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Aortic Valve Replacement in a Patient With Thalassemia Intermedia

Dimitrios Farmakis, MD, PhD, Aikaterini Polonifi, BS, Spyros Deftereos, MD, PhD, Maria Tsironi, MD, PhD, Ioannis Papaioannou, MD, and Athanasios Aessopos

First Department of Internal Medicine, University of Athens Medical School, Laiko Hospital, and Department of Cardiac Surgery, Ippokratio Hospital, Athens, Greece

Pseudoxanthoma elasticum-like diffuse elastic tissue defects and hypercoagulability are two well-established features in β-thalassemia, which play a key role in the development of a spectrum of collateral complications in these patients. We present here a middle-aged thalassemia intermedia patient with severe aortic stenosis caused by heavy calcification of the valve, a hallmark of pseudoxanthoma elasticum. The patient underwent a successful replacement of the valve, which is the first such operation ever reported in these patients. However, rapid thrombosis leaded to failure of the mechanical valve, despite proper antithrombotic therapy.

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Heart disease is the leading cause of mortality in β-thalassemia [1]; it classically involves iron-induced left ventricular dysfunction in regularly transfused thalassemia major patients or pulmonary hypertension with right heart failure in non-transfused thalassemia intermedia ones [2]. The prolonged survival of patients accomplished by the application of modern therapy over the past decades is followed by a continuous revelation of novel, previously unknown, cardiac or other complications [3]. In this context, we present the case of a middle-aged thalassemia intermedia patient with severe aortic stenosis, due to heavy valvular calcification, who underwent a successful replacement of the valve. However rapid thrombosis led to failure of the prosthetic valve despite proper anticoagulation therapy.

This is the case of a 46-year-old woman with thalassemia intermedia who was followed regularly in our unit. According to her medical history, she received blood transfusions only on an occasional basis and had undergone splenectomy at age 20. Her mean hemoglobin and serum ferritin levels for the past 6 years were 9.2 g/dL and 750 ng/mL, respectively. At age 25, she was diagnosed as having thalassemia-related pseudoxanthoma elasticum (PXE), manifested by typical cutaneous and ocular lesions; this diagnosis was confirmed by a biopsy of one of the affected skin areas. At age 39, Doppler echocardiography revealed a maximum systolic pressure gradient of 40 mm Hg across the aortic valve, along with calcification of the aortic and mitral valves. The patient had no previous history of aortic valve stenosis. At that time she was advised to maintain her hemoglobin level higher than 9 g/dL and to receive subcutaneous deferoxamine at 40 mg/kg for at least 3 day per week. She was also started on a closer cardiac follow-up. Six years later she was compliant with the previously described recommendations and remained asymptomatic, but physical examination during a regular follow-up visit revealed a fourth heart sound and a clear III/VI systolic ejection murmur over the aortic area. Her electrocardiogram was indicative of left ventricular hypertrophy and Doppler echocardiography showed a maximum systolic aortic gradient of 85 mm Hg. During the following year the patient was experiencing frequent episodes of palpitations associated with premature atrial contractions, and she finally had atrial fibrillation develop that was converted by intravenous amiodarone. Cardiac catheterization confirmed the diagnosis of severe aortic stenosis and revealed normal coronary arteries and normal systolic left ventricular function. She was then advised to undergo aortic valve replacement.

Preoperative investigation revealed thrombocytosis (platelet count, 600,000/μL), increased indirect serum bilirubin (2.5 mg/dL), and slightly elevated gamma globulins (2.9 g/dL). Investigation for protein C and S deficiency, lupus anticoagulant, Leiden factors, or von Willebrand factors deficiency proved negative. Cardiac magnetic resonance imaging study for the estimation of iron load showed mild iron deposition, with a T2* score of 29. She subsequently underwent a successful aortic valve replacement with a mechanical valve. A standard surgical and anesthetic procedure was followed. The aortic valve was found heavily calcified with complete fusion of the right and left coronary cusps so that a bicuspid valve could not be excluded. After removal of the calcifications, a rather clean annulus was achieved. A bi-leaflet St. Jude Medical valve (No. 26, St. Jude Medical, St. Paul, MN) was chosen. The valve was sutured with a continuous 2.0 Prolene suture (Ethicon, Somerville, NJ) with the knots tied over pledgetted on the outside aortic wall, aiming at a completely smooth annulus with absence of knots that could be the site of a thrombotic

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Address correspondence to Dr Farmakis, 182 Kallergi St, Piraeus, 185 44 Greece; e-mail: dfarm1@panafonet.gr.

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procedure. The recovery was completely uneventful and the patient was started on warfarin with a target international normalized ratio of 3.0 to 3.5.

Postoperatively, echocardiography revealed a normally functioning prosthetic valve with a maximum systolic gradient of 15 mm Hg; the patient did not require additional blood transfusions to maintain the preoperative hemoglobin level, and serum bilirubin concentration was similar to that before surgery. Ten months after the operation a regular Doppler echocardiographic examination revealed a novel increase of maximum systolic gradient at the aortic valve (45 mm Hg), whereas 6 months later the patient had acute dyspnea develop at rest and was admitted to the hospital with the diagnosis of acute pulmonary edema. At that time, Doppler echocardiography revealed a maximum systolic aortic gradient of 90 mm Hg and findings consistent with thrombosis of the prosthetic valve, despite the fact that the patient had had a strict compliance with the antithrombotic therapy and had constantly maintained an international normalized ratio level between 3.0 and 3.5. The patient was operated on, once again with a standard anesthesia approach and surgical technique. On reoperation, one leaflet of the valve was found heavily thrombosed and completely immobile, whereas some thrombi had already affected the opposite leaflet. The valve was removed and replaced by a St. Jude Medical valve without any noticeable complications. However, during the second postoperative day, the patient had disseminated intravascular coagulation develop, and she died from a hemorrhage shortly thereafter.

Comment

The importance of the present case report is based on a number of different aspects, including the pathogenesis of severe aortic stenosis at a relatively young age, the development of prosthetic valve thrombosis in the presence of standard antithrombotic therapy, and primarily on the fact that both severe aortic stenosis and open heart surgery were well tolerated by a "thalassemic" heart.

Patients with thalassemia are characterized by a marked cardiac vulnerability, mainly due to volume overload and iron overload [2]. Heart failure in these patients develop either after a prolonged and gradual impairment of ventricular function or under the stress of an additional event, such as a myocardial infection [4]. However, the present patient, who had the milder form of the disease, namely thalassemia intermedia, had kept her hemoglobin level higher than 9 g/dL and lacked significant cardiac iron load due to the low transfusion rate and concomitant chelation therapy. As a result, she was able to put up with the presence of severe aortic stenosis and overcome the stress of vulvular replacement at age 46. This is the first report of cardiac valve replacement in β-thalassemia, and the second report of a successful open heart surgery in these patients, with the first one being a resection of multiple right atrial masses in a child with thalassaemia major [5]. In the face of recent therapeutic achievements regarding survival and thalassemia heart disease, additional cardiac complications may be managed and serious therapeutic procedures, such as open heart surgery should rather be considered feasible in these patients.

In the present case, aortic stenosis was associated with severe calcification of the valve. Bicuspid aortic valve could not be excluded, either by echocardiography or pathology, due to the coexistent calcification. Furthermore, rheumatic fever might have also been the case, despite the fact that mitral stenosis or aortic regurgitation was not detected.

Valvular calcification in general represents an aging process that may lead to aortic stenosis in the elderly. Valvular abnormalities, such as a bicuspid valve, may accelerate this degenerative process. However, in the present patient, severe aortic calcification was encountered at age 46. This implies the presence of an additional factor accelerating the calcification process, and this factor was the coexistent elastic tissue defect. Indeed, the patient had been diagnosed as having thalassemia-related PXE, an acquired diffuse elastic tissue disorder, which is clinically and histopathologically identical to inherited PXE, and is observed with a notable frequency in patients with β-thalassemia and other hemoglobinopathies [6]. The syndrome involves cutaneous, ocular, and cardiovascular manifestations and is held responsible for a continuously growing spectrum of complications observed in patients with hemoglobinopathies. Tissue calcium deposition is a hallmark of PXE; it is a secondary process after the diffuse degeneration of elastic fibers throughout the body. As a result, calcification of coronary and peripheral arteries and cardiac valves has been reported in patients with thalassemia [2, 3, 7].

Postoperatively, the patient had rapid thrombosis of the mechanical valve develop, despite her strict compliance with a standard warfarin-based antithrombotic regimen. Hypercoagulability is a well-established entity in β-thalassemia [8]. It is believed to be of multifactorial origin, with the most important factor being the procoagulant surface of patients' native erythrocytes; consistent with that is the fact that regular blood transfusions have been shown to reduce a hypercoagulable state in these patients [9]. Other factors contributing to hypercoagulability in β-thalassemia include the splenectomy-induced platelet abnormalities and a number of coexistent inherited deficiencies of coagulation factors, such as protein C and S, Leiden factor, and von Willebrand factor [8]. Thus, given the coexistent hypercoagulable state in β-thalassemia, a rising question is whether the biological prosthetic valves should be preferred over the mechanical ones.

In the present case, we chose a mechanical valve based on the assumption that the age of the patient (46 years) would compromise the longevity of a biological valve, considering the possibility of an aggressive early calcification. However, although a number of inherited deficiencies of coagulation were excluded, the patient had not been regularly transfused, and furthermore she had undergone splenectomy with a resultant thrombocytosis, factors that predisposed to hypercoagulability and prob-

ably led to the rapid thrombosis of the mechanical valve. It seems that the choice between a mechanical and biological valve should be based on an individually tailored approach that would take into consideration the patient's age, general prognosis, and life expectancy with respect to the main disease, as well as the aforementioned factors predisposing to hypercoagulability and any past history of thrombotic complications. On the other hand, the therapeutic targets of the anticoagulation therapy in the case that a mechanical valve is chosen should also be reconsidered in these patients.

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Total Anomalous Pulmonary Venous Connection With Intact Interatrial Septum

Amit Mishra, MCh, FPCS, Rajnish Garg, MD, Raghunath CN, MD, Sunita Maheswari, ABP, ABPC, and Rajesh Sharma, MCh

Division of Pediatric Cardiac Surgery, Department of Cardiothoracic and Vascular Surgery, Narayana Hrudayalaya, Bangalore, India

The presence of an interatrial communication is considered an integral part of the diagnosis of total anomalous pulmonary venous connection and is believed to be essential for survival. We report a 9-month-old infant with obstructed supracardiac total anomalous pulmonary venous connection without an interatrial communication.

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Restrictive atrial septal defect in total anomalous pulmonary venous connection (TAPVC) is a well-known cause of obstruction to pulmonary return. The extreme situation of an intact interatrial septum thus far was believed to have been incompatible with life.

A 9-month-old male child was referred to our hospital with a history of recurrent cough and bluish discoloration since 1 month of age. On examination the child was thinly built, weighing 4 kg. There was mild cyanosis. Auscultation revealed conducted sounds in both lung fields. There was mild hepatomegaly. Chest skiagram showed cardiomegaly with pulmonary venous congestion. An electrocardiogram showed right axis deviation and right ventricle hypertrophy.

Transthoracic echocardiography revealed situs solitus with atrioventricular and ventriculo-arterial concordance. There was obstructed supracardiac total anomalous pulmonary venous connection with a vertical vein draining to the right superior vena cava. The right atrium and right ventricle were dilated with poor right ventricular function. The left ventricle was compressed and pancaked. The mitral valve annulus was 9 mm (normal for body surface area, 11 mm), and the tricuspid valve annulus was 16 mm. There was a large patent ductus arteriosus (PDA) with bi-directional shunting and severe pulmonary artery hypertension. No right to left shunting could be demonstrated at the atrial level.

The child was prepared for surgery. Echocardiographic findings of a supra cardiac type of TAPVC with a vertical vein draining to the superior vena cava right atrial junction were confirmed. The PDA was looped. Trial occlusion of the PDA resulted in complete loss of pressure in both the ascending aorta and femoral arterial lines with bradycardia. Absence of an atrial septal defect with right ventricle dependent systemic circulation through a PDA and nonfunctional left ventricle (LV) was postulated. A transesophageal echocardiogram was then conducted in the operating room to confirm the findings. The transesophageal echocardiogram showed a small left atrium and LV with trivial flow across the mitral valve. There was no flow across the aortic valve with leaflets not opening in systole.

It was therefore concluded that the LV was not contributing to systemic output and the right ventricle was supporting both pulmonary and systemic circulations. Treatment options considered were as follows: (1) treatment on lines of a single ventricle type of repair (ie, pulmonary veins to left atrium connection with excision of the interatrial septum along with a Stansel type of aortopulmonary connection leaving the distal pulmonary arteries dependent on a systemic to pulmonary artery shunt); and (2) TAPVC repair with postoperative extracorporeal membrane oxygenation if the LV did not sus-

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Address correspondence to Dr Sharma, Division of Pediatric Cardiac Surgery, Department of Cardiothoracic & Vascular Surgery, Narayana Hrudayalaya, No. 258/A, Bommasandra Industrial Area, Anekal Taluk, 560 099 Bangalore, India; e-mail: rsharmacvs@hotmail.com.

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