



## The eyes are the window to the heart: one case of cardiac amyloidosis with eyelid swelling as the initial symptom

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Cardiac amyloidosis (CA), a disease caused by the precipitation of amyloid proteins in myocardial extracellular matrix, is difficult to diagnose due to its lack of specific clinical manifestations, and can be easily misdiagnosed.<sup>[1]</sup> However, due to the recent improved awareness and wide use of biopsy, most patients are now correctly diagnosed prior to death. This report concerns a 59-year-old male who presented with symptoms of double eyelid swelling and chest tightness without obvious causes.

In 2013, a 59 year-old male presented with symptoms of double eyelid swelling and chest tightness without obvious causes. The symptoms became more significant after strenuous activity. On February 7, 2013, the patient received an outpatient electrocardiograph (ECG) test at Hunan Provincial People's Hospital, and the results indicated sinus rhythm and poor progression of R waves in V1-V3. On September 15, 2014, outpatient transthoracic echocardiography (TTE) showed that the patient's left atrium was slightly enlarged, and also some mild aortic and tricuspid regurgitation accompanied by a small amount of pericardial effusion. The measured values for left ventricular function were in the normal range [specifically, interventricular septum (IVS): 10 mm, left ventricular posterior wall (LVPW): 10.7 mm, and ejection fraction (EF): 62%]. However, the patient was not systematically examined and treated.

On October 30, 2014, the patient was treated in a hospital for symptoms of “double eyelid swelling and chest tightness after activity for over one year.” After admission, a coronary computed tomography angiogram (CTA) showed no obvious abnormalities. Furthermore, no abnormalities were found after tests were conducted for anti-neutrophil activating cytoplasmic antibodies (ANCA), epithelial neutrophil activation (ENA), lupus, kidney function, 24 h urine protein

levels, and thyroid function. Ultrasound examinations of the neck region and lower limb arteries also showed no abnormalities. On November 7, 2014, the patient was discharged. An orbital tumor or venous sinus thrombosis were indicated as possible causes for the eyelid swelling, and an orbital MRI examination was recommended. On December 10, 2015, results of orbital MRI performed at the other hospital revealed: (1) bilateral exophthalmos and extraocular muscles with varying degrees of bilateral thickening, in line with the possibility of thyroid-associated ophthalmopathy; (2) mild paranasal sinusitis. The double eyelid swelling could not be eliminated by diuretics, and its cause remained unclear. Because the patient's double eyelid swelling and chest tightness had worsened since January 24, 2016, he was admitted to the Hunan Provincial People's Hospital Department of Geriatrics on January 28. A physical examination performed upon hospital admission showed the following results: T, 36.5°C; P, 80 bpm; R, 22 times/min; BP, 103/70 mmHg; SpO<sub>2</sub>, 95%; obvious jugular vein engorgement; double eyelid swelling (Figure 1); a small heart boundary; heart rate of 80 bpm; premature ventricular contractions without noise; mild pitting edema of the lower limbs. On January 27, 2016, outpatient TTE showed that both atria were slightly enlarged, the presence of a thickened left ventricular wall (IVS: 12.8 mm, LVPW: 12.5 mm), and ultrasonographic changes in the atrial septum. Those findings suggested the presence of a small atrial septal defect or patent foramen ovale. The patient also showed signs of mild pulmonary and mitral regurgitation plus moderate tricuspid regurgitation, left ventricular diastolic dysfunction (E > 2A, EF, 60%), and some slight pericardial effusion. An ECG performed upon admission showed low voltage in the limb leads and poor progression of R waves in V1–V3. The results of thyroid and renal function tests performed upon admission were normal. The patient's peripheral venous

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**Figure 1. Double eyelid of the patient. Double eyelid swelling had been present since January 24, 2016.**

pressure was 19 cmH<sub>2</sub>O.

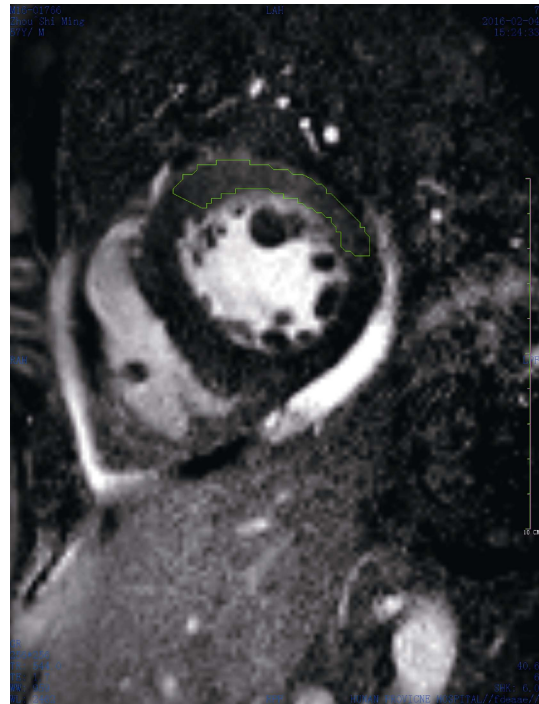
Because the patient had an increased cTnI level and displayed QR morphology on ECG leads V1-V3, coronary angiography (CAG) was performed on January 28, 2016 to exclude the possibility of myocardial infarction. The results suggested a myocardial bridge in the middle section of the left anterior descending artery, with no coronary stenosis.

To further exclude any possibility that the patient's chest tightness was caused by an interstitial lung disease, pulmonary embolism or pericardial constriction, a contrast-enhanced lung CT scan and pulmonary CTA were performed. The results revealed several small gas-containing cysts in the right upper lung, bilateral pleural effusion, but no obvious abnormality was seen on the pulmonary CTA.

The patient showed jugular vein engorgement and had increased peripheral venous pressure. Results from the first two echocardiography tests performed prior to hospital admission were reviewed, and indicated that the interventricular septum and left ventricular posterior wall each had thickness between 10–12.8 mm. To exclude hypertrophic cardiomyopathy, cardiac magnetic resonance (CMR) was performed, and the results indicated a slightly thickened atrial septum and left ventricular posterior wall. Myocardial gadolinium-delayed enhancement at sections 7, 13, and 14 of the left ventricle suggested the possibility of hypertrophic cardiomyopathy (HCM) and showed some slight pericardial effusion (Figure 2).

The patient's CAG results revealed a myocardial bridge and excluded myocardial infarction (MI). Moreover, the enhanced CT scan excluded constrictive pericarditis and pulmonary disease, the TTE results suggested left ventricle hypertrophy (10–12.8 mm), and cardiovascular magnetic resonance (CMR) imaging results showed slight thickening of the IVS and LVPW, and suggested the possibility of hypertrophic cardiomyopathy.

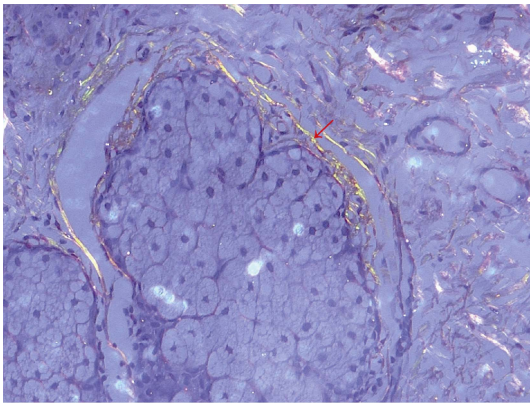
It was noteworthy that the results of echocardiography and CMR were contradictory. To further characterize the patient's myocardial parameters, another echocardiography was performed on March 10, 2016, and the results showed symmetric thickening of the left ventricle (IVS: 12 mm, LVPW: 12 mm), granular echoes in the myocardium, a high



**Figure 2. Cardiovascular magnetic resonance results.** The gadolinium extension of reinforcement is within the green coil.

probability of myocardial amyloidosis, slightly enlarged bilateral ventricles, mild pulmonary and mitral regurgitation, moderate tricuspid regurgitation, and left ventricular diastolic dysfunction (level III) (EF = 57%). Because the patient's urine K light chain level was < 0.1 mg/L (normal range: 0–7.1 mg/L), and his urine  $\lambda$  light chain level was 30.39 mg/L (normal range: 0–3.9 mg/L), a diagnosis of CA was highly suspected. CA patients are typically complicated with plasma cell dyscrasia; however, in this case, the bone marrow results showed no significant plasma cell dyscrasia. Because the gold standard for CA diagnosis is a histopathological examination, skin and muscle biopsies of both eyelids were completely examined, and hematoxylin and eosin (HE) and Congo red staining were performed. The results obtained from Congo red staining were positive, and a polarized light examination (Figure 3) showed an apple green birefringence. Next, the patient's serum was analyzed by immunofixation electrophoresis and his urine was analyzed by Bence-Jones protein electrophoresis, and results suggested M-proteinemia of LAM. Final diagnosis: Immunoglobulin light chain amyloidosis cardiomyopathy.

The characteristic echocardiography findings in CA patients include: obvious symmetric hypertrophy of the ventricular wall and septum, a left ventricular cavity of normal or reduced size, left ventricular diastolic dysfunction, and myocardial echo enhancement (particle-like blinking). In particular, the parameter of myocardial echo enhancement



**Figure 3. Polarized light examinations of skin and muscle biopsies of both eyelids.** Results showed an apple green birefringence.

(particle-like blinking) has a sensitivity of 87% and a specificity of 81% for diagnosing cardiac amyloidosis, and its specificity can reach 100% when combined with the parameter of atrial thickening.<sup>[2]</sup> Tissues which typically show high positive CA biopsy rates include the affected organs (kidney, liver, and heart), the tongue, subcutaneous fat in the abdominal wall, bone marrow, and the labial gland. However, the initial symptom of this patient was double eyelid swelling; therefore, his eyelid skin and muscle tissue were sampled for biopsy. Amyloidosis patients have a poor prognosis, which may become even worse after cardiac involvement, regardless of the treatment methods used. Thickening of the left ventricular wall is negatively correlated with patient survival rates, and is closely related to the severity of heart failure.<sup>[3]</sup> The levels of BNP, NT-pro-BNP, and cTnI are sensitive markers for the prognosis of patients with cardiac amyloidosis.<sup>[4]</sup> The CA patient in this case showed insignificant cardiac involvement during the early onset of CA in 2013. In September 2014 and January 2016, outpatient TTE results indicated an acceptable ejection fraction, and congestive heart failure was not found, but manifested as diastolic dysfunction instead. Later however, the patient rapidly progressed, and his EF progressively decreased. Laboratory tests performed during a followup examination on June 7, 2016 gave the following results: BNP

= 2238 pg/mL (Reference range: 0–450 pg/mL); urine K light chain = 21.1 mg/L (Reference range: 0–7.1 mg/L); urine  $\lambda$  light chain = 68.3 mg/L (Reference range: 0–3.9 mg/L). All of these results showed a trend of progressive increase, and suggested a poor prognosis.

The low voltage of the CA patient's QRS complex seen on an ECG was contradictory to ventricular hypertrophy,<sup>[5]</sup> and the ECG results suggested pseudo myocardial infarction.<sup>[6]</sup> Amyloidosis produces its toxic effects via the precipitation of amyloid protein fibrils in affected tissues. These protein deposits can result in left ventricular diastolic dysfunction, venous flow obstruction, and increased peripheral venous pressure. The patient in this case visited our clinic for treatment of double eyelid swelling, and was eventually diagnosed as immunoglobulin light chain amyloidosis cardiomyopathy.

In this case, the initial symptom manifested in the eyelid, and the patient was finally diagnosed as cardiac amyloidosis via an eyelid biopsy, fully demonstrating that “the eyes are the window to the heart.”

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