticoagulant therapy.

Case report

A 50-year-old woman presented to our hospital complaining of progressive dyspnoea during activity. Blood pressure, 103/64 mmHg; Heart rate, 90 bpm; presence of periorbital purpura, enlargement of the tongue, and atrophy of the nail bed.

Results of relevant laboratory and physical examination: N-terminal pro b-type natriuretic peptide, 3233 pg/mL; cardiac-specific troponin I, 0.083 ug/L; serum free light chain-λ, 1012.5 mg/L; serum free light chain-κ, 10.5 mg/L (Supplement table 1). An electrocardiogram showed poor R wave progression in the
chest leads and low voltage in the limb leads (Fig. 1a). TTE showed left and right ventricular wall hypertrophy, left atrial enlargement, increased pulmonary artery pressure, decreased left ventricular restrictive diastolic function, ejection fraction of 55%, and fractional shortening of 28% (Fig. 1b). CMR showed ventricular wall thickening due to the infiltration and delayed enhancement of the ventricular wall (Fig. 1c). Bone marrow smear and biopsy showed an increase in the proportion of immature plasma cells (Fig. 1d). A fat pad biopsy was negative, and an endocardial biopsy showed the deposition of amyloid (Fig. 1e). The patient was diagnosed with AL-CA, after treatment with bortezomib, lenalidomide, and dexamethasone the condition improved.

During the onset and course of treatment, the patient repeatedly exhibited limb dysfunction with speech disorder at least three times (Fig. 2). After administering treatment to improve circulation, the symptoms were relieved within a short time after the attack, and with no significant sequelae. The patient had no chronic diseases such as hypertension and diabetes, had never smoked or drunk and no cardiovascular disease risk factors. Color Doppler ultrasound did not show cerebrovascular and carotid artery stenosis. When the neurological symptoms first attack (before diagnosis), head CT showed no abnormalities (Fig. 2a). During the second attack (after treatment), CT showed left basal ganglia cerebral infarcts and softening foci (Fig. 2b). During the third attack, a combination of CT and magnetic resonance imaging with diffusion-weighted imaging showed subacute lacunar infarctions and old multiple lacunar infarctions (Fig. 2c – i). Magnetic resonance angiography showed no significant narrowing of the large intracranial vessels (Fig. 2j). Susceptibility weighted imaging revealed an old intracerebral haemorrhage (Fig. 2k, l). No atrial or ventricular wall thrombosis was observed in the TTE, and no patent foramen ovale was discovered in the foaming test. The speckle-tracking echocardiography is consistent with the characteristic of "escape" from the apex of CA (Fig. 1f).

**Discussion**

CA is a rare monoclonal plasma cell disorder characterized by the deposition of misfolded immunoglobulin light chains in the heart. Due to the insufficient understanding of the disease, delay in diagnosis, multiple organ involvement, treatment methods, and so on, the average survival time of patients is short.[2]

Retrospective analysis showed that ischemic stroke was a complication of CA, is closely associated with poor prognosis and increased all-cause mortality, some patients presented with cerebral infarction as the first symptom, while a few patients presented with recurrent cerebral infarction.[3] A cohort study of 406 CA patients revealed a 7.6% incidence of arterial thrombotic events, mostly cerebrovascular events, with the CHADS2-VAsc score $\geq 3$ being the only predictive factor for thrombotic events in Cox analysis, especially in patients with sinus rhythm. [4] Studies by Park et al. have shown that for newly diagnosed patients with AL-CA, a greater free light chain difference and $\beta$2 microglobulin levels were risk factors for thromboembolic events. [5] Ischemic stroke is closely related to intracardiac thrombosis caused by atrial arrhythmia and atrial mechanical dysfunction caused by amyloid deposition. [1, 3, 4] Non-cardiac factors such as nephrotic syndrome-induced loss of natural anticoagulant factors, increased synthesis of
procoagulant factors, decreased patient mobility, and therapeutic drugs all increased the risk of thrombotic events in CA. TTE, TEE, and CMR are not only a part of CA diagnostic examination, but are also an important means of thrombus event evaluation.[6] Enhanced systematic assessment and close monitoring of thrombus events in high-risk patients may help improve outcomes.

Anticoagulant therapy reduces the risk of intracardiac thrombosis associated with AF and left ventricular diastolic dysfunction in patients with CA. [7] The incidence of AF in AL-CA can reach 56%, Consensus states that anticoagulation therapy is recommended for patients with AF regardless of the CHA2DS2-VASC risk score. [8, 9] Warfarin's efficacy varies significantly between patients and necessitates close monitoring of INR, which is challenging to apply in CA patients with bleeding risk. In patients with nonvalvular heart disease, where the risk of cerebral hemorrhage is higher with traditional anticoagulants such as warfarin, new oral anticoagulants (NOACs) such as rivaroxaban and dabigatran reduce the risk of stroke and bleeding. Specific reversal agents can reverse the anticoagulant effect of NOACs when severe post-anticoagulant bleeding occurs, but they are expensive and may increase the risk of thrombotic complications. [10] Both warfarin and NOACs may interact with drugs used to treat CA, and the choice of different anticoagulants for this specific population needs more exploration.

A retrospective observational cohort study of 72 patients with ATTR-CA complicated with AF found that ablation was associated with a reduction in the hospitalization for AF or heart failure and improved survival. [11] During the follow-up, nearly half of the patients had no recurrent arrhythmia, and the benefit was the greatest when ablation was performed earlier in the disease course. Another retrospective analysis included 26 patients with CA complicated with AF (AL-CA 7, ATTR-CA 19), catheter ablation treatment improved arrhythmia but had uncertain effect on long-term prognosis such as survival rate. [12] A case of AL-CA with atrial tachycardia survived well after 5 years of radiofrequency ablation, particularly, the patient experienced sinus arrest and was implanted with a single ventricular pacemaker, [13] and conduction dysfunction is another possible complication of CA. Whether the contribution of radiofrequency ablation in the treatment of CA complicated with arrhythmia is limited to the elimination of symptoms or the improvement of long-term prognosis still needs more cases to explore. Thrombolysis within the effective time window is an effective means of treating stroke and reducing the sequelae of the nervous system. During the review, it was discovered that two patients received thrombolytic therapy and survived the follow-up period. However, the long-term prognosis remains unknown. [14, 15] Thrombolytic therapy significantly increased the risk of bleeding in patients with CA, and its benefits remain to be studied.

Marques P et al. described a patient with AL amyloidosis who had an ischemic stroke as the first symptom and intracranial haemorrhage as the disease progressed. The patient had AF, left auricular thrombosis, and nephrotic syndrome. After the intracranial haemorrhage was stabilized, warfarin was given as anticoagulant therapy, and amyloidosis was also treated, but she died 2 months later of a second ischemic stroke. [16] Despite the fact that our patient had no AF and atrial or ventricular thrombosis, or other high risk factors for cardiovascular and cerebrovascular events, she still experienced multiple cerebral infarctions with concurrent intracerebral microbleeding. No anticoagulant
or thrombolytic treatment was given when the patient experienced neurological symptoms. No CMR examination was performed again during treatment follow-up, there may be hidden thrombi that cannot be detected by echocardiography or the thrombus may have been dislodged. Although multiple electrocardiogram and dynamic electrocardiogram examinations were performed during the course of the disease, there may be paroxysmal AF that was not captured. Clinicians should perform TTE, TEE, and CMR in patients with a definite diagnosis of CA to fully assess and monitor thrombosis. CA combined with AF, active anticoagulation therapy has positive significance in preventing atrial or ventricular thrombosis and cardiogenic cerebral embolism. Based on the bleeding tendency of the disease, more clinical data are needed to support the complete assessment of bleeding risk (especially cerebral haemorrhage) before anticoagulant treatment and whether there are differences among different drugs (e.g. heparin, low molecular weight heparin, warfarin, rivaroxaban, and dabigatran). In the absence of capture of AF and atrial or ventricular wall thrombosis, ischemic and haemorrhagic stroke coexist, and it is worth exploring how clinicians decide on anticoagulant treatment.

Declarations

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Author contributions: MZ collected patient clinical data and was a major contributor in writing the manuscript. QZ and TY collected and sorted imaging data. BX and RL were in charge of analyzing and interpreting the patient data, and revising the draft critically for important intellectual content. All authors read and approved the final manuscript.

Conflict of interest: The authors declare that they have no conflict of interest.

Data Availability Statement: The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Compliance with ethical standards: According to ICH-GCP, Ethical Review Measures for Biomedical Research Involving People (2016), WMA Declaration of Helsinki and CIOMS The ethical principles of the International Ethical Guide for Human Biomedical Research have been reviewed by the ETHICS Committee and approved to conduct the clinical trial at the center. All procedures designed in this study were approved by the Ethics Committee of the First Hospital of Jilin University, Number (2021-531). Informed consent of subjects has been obtained and signed.

References


Figures
a. Electrocardiogram. b. Transthoracic echocardiography, myocardial echo revealed ground, glass-like changes, left ventricular wall thickness of 12 mm, and right ventricular wall thickness of 7 mm. Left atrium upper and lower of 47 mm and left and right of 45 mm. Pulmonary artery pressure was 44 mmHg. c. Cardiac magnetic resonance imaging, localized thickening of ventricular septum (thickest site, 14 mm), delayed enhancement of left atrium, left ventricular intima and muscle wall can be seen. d. Bone smear and marrow biopsy, heterotropic plasma cells were scattered and distributed in clusters (5−10%), expressing lambda. Bone smear (10×100), bone marrow (10×40). e. Myocardial muscle bundles are arranged irregularly, and powdery substances can be deposited around the focal and small blood vessels. Congo red was positive. f. Speckle-tracking echocardiography of the left ventricle demonstrated abnormal regional and average global longitudinal peak systolic strain rates with relatively normal strain rates in the apex, consistent with apical sparing.
Neurological symptoms: limb dysfunction, speech disorder

Figure 2

a. Computed tomography (CT), normal. b. CT, left basal ganglia with low-density shadows. c-e. CT, bilateral basal ganglia and right frontal parietal lobe with patchy low-density shadow. f. Diffusion-weighted imaging, patchy and slightly higher signal shadow in the centre of the left semiovale and parietal lobe. g-i. Magnetic resonance imaging, multiple lacunar cerebral infarction, softening lesion with glial proliferation in the right frontal parietal lobe. j. Magnetic resonance angiography, no significant narrowing of intracranial large vessels. k, l. Susceptibility-weighted imaging, nodular hemosiderosis is seen in the left lateral fissure, and abnormal strip-like and nodular signals are seen in the right frontal lobe, which is hemosiderosis.

Supplementary Files

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- Supplementtable1.docx