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Case Report

A tale of two sisters with hypertrophic cardiomyopathy and recurrent embolism: When is the optimal timing of the intervention for left atrial appendage?

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ABSTRACT

Hypertrophic cardiomyopathy (HCM) is an extremely heterogeneous genetic disease that affects the left ventricle (LV) and has a varied clinical course and phenotypic expression. Here, we report a case of two sisters with HCM who developed a massive refractory left atrial appendage (LAA) thrombus and recurrent embolism. The older sister, who was at a high surgical risk due to progressive LV systolic dysfunction with an ejection fraction of 19%, underwent LAA plication in combination with implantation of an LV assist device after progression to treatment-refractory heart failure at the age of 49. The younger sister underwent surgical thrombectomy, LAA plication, and Maze surgery before deterioration of heart failure at the age of 47. She was free from embolism and atrial fibrillation for 2 years after surgery. Individualized therapeutic approaches targeting the LAA at a relatively early stage are required in the subgroups of HCM patients with left atrial dysfunction.

Introduction

Hypertrophic cardiomyopathy (HCM) is characterized by genetic heterogeneity, with various phenotypes. We report two cases of familial HCM that were characterized by massive refractory left atrial appendage (LAA) thrombus formation and recurrent embolism.

Case report

A 49-year-old woman (Fig. A, subject II-2) was diagnosed with HCM at the age of 20. Following progression to dilated HCM at the age of 32, progressive left ventricular (LV) systolic dysfunction developed, leading to two hospitalizations for acute decompensated heart failure. In cardiovascular magnetic resonance imaging, late gadolinium enhancement was shown in the whole circumference at apical and mid-ventricular level of LV free wall and the interventricular septum as well as apical level of right ventricular free wall, in association with significant left atrial (LA) dilatation at the patient's age of 44 (Fig. B and C). She also experienced two episodes of cerebral embolism of a cardiac origin, both of which were treated with tissue plasminogen activator without complications. The first attack occurred in normal sinus rhythm at the age of 44, and the second occurred at the age of 48, despite receiving oral anticoagulant therapy for atrial fibrillation (AF). Transesophageal echocardiography revealed a massive thrombus in the LAA, with intense spontaneous echo contrast (Fig. D, Movie 1), leading to consideration of surgical thrombectomy and LAA plication. Because of the high surgical risk due to severe LV dysfunction with an ejection fraction of 19%, anticoagulation was continued. Fortunately, she had no further thromboembolic events; however, the risk of stroke remained high. Following progression to treatment-refractory heart failure, the decision was made to perform LAA plication in combination with implantation of an LV assist device (LVAD) at the patient's age of 49. During the period that the patient was waiting for heart transplant 37 months after LVAD implantation, HF hospitalization and thrombosis-related complications (i.e. embolism and thrombosis of LVAD) did not occur.

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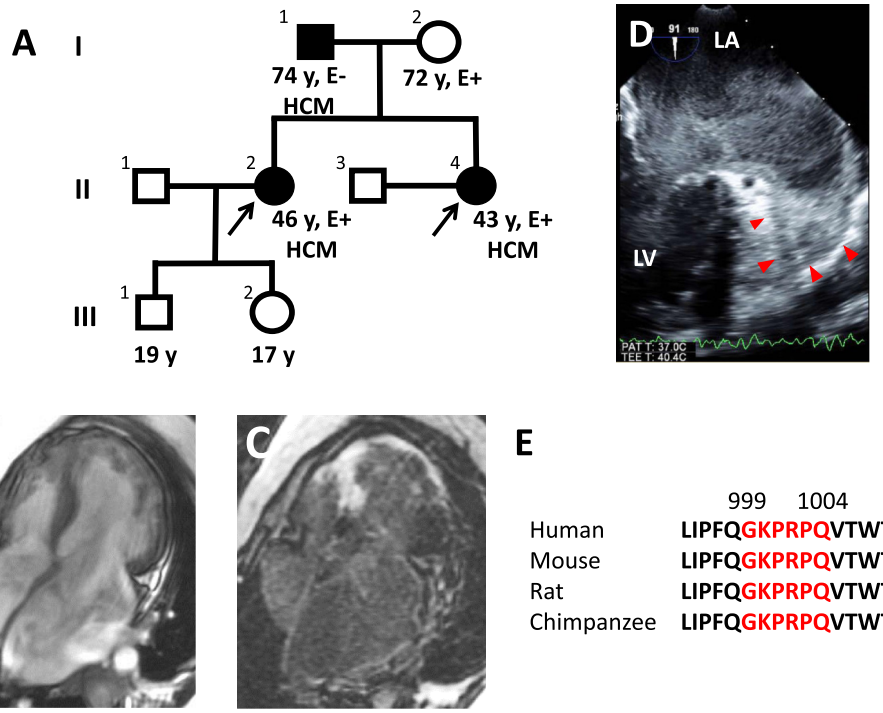

Fig. (A) Pedigree information of the family. The black symbols denote clinically affected individuals with HCM. The white symbols denote clinically unaffected individuals. The results of the *MYBPC3* genetic screening test are marked as positive (E+) or negative (E−). (B) Cardiovascular magnetic resonance imaging of the elder sister. ECG-gated cine MRI showed thinning at apical and mid-ventricular level of LV free wall and the interventricular septum, in association with significant LA dilatation. (C) Late gadolinium enhancement was observed in the whole circumference at apical and mid-ventricular level of LV free wall and interventricular septum as well as apical level of right ventricular free wall. (D) Transesophageal echocardiogram of the older sister showed massive thrombus (arrowheads) in the LAA with intense left atrial spontaneous echo contrast. (E) The G999 to Q1004 region of *MYBPC3* is highly conserved across the species.

Her younger sister (Fig. A, subject II-4) was diagnosed with HCM with LV outflow obstruction at the age of 29. She underwent pacemaker implantation at the age of 35, which improved her heart failure symptoms and hemodynamics. Progression of LV dilation with regression of the LV outflow obstruction occurred in her 40s. She also experienced recurrent embolism (cerebral embolism in normal sinus rhythm at the age of 43, and renal embolism despite receiving oral anticoagulant therapy at the age of 46 and 47), resulting from the refractory LAA thrombus (Supplementary Fig. 1A, Movie 2). Persistent AF was detected 6 months before her second renal embolism. She underwent surgical thrombectomy, LAA plication, and Maze surgery at the age of 47, with preserved LV function. She was free from embolism and AF for 2 years after surgery, although transthoracic echocardiography 1 year after surgery showed depressed A wave velocity in LV inflow, suggesting highly impaired LA function (Supplementary Fig. 1B).

The presence of thrombotic risk factors, including abnormalities of antithrombin III, protein C, and protein S, as well as antiphospholipid syndrome, collagen diseases, and malignant diseases, were ruled out in the sisters. A genetic analysis targeting 8 major genes encoding sarcomeres was performed,[1] and revealed a novel heterozygous deletion at position 999 to 1004 of the cardiac isoform of myosin-binding protein C (*MYBPC3*) gene, p.Gly999_Gln1004del, which is located at the highly preserved region (Fig. E), in the sisters (Fig. A, subject II-2, 4) and their mother (subject I-2).

Discussion

HCM, an extremely heterogeneous genetic disease, affects the LV and has a varied clinical course and phenotypic expression.[2] In this report, we presented familial HCM cases with unique LA characteristics. Both patients had recurrent embolisms due to refractory massive LAA thrombus formation. Although thromboembolic events are known to occur as a complication of HCM, the incidence was approximately 1.0% per year in an HCM cohort,[3] suggesting that the frequency of thromboembolic events in the two patients in the present report was extremely high. The importance of the LAA in thromboembolic risk provides the rationale for LAA plication in patients who are undergoing cardiac surgery for other indications, such as mitral or Maze surgery as well as thrombectomy. However, in high surgical risk patients with a refractory LAA thrombus, the treatment options are limited. In the older sister, we waited for progression of heart failure, which permitted the implantation of an LVAD, and LAA plication was performed simultaneously. Based on our experience with the older sister, the younger sister underwent surgical thrombectomy, LAA plication, and Maze surgery at a relatively early stage. Our experience in two sisters hints to us the optimal timing for the intervention for LAA in HCM patients with extreme LA dysfunction. We postulate that LAA plication must be performed at the timing of the LAA thrombus development, in spite of anticoagulant treatment, as well as before the progression to extreme LV dysfunction. Therefore, in order not to miss this optimal timing, treating physicians should perform the periodic assessment of LV function and subclinical LAA thrombus by transthoracic and transesophageal echocardiograms. Percutaneous LAA occlusion procedures, which mechanically prevent embolization of LAA thrombus, have been recently developed and shown to be effective. Although the precise indications remain under discussion, early invasive strategy using percutaneous approaches could be considered in the subgroup of HCM patients with a very high risk of thrombotic embolism, as in the present report.

Recently, the concept of atrial cardiomyopathy has been introduced, and is defined as any complex of structural, architectural, contractile, or electrophysiological changes affecting the atria, with the potential to produce clinically-relevant manifestations including

arrhythmia and embolism.[4,5] Many diseases or conditions are known to contribute to atrial cardiomyopathy,[4] and atrial cells are susceptible to a range of genetic influences,[4,6] suggesting that genetic effects are associated with atrial cardiomyopathy. Our preliminary genetic screening identified a novel *MYBPC* mutation. This mutation was not detected in the father, who had HCM, but did not have recurrent embolism. One family member with a normal phenotype (subject I-2) was found to carry this novel mutation, suggesting an incomplete penetrance or variants of unknown significance. Although further studies are required to evaluate the function of this sarcomeric protein mutation as well as to analyze the mutation more comprehensively, genetic evaluation could be useful to identify the phenotype of atrial cardiomyopathy among patients with HCM.

In conclusion, we reported the cases of two sisters with HCM, massive LAA thrombus formation, and recurrent embolism. Although the specific mechanism underlying these unique characteristics remains unknown, individualized therapeutic approaches targeting the LAA should be used in the subgroup of HCM patients with left atrial dysfunction.

Statement of ethics

This study was approved by the Keio University School of Medicine Ethics Committee. Informed consent was obtained from patients.

Conflicts of interest

The authors declare no competing financial interests.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.hrtlng.2018.08.010.

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