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CASE REPORT

Mitral bioprosthesis hypertrophic scaring and native aortic valve fibrosis during benfluorex therapy

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ABSTRACT

The authors describe the case of a simultaneous mitral bioprosthesis hypertrophic scaring and native aortic valve fibrosis during benfluorex therapy in a 40-year-old woman. Four years before, she underwent a mitral valve replacement after the diagnosis of mitral regurgitation during benfluorex treatment (150 mg/day). This drug was reintroduced postoperatively. She presented with exercise and sometimes resting dyspnoea. The bioprosthesis and aortic valves exhibited similar histopathological lesions. Thickening and plaque deposits made by smooth muscle alpha actin- and vimentin-positive cells in a glycosaminoglycan matrix were observed. The study discusses the putative contribution of circulating progenitor cells activated by 5-HT_{2B} receptor agonists in the development of drug-induced heart disease.

Benfluorex Mediator® was marketed in patients with hypertriglyceridemia or diabetes with overweight. Owing to its close structural relationship with amphetamines, it was classified and widely used as an appetite suppressant. Moreover, it was considered as a doping molecule added to the list of the World Anti-Doping Agency in 2010 [1]. The association between the use of ergot alkaloids such as methysergide and ergotamine and the development of valvular heart disease is not new. The so-called drug-induced fibrotic valvular disease appears as an adverse drug reaction of many compounds such as pergolide, cabergoline, fenfluramine and the recreational drug ecstasy (3, 4-methylenedioxymethamphetamine; MDMA) [2]. All these drugs share in common the pharmacological property to activate a serotonergic receptor subtype, the 5-HT_{2B} [3]. This activation would drive to lesions that are quite similar to those observed in the carcinoid heart, a cardiac valvular disease caused by serotonin-secreting tumours. One of the benfluorex liver metabolites is norfenfluramine [1], a high affinity 5-HT_{2B} receptor agonist [3]. The current dogma is that agonists of the 5-HT_{2B} receptor would stimulate locally resident valvular interstitial cells leading to proliferation and extracellular cell matrix deposit. But, surprisingly, chronic exposure of mitral valve organ cultures to serotonin and norfenfluramine induce no or only minor plaque deposits and extracellular cell matrix activation [4].

We present the case of a 40-year-old woman in whom a simultaneous mitral bioprosthesis hypertrophic scaring and native aortic valve fibrosis were observed during benfluorex therapy. In 2007, the patient presented with exercise dyspnoea and asthenia. In her medical history, it is noted a supraventricular arrhythmia (atrial tachycardia and supraventricular extrasystoles). She underwent an unsuccessful ablation in 1996. This arrhythmia was assumed as the cause of a left ventricular dilatation and the reduction in the ejection fraction around 50–55%. Asthma and allergy were also noticed. Concerning her cardiovascular risk factors, she was obese (BMI = 35; 1.61 m; 91 kg) with an untreated

hypercholesterolemia (cholesterol: 2.43 g/L, HDL: 0.57 g/L, LDL: 1.67 g/L, triglyceride: 0.93 g/L), and tobacco smoke was stopped in 1993. The glycaemia was normal with a 5.3% HbA1c. At that time, her treatment was carried out by giving atenolol (100 mg/day), inhaled fenoterol plus ipratropium bromide and topiramate (100 mg/day). She started a treatment with benfluorex (150 mg/day) 15 months before (November 2005). She never used any other appetite suppressant such as fenfluramine or phentermine or any ergot derivative. Transthoracic echocardiography identified a slight thickening of three aortic cusps with an opening diameter of 14.5 mm. A small grade II regurgitation was observed with a 466–471 ms pressure half-time and a 15 cm/s end-diastolic aortic regurgitation velocity. The pressure gradient was normal. Concerning the mitral valve, a grade III/IV regurgitation was observed with a diastolic and systolic restrictive motion of the small valve. The regurgitant surface was evaluated at 29 mm^2 and the regurgitant volume around 45 mL. At a morphological point of view, the leaflets appeared slightly remodelled with the small valve showing a systolic restrictive tenting. The subvalvular apparatus showed increased thickness and tendinous cords appeared moderately shortened (17–17.5 mm). Transoesophageal echocardiography of the mitral valve identified two regurgitant jets because of retraction of the whole posterior leaflet (P1, P2, P3) and the retraction of the A1/A2 segments of the anterior leaflet. Subvalvular apparatus was thickened and retracted (12–15 mm). The three aortic cusps were moderately thickened with a moderate grade II regurgitation. Signs of diseases known to affect valves (rheumatic, infectious endocarditis, carcinoid heart, lupus erythematosus, congenital defect …) were not identified in her medical history. The patient underwent a mitral valve replacement by St Jude EPIC bioprosthesis. The postoperative follow-up was simple. Early control echocardiography (day 7) showed a reduction in the end-diastolic left ventricular diameter (56–50 mm), a usual postoperative reduction in the ejection fraction (45%) and a normal function of the bioprosthesis. Anatomopathological examination confirmed thickened leaflets and retraction, and remodelling of the subvalvular apparatus. The relevant postoperative medications were rosuvastatine (5 mg/day), amiodarone (400 mg/day), aspirin (160 mg/day) and omeprazole (20 mg/day). Less than 2 months after surgery, benfluorex (300 mg/day followed by 150 mg/day) was reintroduced. She will be treated with benfluorex the same dose from March 2007 to November 2009.

In November 2009, at the time of benfluorex withdrawal from the French market, she stopped this treatment and that was replaced by pravastatine (20 mg/day). On the top of pravastatine, she was treated by diltiazem (200 mg/day), furosemide (40 mg/day), levothyroxine (50 μg/day), inhaled fenoterol plus ipratropium bromide and topiramate (100 mg/day). In February 2010, she presented once more exercise and sometimes resting breathlessness. Echocardiography identified a slight leaflets thickening of the mitral bioprosthesis, a stenosis with a 13 mmHg mean pressure gradient and no regurgitation. The aortic valve was dystrophic and showed a grade III/IV regurgitation with a 300–310 ms pressure half-time. No left ventricular dilatation (left-ventricular end-diastolic diameter: 52 mm) and alteration of contractility (ejection fraction: 52%) were observed. The systolic pulmonary pressure was estimated on the basis of a grade I tricuspid regurgitation at 37 mmHg. She proceeded to have mitral and aortic mechanic valve replacements in March 2011. The explanted bioprosthesis showed no alteration of the three cusps but a parastent hyperplastic tear pannus stenosis (*Figure 1a,b*) made by smooth muscle alpha actin (SMA)- (*Figure 1c*, brown staining) and vimentin-positive cells, in a glycosaminoglycan (GAG)-abundant matrix (*Figure 1d*, blue staining). The three aortic cusps exhibited a similar pannus with massive thickening of the Arantius nodule area (*Figure 1e*) made by SMA-positive cells (*Figure 1f* upper) in an intense GAG deposit (*Figure 1f* lower).

The total cumulative doses of benfluorex for the aortic, mitral and bioprosthetic valves were respectively 201.6 g during 48 months, 63 g during 15 months and 138.6 g during 33 months. *In vivo*, benfluorex is rapidly metabolized in the liver to various compounds hydroxyethylnorfenfluramine, carboxymethylnorfenfluramine, norfenfluramine, benzoic acid and finally the glucuronide of hydroxyethylnorfenfluramine [1,5].

This is the first reported case of rapid (4 years) bioprosthesis alteration observed during benfluorex therapy. The demonstration of the link between valvular heart disease and the use of a drug is always difficult to do. Nevertheless, the combination of a clinical history, a treatment with a compound suspected to induce valvular heart disease [6,7] and a close similarity with histopathological lesions observed in the carcinoid heart reinforce the hypothesis of drug imputability. In this rare carcinoid heart, valve lesions are made of superficial plaque-like thickening of leaflets and subvalvular apparatus [8]. The hypothesis is that 5-HT activates 5-HT_{2B} receptors of the

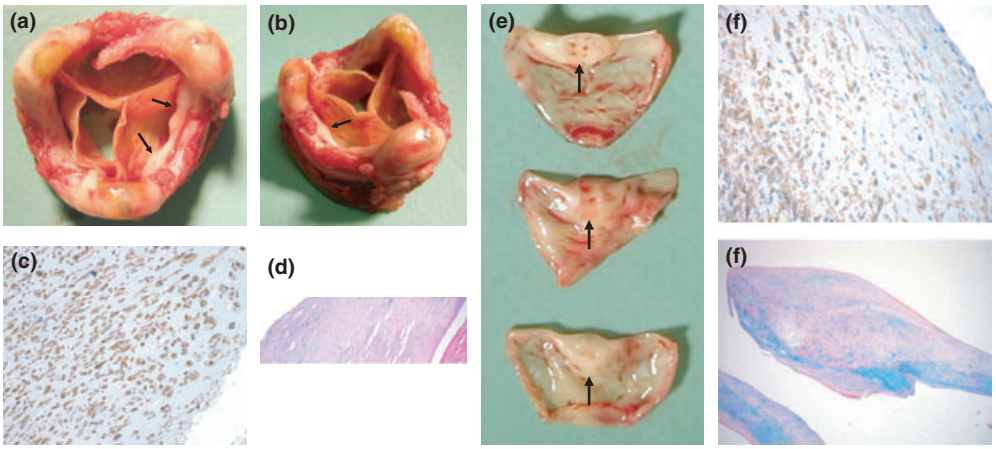

Figure 1 Histopathological examination of the explanted mitral bioprosthesis and the native aortic sigmoid valves. (a, b) No alteration of the three cusps but a parastent hyperplastic tear pannus stenosis was observed on the bioprosthesis (black arrows). (c) Pannus on the prosthesis is made by smooth muscle alpha actin (SMA) (brown staining) and vimentin-positive cells, in a (d) glycosaminoglycan (GAG)-abundant matrix (blue staining). (e) The three aortic cusps exhibit a massive thickening of the Arantius nodule area made by SMA-positive cells (f upper) in an intense GAG deposit (f lower).

valve interstitial cells promoting their proliferation and the deposit of a dense glycosaminglycan (GAG) and collagen matrix. Importantly, calcified lesions are usually not observed. In drug-induced valvulopathy, lesions are nearly similar but with a greater proportion of GAG and few vessels. Valve tissues express mainly 5-HT_{2A}, 5-HT_{2B} and 5-HT_4 receptors [9]. The poor receptor selectivity of serotonin could explain some differences with drug-induced valve lesions. Echocardiography is the key examination to diagnose a toxic valvulopathy. In young healthy subjects (<50 years old) with no cardiovascular risk factor and without any cause of restrictive valve heart disease (ischaemic mitral regurgitation, rheumatic heart, carcinoid syndrome, cardiac mass, infectious endocarditis or any congenital abnormality), the diagnosis can easily be suggested in front of a thickening of mitral leaflets with thickening and shortening of the subvalvular apparatus leading to retraction and reduced mobility of the leaflets. Importantly, commissural fusion is typical of degenerative valve disease and usually not observed in drug-induced valvulopathy [10]. Concerning the aortic valve, leaflets exhibit a reduced mobility with thickening and incomplete diastolic coaptation. In young subjects or in people without any pre-existing degenerative valve lesion and taking fenfluramine/phentermine, US FDA suggested to evoke the diagnosis of induced valvulopathy in front of a mild-to-moderate aortic and/or mitral regurgitation (quantified by colour Doppler) [11]. In pergolide-induced valve heart disease, this ergot-derived dopamine receptor agonist that also stimulates 5-HT_{2B} receptors, a scoring from 1/4 to 4/4 was proposed to classify restrictive valvular disease in patients with pre-existing valve lesions: 1, proven restrictive valvular heart disease (pathology, regression after interruption of pergolide treatment, or both); 2, important valvular disease (regurgitant jet ≥2/4) suggestive for restrictive valvular heart disease or restrictive tricuspid even if less than 2/4; 3, mild-to-moderate (regurgitant jet < 2/4) restrictive valvular disease; and 4, no restrictive valvular dysfunction [12].

In the present reported case, numerous factors (clinical history, echocardiography and anatomopathology) argue in favour of the involvement of benfluorex in cardiac valve lesions. In 2007, the patient was treated with this compound for 15 months. The echocardiographic description is typical of a restrictive mitral valvulopathy with increased leaflets thickness and subvalvular apparatus retraction and severe regurgitation. This pattern would be classified as 2 in the previous pergolide scale [12]. The aortic valve was moderately affected but lesions were also typical (retraction of the three cusps without fusion and no calcification) and a moderate regurgitant jet that would be given 3 in the same scale. At the time of first surgery, we have no idea about the possible regression of these aortic lesions because benfluorex was in fact only stopped during the surgical period. Four years later, aortic valve lesions have quickly progressed in a timeline that is similar to fenfluramine-induced valve disease. The aortic valve

shows an important regurgitant jet and histopathology identified 'stuck-on' plaques at the tip of the leaflets with a content showing close similarities with carcinoid and fenfluramine deposits (GAG rich and numerous myofibroblasts) [13]. Importantly, at the opposite of age-dependant degenerative lesions, aortic leaflet alterations were only located on the free margin of the cusps and were quite similar to the bioprosthesis deposit. Moreover, no fusion between cusps was observed. A score of 1, highly suggestive of a drug-induced valvulopathy, would then be given at that time. Interestingly, no tricuspid insufficiency was noticed in 2007 but a grade I regurgitation was used 4 years later to evaluate pulmonary pressures. One can wonder if this evolution could not point out the start of a tricuspid restrictive disease sharing the same mechanism than for the two other valves.

The rapid remodelling of a cardiac bioprosthesis during benfluorex treatment has never been described and asks numerous questions. A cardiac valve bioprosthesis is usually considered as an inert biological material. The glutaraldehyde and photo-oxidation treatments of the biomaterial drive to leaflets typically devoid of intact cells. These treatments are a prerequisite to prevent host-graft early rejection of, in the present case, a porcine mitral valve. Therefore, degeneration and calcifications that limit the long-term bioprosthesis outcome is considered to be the only consequence of a passive calcium deposit from circulating blood. In fact, the implantation of such a biomaterial initiates an inflammatory reaction of the non-specific immune system commonly known as the foreign body reaction [14]. After implantation, the biomaterial matrix is invaded by Sca-1^+, $CD34^+$, c-kit^+ and $CD271^+$ stem/progenitor cells that differentiate into adipo-, osteo- and myofibroblasts. Such a migration could also contribute to the cellular repopulation of native valves from hematopoietic stem cells [15]. Depending on physiological and pathological circumstances, these cells could proliferate and differentiate in the various cell populations usually summarized as the 'valvular interstitial cells'.

The present clinical case underlines the fact that serotonergic agonists could favour migration and/or differentiation of progenitor cells in a biomaterial matrix. Moreover, the close similarity between lesions observed in the mitral bioprosthesis and the native aortic valves could suggest the involvement of similar molecular mechanisms. Finally, this case emphasizes that benfluorex and its metabolites could not only favour native cardiac valve disease but could also promote the remodelling of cardiac valve bioprostheses.

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