Unusual presentation of cryolife O’Brien® stentless aortic valve
bioprosthesis dysfunction mimicking infective endocarditis

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Abstract

OBJECTIVES: We previously reported a possible but unusual prosthetic-valve infective endocarditis (PV-IE) occurring on a Cryolife O’Brien Stentless Porcine Xenograft (CLOB) (anatomic damages suggestive of IE but negative inflammatory and microbiological markers). We reviewed all cases of aortic PV-IE admitted in our institution and compared the clinical presentation, bacteriological and echocardiographic features according to the type of prosthesis.

METHODS: Sixty consecutive cases with possible or definite aortic PV-IE (23 CLOB, 26 mechanical valve and 11 stented bioprosthesis) were admitted between 2002 and 2008.

RESULTS: Patients with CLOB had more prosthetic dehiscence (P = 0.006) and severe regurgitation (P = 0.01) than those with mechanical or stented prosthetic valves. In contrast, they had less fever (P = 0.003), lower C-reactive protein (CRP) levels (P = 0.02) and more frequently negative blood cultures (P = 0.08). Differences were due to seven patients who presented with no fever, low CRP, negative blood culture and PCR when performed, despite echocardiographic features suggestive of IE (abscess or valve dehiscence). All were first operated on since 2004 when the manufacturing process changed and required a second surgery. The French Authority of Health was informed leading to the withdrawal of the CLOB from the market in 2010.

CONCLUSIONS: One-third of patients with CLOB admitted for possible or definite PV-IE presented with anatomic damages suggestive of IE but with negative inflammatory and microbiological markers. The exact aetiology remains unclear, but the present data have led to the worldwide withdrawal of prosthesis in 2010. A close follow-up of patients implanted with CLOB should be advised, especially if it has been manufactured since 2004.

Keywords: Infective endocarditis · Aortic valve prosthesis · Stentless bioprosthesis · Complications

INTRODUCTION

Stentless aortic valve bioprosthesis were introduced into clinical practice as aortic valve substitutes over 2 decades ago. They were expected to provide more physiological haemodynamic behaviour when compared with stented bioprosthesis, a lower rate of prosthetic valve endocarditis (PV-IE) and a better durability [1–3]. Whereas they indeed exhibit an excellent haemodynamic profile, the rates of PV-IE and of structural valve deterioration are not better than that of other bioprosthesis [4, 5].

Recently, we were intrigued by a possible but unusual case of infective endocarditis (IE) 2 years after the implantation of a Cryolife O’Brien Stentless Porcine Xenograft (CLOB) (Cryolife International, Atlanta, GA, USA). The patient presented with congestive heart failure (CHF) and severe aortic regurgitation (AR) due to a prosthetic abscess and valve dehiscence but had no fever, negative inflammatory markers and negative blood cultures [6]. Similar cases eventually occurred. Since CLOB were widely used in our institution [7], we decided to review all cases of possible or definite aortic PV-IE admitted in our institution since 2002 and to compare the clinical presentation, bacteriological and echocardiographic features according to the type of prosthesis, CLOB, mechanical prosthesis and stented bioprosthesis, hypothesizing that the above-mentioned features were specific to CLOB.

METHODS

Study population

We retrospectively reviewed all cases of possible or definite aortic IE according to the modified Duke criteria [8] hospitalized...
at Bichat Hospital, from 2002 to 2008. Cases were collected from our medical information system and from a registry on IE started in 2005. Four hundred and five patients were admitted for possible or definite IE between 2002 and 2008. Among them, 62 patients presented with aortic PV-IE. Two patients had aortic homografts and were excluded due to the limited size of this group. The remaining 60 patients constituted our study population. Medical records were obtained for all patients, including demographic characteristics, date of prosthesis implantation, clinical presentation, echocardiographic and biological data and surgical reports.

Definitions

Symptoms were classified according to the New York Heart Association functional class. CHF was defined according to the Framingham criteria [9] and fever as hyperthermia ≥38.5°C. Critically ill patients designated patients requiring admission in the intensive care unit for acute respiratory or circulatory failure, or renal replacement therapy. Previous antibiotic therapy was defined by the use of antibiotics (oral or intravenous) within 15 days before the diagnosis of PV-IE and performance of blood cultures. Early IE was defined as a PV-IE occurring within 12 months after surgery [10].

Echocardiography

Echocardiographic data were obtained from transthoracic and/or transoesophageal reports. Vegetation length was measured in multiple planes and the largest vegetation length was recorded. Abscesses were defined as abnormal echodense or echoluent areas within the valvar annulus or perivalvular tissue, seen in at least two different echocardiographic planes [11]. Prosthetic valve dehiscence was defined as a swinging motion of the prosthetic valve with an excursion of ≥15° in at least one direction [12]. AR was semi-quantitatively graded as mild, moderate, moderate to severe and severe on the basis of a comprehensive assessment using colour jet extent, vena contracta and diastolic flow reversal in the descending aorta [13, 14].

Biological data

C-reactive protein (CRP) was collected at the time of diagnosis. A threshold of 30 mg/l defined a low CRP. Information on blood culture, valve culture, molecular bacteriological analysis of the explanted valves (polymerase chain reaction, PCR) and pathological examination of explanted valves were also collected when available.

The Cryolife O’Brien Stentless Porcine Xenograft valve

The CLOB valve is a porcine stented bioprosthesis composed of three individual non-coronary porcine cusps fixed in glutaraldehyde. Operations were performed according to the standard technique described previously by Dr O’Brien. The CLOB valve is implanted in a supraannular position and secured to the patient’s aortic root with a single continuous running suture line.

Statistical analysis

Results were expressed as mean ± standard deviation or number of patients (%) as required. Comparisons between the groups were performed using one-way analysis of variance, χ² test, the Wilcoxon/Kruskal-Wallis test or the Fisher exact test as appropriate. A two-sided P-value of 0.05 was considered significant. All analyses were performed using JMP® software. As this was a retrospective analytical study only, no formal ethical permission was required.

RESULTS

Baseline characteristics

Sixty patients with possible or definite aortic PV-IE constituted our study population. Baseline characteristics are presented in Tables 1–3. Prosthetic valves were implanted between 1987 and 2007, on average 47 ± 48 months [median 26, range (1–237)] before the current episode. Type of prosthesis was stentless CLOB in 23 patients (38%), mechanical prosthesis in 26 patients (44%) and stented bioprosthesis in 11 patients (18%). Patients in the stentless group were older (P = 0.003), tended to be more frequently operated on for prior IE (P = 0.08) and to present more frequently in CHF (P = 0.10).

Echocardiographic characteristics

Transthoracic echocardiography was performed in all patients and transoesophageal echocardiography in all but two (96%). Vegetations were observed in 27 patients (45%), less frequently in patients with stentless than in those with mechanical or stented prosthesis (22 vs. 58 and 63%, respectively, P = 0.01). In contrast, patients in the stentless group were more likely to present prosthetic valve dehiscence (68 vs. 23 and 22%, P = 0.006) or severe AR (65 vs. 23 and 36%, P = 0.01) than those with mechanical or stented prosthetic valves and there was a trend towards higher rates of annular abscesses (70 vs. 50 and 54%, P = 0.40) (Table 2).

Markers of inflammation

Fever was observed in 65% of patients (n = 39), 77% (n = 20) in patients with mechanical prosthesis, 91% (n = 10) in patients with stented bioprosthesis and only 39% (n = 9) in patients with CLOB (P = 0.003). Fever at presentation remained less frequent in patients with stentless CLOB than in those with mechanical or stented prosthesis after exclusion of the 21 patients who received an antibiotic therapy before admission (20, 77 and 83%, respectively, P = 0.01). Mean CRP was 114 ± 103 mg/l [median 107, range (1–415)]. CRP was significantly lower in patients with CLOB than in those with mechanical prosthesis or stented bioprosthesis (69 ± 70 vs. 144 ± 106 and 145 ± 123 mg/l, respectively, P = 0.02). The percentage of patients with low CRP (<30 mg/l) was also
significantly higher in patients with stentless bioprosthesis than in those with mechanical or stented bioprosthesis (48, 17 and 18%, respectively, \( P = 0.04 \)).

### Microbiological characteristics

Blood cultures were negative in 24 patients (40%), more likely in patients with CLOB than in those with mechanical or stented prosthesis overall (57, 35 and 18%, respectively, \( P = 0.08 \)) and after exclusion of patients who received antibiotics before admission or blood culture (65, 23 and 18%, respectively, \( P = 0.03 \)). Among the 13 patients with CLOB and negative blood cultures, valve culture was positive for *Streptococcus oralis* in one patient and PCR positive for *Streptococcus sanguis* in another one. Valve culture was negative in the remaining 11 patients as well as PCR (performed in 7 patients). Finally, we could identify that seven patients in the CLOB group (30%) had no fever, low CRP, negative blood culture, negative valve culture and PCR when performed. These features were referred as aseptic CLOB dysfunction.

#### Aseptic Cryolife O’Brien Stentless Porcine Xenograft dysfunction

All the seven patients were admitted for severe symptoms (NYHA class III/IV or CHF) or occurrence of new severe AR. Since they had no fever, none received antibiotics before admission or blood culture and importantly none of them had a previous IE. Mean CRP was \( 14 \pm 10 \text{ mg/l} \). Anatomic lesions, as assessed by
echocardiography, were severe and suggestive of IE (six of the seven had abscesses, five of the seven had valve dehiscence and six of the seven severe AR) (Fig. 1). In contrast, cusps were thin and appeared normal and no vegetations were observed. Mean S-PAP was 54 ± 13 mmHg. Of note, all the seven prosthesis were well functioning at discharge after the index surgery.

All patients were operated on in emergency (within 24 h, n = 5) or urgently (within a few days, n = 2). Peroperative examinations confirmed that aortic cusps were thin without vegetation or sign of early structural valve deterioration but all presented with valve dehiscence or annular lesions suggestive of abscesses. The seven patients received conventional antibiotic therapy for negative blood culture PV-IE. In-hospital mortality was 43% (n = 3) and hospital stay 33 ± 21 days. Mean time between the first surgery and the present episode was 22 ± 7 months and importantly, all CLOB were implanted since 2004. These striking features have led to a declaration to the French Authority of Health (AFSSAPS—Agence Française de Sécurité Sanitaire des Produits de Santé) and to the Company. In regard to similar cases reported from other institutions and 14 additional cases from our institution, the CLOB was withdrawn from the market in February 2010 (http://www.afssaps.fr/content/search?SearchText=cryolife).

DISCUSSION

In the present study, we reviewed all consecutive cases of possible or definite aortic PV-IE admitted in our institution since 2002 and compared their clinical presentation, bacteriological and echocardiographic features according to the type of prosthesis, CLOB, mechanical prosthesis and stented bioprosthesis. Patients with CLOB presented less frequently with fever, elevated CRP, positive blood culture despite more destructive periannular lesions. These differences were mainly due to approximately one-third of patients, all operated on since 2004, who presented with aseptic CLOB dysfunction. These patients had no fever, low CRP, negative blood culture, negative valve culture and PCR when performed despite echocardiographic features mimicking infective endocarditis. These results have led to the withdrawal of the CLOB from the market.

Since we reported the first case of possible CLOB PV-IE with this atypical presentation [6], other cases were observed and we aimed to evaluate precisely the number of patients with these atypical features and whether these features were specific or not of the CLOB. For that purpose, we reviewed all consecutive cases of possible or definite aortic PV-IE admitted in our institution between 2002 and 2008 and collected both inflammatory and microbiological data as well as echocardiographic reports. The present study clearly shows that if ‘regular’ infective endocarditis could of course occur with CLOB as for stented bioprosthesis or mechanical valve, one-third of patients with CLOB presented with aseptic dysfunction (anatomic damages suggestive of endocarditis but negative inflammatory and microbiological data).

These seven patients had no fever, low CRP and negative blood culture, negative valve culture and PCR when performed. Fever is one of the Duke’s criteria [8] and is a very common feature in IE

| Table 3: Infectious and microbiological characteristics |
|-------------------------------------------|--|--|--|--|--|
| Overall (n = 60) | Stentless bioprosthesis (n = 23) | Mechanical prosthesis (n = 26) | Stented bioprosthesis (n = 11) | P-value |
| Previous antibiotic therapy | 21 (36) | 5 (23) | 12 (48) | 4 (40) | 0.20 |
| Fever | 39 (65) | 9 (39) | 20 (77) | 10 (91) | 0.003 |
| CRP, mg/l | 114 ± 103 | 68 ± 70 | 144 ± 106 | 144 ± 123 | 0.02 |
| CRP < 30 mg/l | 17 (29) | 11 (48) | 4 (17) | 2 (18) | 0.04 |
| CRP < 50 mg/l | 19 (33) | 12 (52) | 5 (21) | 2 (18) | 0.04 |
| Negative blood cultures | 24 (40) | 13 (57) | 9 (35) | 2 (18) | 0.08 |
| Definite infective endocarditis | 37 (62) | 10 (43) | 19 (73) | 8 (73) | 0.07 |

Values are number of patients (%) or means ± SD.

Figure 1: Example of CLOB dehiscence. Transthoracic echocardiography, parasternal short-axis view on left side, long-axis view on right side. The large arrow indicates the prosthesis dehiscence and the small arrow the rim of the prosthesis. The dehiscence causes deformation of the prosthesis resulting in leaflet prolapse.
since 2004 on a regular basis and transoesophageal echocardiography. The high in-hospital mortality, we recommend performing such presentation. In regard to the severe clinical presentation were worldwide implanted and physicians should be aware of institution. From the clinical point of view, thousands of CLOB implanted with CLOB manufactured since 2004 is ongoing at our institution. From the market in February 2010. A survey of all patients incidental and have led to a worldwide withdrawal of the CLOB and the Company were informed. Similar aseptic CLOB dysfunctions were also observed in other institutions (AFSSAPS investigation). Secondly, we decided to compare clinical, microbiological and echocardiographic features according to prosthesis instead of only reporting the rate of possible or definite PV-IE occurring with CLOB. Indeed, our aim was first to demonstrate that this aseptic dysfunction was specific to CLOB. Nevertheless, we also provided a gross estimation of the rate of aseptic CLOB dysfunction (21 cases since 2004, rate of 9.5%). Thirdly, we could not provide any estimation of the incidence of PV-IE occurring with other type of prosthesis. Indeed, CLOB were all implanted at our institution whereas stented bioprosthesis or mechanical valve were frequently implanted elsewhere and referred to us for IE. Finally, as above mentioned, the exact aetiology as well as the precise mechanism could not be established based on present data. Additional studies would require access to CLOB samples and the investigation of the manufacturing process.

**CONCLUSION**

In the present study, we reviewed all consecutive cases of possible or definite aortic PV-IE admitted in our institution between 2002 and 2008. We identified an atypical presentation occurring in one-third of patients with the CLOB. These patients, all operated on since 2004, presented with severe anatomic damages suggestive of infective endocarditis and severe AR but with negative inflammatory and microbiological markers (aseptic CLOB dysfunction). The exact aetiology remains unclear, but these striking features have led to a declaration to the French Authority of Health resulting in a worldwide withdrawal of the CLOB from the market in February 2010. Physicians should be aware of such presentation and patients closely monitored, especially if CLOB manufactured since 2004.

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**REFERENCES**


