



Unusual Early Aortic Valve Bioprostheses Failure due to Fungal Infection

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Abstract

We report an early failure of a 19 mm mitroflow A12 aortic pericardial bioprosthetic valve. We excluded all described causes related with early bioprostheses calcification and degeneration. Neither inflammatory cells nor bacterial colonization were identified in microscopic analysis, but fungal hyphae were observed in the tissue sections from both leaflets, suggesting sub-clinical fungal endocarditis, which might have contributed to early failure.

Keywords

Endocarditis, Heart valve bioprostheses, Infection, Calcification, Inflammation

Introduction

Anti-calcification treatment providing biological material stability is the determinant factor to avoid structural bioprosthetic valve degeneration. Implantation age under 65-70 years, diabetes mellitus, female sex, dyslipidemia, prosthesis-patient mismatch, metabolic syndrome, smoking habit and calcium metabolism disorders were proposed factors favouring bioprosthetic valve degeneration [1,2]. Proinflammatory reactions involving valve tissue might precipitate or contribute, to early bioprostheses degeneration. In this case, associated fungal bioprostheses colonization and induction of proinflammatory toll-like receptor 2 TLR-2-mediated response are suggested as unusual mechanisms precipitating early structural failure.

Case Report

A 70-year-old female, with arterial hypertension, diabetes mellitus type 2, hypertriglyceridemia, factor V deficiency, hypothyroidism in thyroid-replacement therapy and right mastectomy due to breast cancer. She chronically received anastrozole. After echocardiographic diagnosis of severe aortic stenosis, rheumatic mitral valve with posterior leaflet calcification and mild mitral regurgitation, the native valve was replaced with a 19 mm Mitroflow 12A pericardial bioprostheses (Sorin Group Inc, Mitroflow Division, and Vancouver, Canada). During the immediate postoperative, patient presented with systemic inflammatory response syndrome (SIRS), severe leukocytosis (25570/ μ l) and increased inflammation markers (highest levels: C-reactive protein: 234.9 mg/L; Lactate: 46 mg/dL; Procalcitonin: 13.92 ng/ml), solved on 6th postoperative day (POD).

She was empirically treated with broad-spectrum intravenous antibiotics between 2nd and 8th POD. All the hemocultures were negative. At 2nd POD, she presented generalized mucocutaneous candidiasis, with favourable response to antifungal therapy (topical clotrimazole and nystatin mouth rinse). Patient was discharged home on 20th POD. Postoperative echocardiographic control showed normofunctional bioprostheses: mean transvalvular gradient (PTG): 17 mmHg. 3 months after surgery, echocardiographic PTG increased (50 mmHg), with normofunctional leaflets. After aortic valve bioprostheses implantation, antiaggregation with dipyridamole 100 mg/12 hours was initiated and maintained after hospital discharge.

At 15 months, the patient was reoperated because of bioprostheses dysfunction, with severe stenosis and regurgitation (peak/mean gradient: 126/81 mmHg, respectively), and severe regurgitation of calcified native mitral valve.

During reoperation, we evidenced rigid and calcified bioprosthetic leaflets, with semi-open valve position. The mitral leaflets, annulus and left ventricular outflow tract showed extensive areas of calcification. Aortic bioprostheses and native mitral valve were replaced with a 19 mm and 25 mm Carbomedics mechanical valve, respectively, in order to avoid a third redo surgery because early and unexpected bioprostheses degeneration. During postoperative, the patient presented again with SIRS (Procalcitonin: 2.64 ng/ml; Lactate: 26 mg/dL; C-reactive protein: 375 mg/L; leukocytes: 15020/ μ l) solved on 6th POD. Postoperative treatment with intravenous meropenem and linezolid was administered between 3rd and 8th POD. No antifungal treatment was initiated because there was no clinical suspicion of prosthesis valve endocarditis. The hemocultures were negatives. Patient was discharged home on 15th POD. Diagnosis of subclinical prosthetic endocarditis was obtained 3 months after surgery. At this moment, clinical and echocardiographic patient evaluations were normal. Blood cultures were negatives and no antifungal treatment was instituted. In echocardiographic control at 6 months, left ventricular ejection fraction was 69% with restrictive left ventricular filling. Severe left ventricular hypertrophy. Normal prosthetic mitral valve function. Mean gradient 6 mmHg. Mean aortic transvalvular gradient: 35 mmHg. Systolic pulmonary pressure: 33 Hg.

Gross examination of explanted bioprostheses showed intrinsic and vegetating calcification in all the leaflets, confirmed by X-ray analysis. Pannus and thrombus formation were observed. Two small holes were detected in two different leaflets (< 2 mm). (Figure 1A

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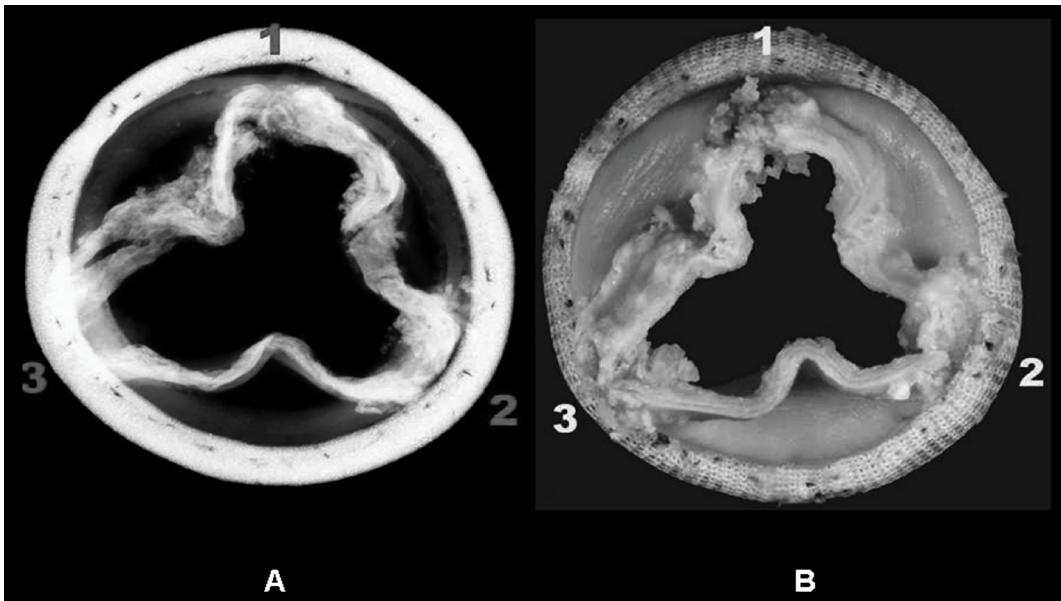


Figure 1: (A) Rx examination: Intrinsic and vegetating calcifications are visible in all the leaflets; (B) Macroscopic view of explanted bioprosthesis.

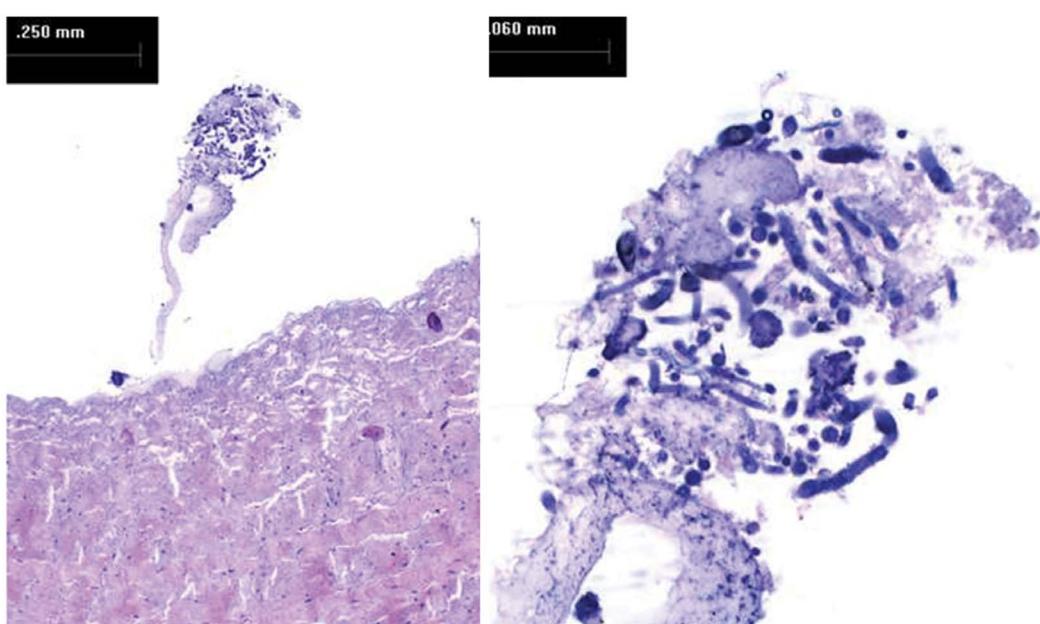


Figure 2: (A) Sample belly towards the adherent margin: the collagen bundles are locally disrupted and homogenized. Small mesothelial ditches are visible in relation to the fold. Some fungal hyphae inside the thrombus deposition are visible on the mesothelial surface. Some native blood vessels are still visible. (B) (Detail) Fungal hyphae are spread inside the pannus.

and Figure 1B) Microscopic analysis of tissue sections confirmed leaflet calcification with Alyizarin Red S staining. Disrupted and homogenized collagen bundles were also observed. We identified pannus and thrombus formation on the mesothelial surface of the leaflet tissue. Calcified nodules were identified within some areas of thrombus formation, with no inflammatory cells or bacterial colonies. We observed fungal hyphae in the tissue sections from both leaflets . (Figure 2A and Figure 2B). Hystological findings of mitral valve described irregular leaflet valve morphology with marked fibrosis, large areas of hyalinization, and multiple foci of dystrophic calcification. No individual cultures of mitral valve was realized.

Discussion

Although female sex, diabetes mellitus and dyslipidemia were present in our patient, none of them have been isolated linked to early structural bioprosthetic degeneration. We excluded calcium metabolism disorders: Calcium: 9.9 mg/dl (normal range: 8-11 mg/dl), Phosphorus: 3.1 mg/dl (normal range: 2.7-4.5 mg/dl),

osteocalcin: 33 ng/ml (normal range postmenopausal women: 13-48 ng/ml), procollagen-1: 32.77 ng/ml (normal range postmenopausal women: 76.3 ng/ml), beta-crosslaps: 1.06 ng/ml, (normal range postmenopausal women: ng/ml), calcitonin: 4.30 pg/ml (normal range: < 10 pg/ml) and intact-parathormone: 87 pg/ml (normal range: 15-68 pg/ml) (probably raised by chronic administration of anastrozole without calcium supplements).

Echocardiography of early structural bioprosthetic degeneration showed initially [2,3] decreased leaflet mobility, without clinical or hemodynamic translation. Later, PTG increased and clinical dysfunction was patent. In our patient, an increased PTG gradient was patent 3-months after surgery, although leaflet mobility seemed normal. As in this case, the most frequent clinical features in bioprosthetic aortic degeneration are incompetence or mixed lesion [3].

Macro and microscopic findings correspond with others already described [1,3]. Nevertheless, presence of leaflet fungal

hyphae suggests a sub-clinical fungal endocarditis that might have contributed to early structural valve deterioration.

Following both cardiac surgeries, the patient presented a SIRS. Long intravenous broad-spectrum antibiotics administration and inflammatory response, could favour mucocutaneous candidiasis and secondary candidemia. Such expression of *Candida* infection depends on the immune status of the host, further immunity restoration prevented *Candida* prosthetic valve endocarditis.

Hyphae are more invasive form of *Candida* tissue infection. Their virulence is secondary to induction of proinflammatory response and TLR-2-mediated protection against fungal infection. Biofilm formation (over host and prosthetic surfaces), secretion of adhesins, acid proteases phospholipases and hydrolases [4] might precipitate an early bioprosthetic degeneration in an aged woman, whose only risk factors were diabetes mellitus and dyslipidemia.

We hypothesize that host tissular hyphae invasion, affected bioprosthetic and host myocardium. *Candida* myocarditis-pericarditis affects more than 50% of patients with disseminated candidiasis [5]. Usually latent, their most frequent presentation form is as myocardial microabscesses, more frequent after antineoplastic, antibiotic or corticosteroid treatment (such as in presented case).

Probably, after acute infection, microabscesses degenerated in calcification foci, which would explain severe calcification observed in

left ventricular outflow tract, aortic and mitral annulus in our patient during re-intervention. In conclusion, subclinical endocarditis could be a risk factor for early bioprosthetic degeneration. Although infrequent, in patients affected by postoperative SIRS and previous history of fungal infection we suggest to investigate the possibility of fungal endocarditis through specific blood cultures.

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