Case 3/2008 – Severe and Rapidly Progressive Dyspnea in a Woman with Mechanical Mitral Valve Prosthesis

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A 58-year-old woman sought hospital care for dyspnea on minimum exertion felt for three days.

At 34 years of age, two months after an episode of arthritis of her right ankle, which was treated with prednisone, the patient developed tiredness on heavy exertion such as climbing up a slope or carrying weight. Then she developed palpitations. On physical examination, at that time, her weight was 69.2 kg, her height was 1.63m, body mass index of 26 kg/m^2, regular pulse of 78 beats per minute, and blood pressure of 120/70 mmHg. Lung examination was normal. Heart examination was significant for apical impulse in the fifth left intercostal space at the midclavicular line. Intensity of S1 was diminished in the mitral area, intensity of S2 was normal in the pulmonic and aortic areas. A grade 1 systolic murmur and grade 1 late diastolic murmur in the mitral area were observed. Abdominal examination was normal.

The electrocardiogram (3/25/1981) showed normal sinus rhythm, ventricular extrasystoles, P wave duration of 80 ms, PR-interval duration of 160 ms, QRS duration of 80 ms, SÂP – 60º and SÂQRS 60º. P wave morphology denoted intra-atrial conduction disturbance (Figure 1).

Echocardiogram (04/01/1981) showed enlarged left atrium as well as mitral valve commissural fusion and thickening (Table 1).

The patient was diagnosed with rheumatic mitral stenosis.

She was started on daily doses of amiodarone 200 mg and chlorthalidone 50 mg (which she did not tolerate). She had follow-up visits in 05/05/1982, 09/06/1982, 03/07/1983 in which she was clinically stable.

During the follow-up her electrocardiogram (09/08/1982) showed atrial fibrillation and an inactive interventricular septal area (Figure 2).

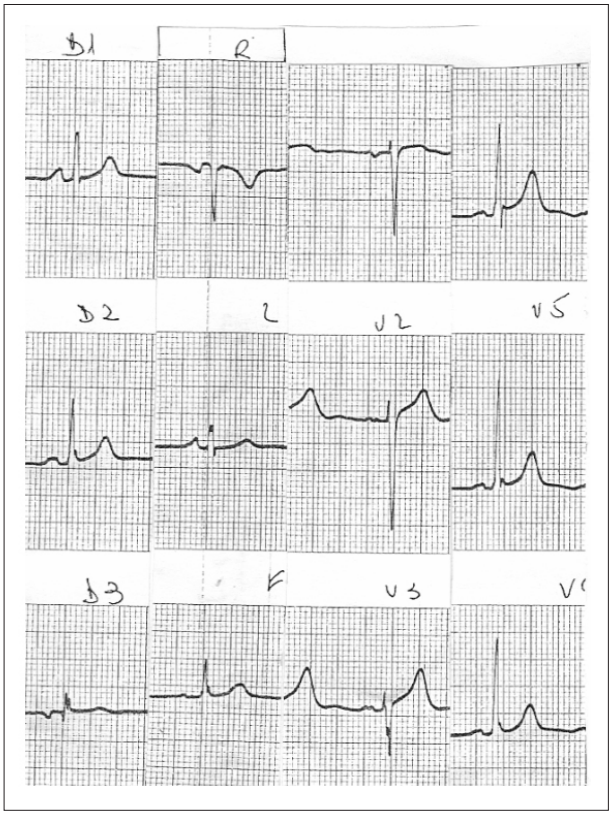

Figure 1 - *ECG. Signs of Probable left atrial overload.*

A repeat echocardiogram (09/08/1982) showed moderate mitral stenosis (Table 1). Daily doses of digoxin 0.25mg and hydrochlorothiazide 50g were prescribed.

Symptoms became very limiting ten years after their onset with dyspnea on minimal exertion, and surgical treatment was indicated (1991).

The operation (11/05/1993) consisted of valve removal, Biocor 29 bioprosthesis implantation at the mitral position, removal of atrial thrombi and left auricular exclusion by suture. Moderate heart and pulmonary artery enlargement, a great amount of thrombi in the left atrium, and calcification of the mitral valve cusps, as well as of the valve annulus, were observed.

The patient was discharged with warfarin and was sent for clinical follow-up in the city where she had been referred from. She had recurrent dyspnea on heavy exertion eight years after

Key words

Mitral valve stenosis; rheumatic fever; heart valve prosthesis.

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surgery (2001), but remained off medication.

On physical examination (10/23/2002) her pulse was irregular, 76 beats per minute, and blood pressure was 170/100 mmHg. A grade 4 diastolic murmur was heard in the mitral area.

Table 1 - Echocardiograms

	4/1/1981	9/8/1982	11/5/2004	6/8/2005
Aorta (mm)	27	25	29	-
Left atrium (mm)	48	43	46	Enlarged
Right ventricle (mm)	-	20	-	Dilated
RV systolic P (mm Hg)	-	-	70	60
Tricuspid valve	Normal	Normal	Normal	Regurgitant
Tricuspid regurgitation	No	No	No	severe
Left ventricle				-
Diastolic diameter (mm)	48	43	45	-
Systolic diameter (mm)	30	-	35	-
Δ diameters (%)	37	-	-	
LVEF (%)	-	69	44	Normal
Interventricular septum (mm)	7	9	-	-
Posterior wall (mm)	7	9	-	-
Mitral valve	Stenosis	Stenosis	Stenotic prosthesis	Prosthesis with decreased motion
Thickening	Yes	Yes	Yes	-
Fusion	Yes	Yes	Calcified	-
Valve area (cm²)	-	1,4	-	-
Transmitral gradient (mmHg)	-	16	17	30

The patient was diagnosed with hypertension and prosthesis degeneration with stenosis, and reoperation was indicated. The patient chose to wait and was treated with enalapril and hydrochlorothiazide.

One year later, the dyspnea was more intense and now triggered by moderate exertion (12/12/2003). Eight months later, it was even worse and occurring on milder than usual exertion for three months. Finally, she had dyspnea on minimal exertion, and sought medical care in the emergency department (11/08/2004).

On physical examination she had irregular pulse, 100 beats per minute, and blood pressure of 130/100 mmHg. Rales were heard on lung bases. A grade 1 systolic murmur was heard in the mitral area. Mild lower limb edema was observed.

Electrocardiogram (11/08/2004) showed atrial fibrillation and an inactive interventricular septal area. Echocardiogram (11/05/2004) showed moderate left ventricular systolic dysfunction, right ventricular hypertension, besides calcification and reduced motion of the mitral prosthesis (Table 1).

Hemodynamic study (11/09/2004) showed the following mean pressures: right atrium of 15 mmHg, right ventricle of 50/0/15, pulmonary trunk of 50/33/39, pulmonary "capillary" of 35 mmHg, left ventricle of 120/0/11 mmHg, and aorta of 120/80/93 mmHg. Coronary angiography showed an 80% obstruction in the distal third of the circumflex artery. Left ventriculography showed increased end-systolic volume due to an inferior aneurysm, which had an aspect suggestive of pseudoaneurysm. There was left ventricular dilation with mild diffuse hypokinesia, and mitral annulus calcification.

Dental evaluation revealed the presence of infectious dental foci, which were treated with periodontal subgingival scaling (11/11/2004).

Reoperation was indicated (11/12/2004). The Biocor 29 mitral bioprosthesis was thickened and ruptured, and was

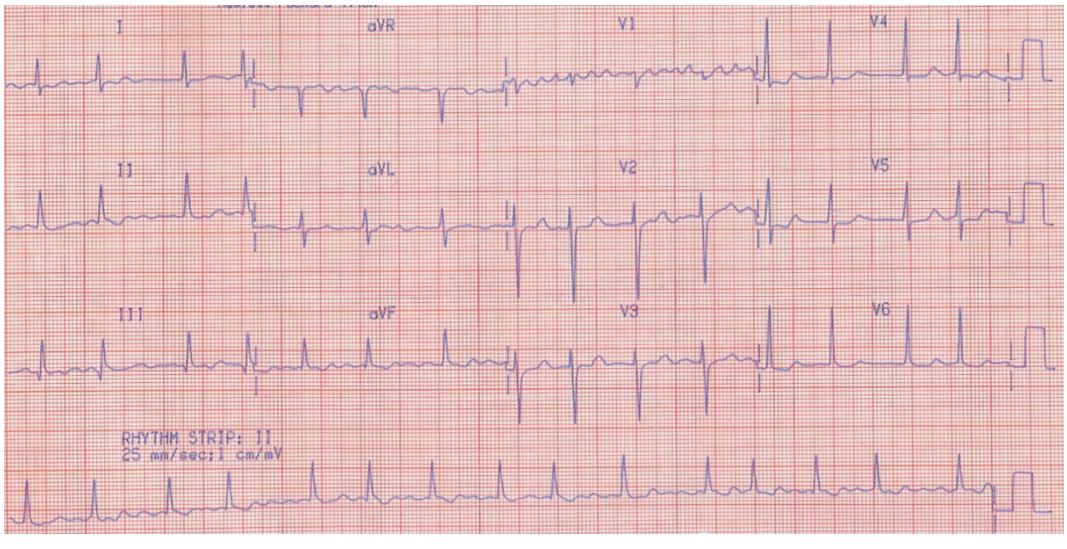

Figure 2 - ECG. Atrial fibrillation, decreased septal forces.

removed. A SJM 82569617 model 23MJ-501 mechanical prosthesis was implanted.

Pathological study of the bioprosthesis revealed dense calcification of the leaflets. Fragments of recent mixed thrombi were also sent for analysis.

The patient was discharged (11/22/2004) with warfarin.

One month later (12/22/2004) she returned to the emergency department due to hematuria and intestinal bleeding and was hospitalized in *Hospital Auxiliar de Cotoxó*. Abdominal ultrasound (12/23/2004) showed kidneys in normal position with no parenchymal abnormalities. INR reached 1.5 (12/28/2004), and the patient was discharged (12/29/2004).

The patient restarted the use of warfarin at daily doses of 5 mg.

In the follow-up clinical evaluation (02/15/2005) INR was 8.8. The warfarin dose was adjusted. No muffled sounds from the prosthesis were observed.

Seven months after the second operation, the patient presented dyspnea on minimal exertion, in addition to nausea, vomiting, orthostatic hypotension, episodes of chills and cough with white expectoration. She sought medical care in the emergency department (6/6/2005, at 9:25p.m.). She was taking enalapril 10mg, warfarin 5mg alternated with 2.5 mg, and propranolol 40 mg at daily doses.

On physical examination her heart rate was 136 beats per minute, blood pressure was 80/60 mmHg and respiratory rate was 18/min. The lung examination revealed rales on lung bases. Heart examination revealed a grade 2 systolic murmur and grade 2 diastolic murmur in the mitral area. Abdominal examination was normal, and no extremity edema was observed.

Electrocardiogram (6/6/2005) revealed atrial fibrillation, heart rate of 140 beats per minute, right bundle branch block and inactive inferior area (Figure 3).

Transthoracic echocardiogram (6/8/2005) showed normal left ventricular dimensions and normal systolic function, right ventricular dilation and hypokinesia, enlarged left atrium, severe tricuspid regurgitation and pulmonary hypertension (Table 1). Transesophageal echocardiogram revealed mean transmitral gradient of 30 mmHg, decreased excursion of the hemidiscs and presence of a large left atrial thrombus filling and lining the left atrium. No typical images of prosthetic valve thrombi were visualized.

The patient was started on oxygen via nasal cannula and received intravenous furosemide, deslanoside C, dobutamine, saline solution, intravenous amiodarone and heparin (5000 U, fast injection, followed by the administration of 1000 U/hour).

Laboratory tests revealed hemoglobin of 12.5 g/dL, hematocrit of 38%, platelet count of 177,000/mm^3, white blood cell count of 14,600/ mm^3 (80% bands, 13% lymphocytes, 1% eosynophils, 6% monocytes), BUN 63 mg/dL, creatinine 1.3 mg/dL, lactate dehydrogenase 327 U/L (reference value:120-240 U/L), total bilirubin 1.53, indirect bilirubin 122 mg/dL, direct bilirubin 0.31 mg/dL, troponin I 0.40 ng/mL, CK MB mass 2.8 ng/mL (normal values up to 4 ng/mL), sodium 137 mEq/L, potassium 4.7 mEq/L, INR 1.31, urinary sediment 37000 white blood cells/mm^3, 200 red blood cells/mm^3, 39600 hyaline casts/mm^3, activated partial thromboplastin time 3.1 (6/7/2007, at 4p.m.).

The patient developed progressive hypotension despite the support measures which included orotracheal intubation, and noradrenaline and fluid administration. Surgical treatment was considered but could not be performed because the patient was critically ill and died (6/8/2005).

Clinical aspects

This case reports a 58-year-old woman diagnosed with rheumatic mitral stenosis who underwent a second operation for implantation of a metallic mitral valve prosthesis and approximately seven months later developed significant dyspnea and refractory hypotension and eventually died on the third hospital day.

The first symptoms she presented at 34 years of age were pain, edema and functional impotence of the left foot which improved with the use of corticosteroids. Although these

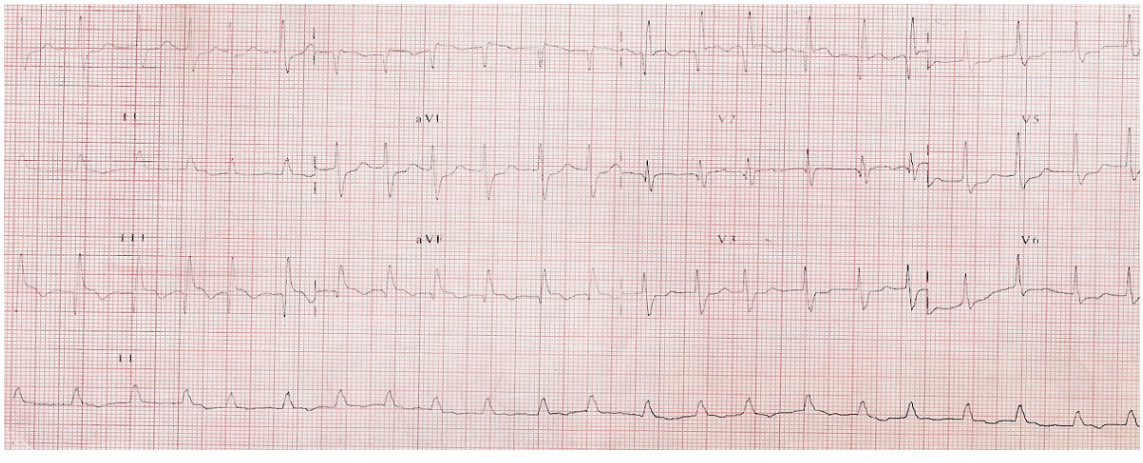

Figure 3 - ECG. Atrial fibrillation, right ventricular overload (right bundle branch block).

manifestations of arthritis may be suggestive of rheumatic disease, arthritis in rheumatic fever is classically defined as a migrating asymmetric polyarthritis affecting the large joints, with a significant disproportion between intensity of pain and functional impotence in relation to edema. It usually progresses without sequelae and is highly responsive to acetylsalicylic acid. However, like in the case reported, some patients present only joint pain affecting one or more joints, which makes the diagnosis difficult[1]. Additionally, the initial attack of the disease occurs most commonly between five and 15 years of age, and the incidence rate after streptococcal infection of the oropharynx ranges from 0.3-3%[2,3]. The manifestations presented by the patient may be consistent with recurrence of the disease, mainly because they had a late onset, out of the usual age range; only a few months later she developed cardiac symptoms, which usually take, on average, between 15 and 40 years to occur after the initial attack.

Recurrence is one of the remarkable characteristics of rheumatic heart disease. It is more frequent within the first three years after the initial attack, and the likelihood of the occurrence of valvular damage increases at every attack[1]. Therefore, all patients diagnosed with rheumatic fever should receive secondary prophylaxis with penicillin G benzathine at the dose of 1200000 IU, with varying frequency and duration, depending on the patient's age at the last attack and on the presence of carditis or valvular damage.

Four months after the initial manifestations, the patient sought medical care for dyspnea and palpitations on heavy exertion. Physical examination was significant for diminished S1 in the mitral area, with normal intensity of S2, systolic murmur (grade 1) and late diastolic murmur (grade 1), with apical impulse in its normal position.

This auscultation is consistent with mitral regurgitation and stenosis with predominance of stenosis. In mitral stenosis alone, we find the apical impulse in its normal position, accentuated S1 due to a sudden and wide closure of the valve cusps, and rumbling diastolic murmur between the apex cordis and the left sternal border, which is characterized by low intensity, presence of presystolic accentuation and opening snap. It is better heard with the patient in the left lateral position. In very advanced stenosis, due to intense cusp calcification with significant reduction of valvular motion, the first heart sound may become diminished and without an opening snap, and the presystolic accentuation may disappear because of the presence of atrial fibrillation (AF). Since this patient did not present signs and symptoms of severe stenosis, the finding of diminished S1 associated with systolic murmur is consistent with associated mitral regurgitation[4].

Baseline electrocardiogram showed intra-atrial conduction disturbance and P wave electric axis leftward deviation suggestive of left atrial overload. Later, the echocardiogram confirmed left atrial dilation and presence of mitral stenosis with commissural thickening and fusion (Table 1), which are marked characteristics of rheumatic involvement.

In Brazil, the major cause of mitral stenosis is rheumatic fever, and women are more frequently affected than men at a 2:1 ratio. Only 50% of the patients have a clinical history consistent with previous rheumatic activity[5]. The condition may remain latent for periods of up to 20 years, and the main clinical features are dyspnea, fatigue, exercise intolerance, palpitations, and embolic phenomena. Precipitating factors such as exercise, emotional stress, pregnancy, infection and hyperthyroidism may produce or aggravate pre-existing symptoms[6]. The severity of mitral stenosis may be classified according to the pulmonary artery systolic pressure (PASP), gradient and valve area in:

• *Mild*: when the valve area is greater than 1.5cm, the gradient is lower than 5mmHg, and PASP is lower than 30mmHg.

• *Moderate*: when the area is between 1.0 and 1.5cm, the gradient between 5 and 10mmHg, and PASP between 30 and 50mmHg.

• *Severe*: when the area is lower than 1.0cm, the gradient higher than 10mmHg, and PASP higher than 50mmHg.

Its progression is variable, with valve area losses of between 0.09 and 0.32cm^2/year as estimated by echocardiography[7].

The patient started outpatient follow-up and during the subsequent nine years we could observe the natural progression of the disease with development of AF – the most common complication in these cases, and progressive limitation on exertion. In 1991, when she was in functional class III, surgical treatment was indicated; this indication is the main decision to be made in the follow-up of these patients.

Even with awareness of the inexorable progression of mitral stenosis, maintenance of the native valve is always preferred. Medical therapy may postpone surgery, and the main drugs used are: diuretics for relief of the associated congestive symptoms; beta blockers; and calcium antagonists or digoxin for the control of heart rate and subsequent decrease of the transmitral gradient and pulmonary pressure in symptomatic patients[8]. Prevention of new attacks of rheumatic activity, endocarditis prophylaxis, advice for the practice of physical activity and anticoagulation in patients with atrial fibrillation are also essential[1,7].

As regards surgical therapy, in brief, there are two possibilities: mitral commissurotomy (surgical or using balloon catheter) and valve replacement. Balloon valvotomy is indicated in patients with symptomatic moderate/severe mitral stenosis with no contraindication (mitral regurgitation, left atrial thrombus, unskilled medical team), and favorable morphology (echocardiographic score < 9). It should also be performed in apparently oligosymptomatic patients with mitral stenosis if they present pulmonary hypertension, if planning pregnancy or when a major surgery is required. Valve replacement, in turn, is indicated in symptomatic patients with moderate/severe mitral stenosis or with pulmonary hypertension and unfavorable morphology or other contraindications for valvotomy[1,7].

The patient's laboratory tests by the time of surgery were not available, but she was already in functional class III and, therefore, with indication for surgical intervention, which was performed in 1993 with bioprosthesis implantation. She remained asymptomatic until 2001, when she developed dyspnea on exertion again, and a grade 4 diastolic murmur was heard in the mitral area. A presumptive diagnosis of degeneration of the stenotic prosthesis was made and confirmed by echocardiography, which showed a calcified valve with very reduced motion and central regurgitation.

This is the main limitation of bioprostheses which, despite the low thrombogenicity, good hemodynamics, easy implantation and absence of noise, have short durability, related mainly to rupture and calcification, thus making the patient subject to several reoperations. Some data indicate that within a period of 10 to 15 years approximately 30% of the prostheses present flaws, and the younger the patient, the greater the likelihood of degeneration (in individuals younger than 40 years, the ten-year flaw rate reaches 40%)[6]. In 2004, when the patient already presented dyspnea on minimal exertion and significant pulmonary hypertension, she agreed on the repeat intervention.

A St. Jude Medical mechanical mitral prosthesis was implanted, and the patient was discharged on the tenth postoperative day. She was in good clinical conditions and was treated with warfarin. This bileaflet prosthesis belongs to the first generation of metallic prosthesis and was first used in 1977. Given its good hemodynamic profile and good durability and biocompatibility, it became used worldwide. In 2001, Remadi et al[9] published the results of a 19-year follow-up of 440 patients undergoing St. Jude metallic prosthesis implantation in the mitral position, and showed low rates of embolic events and no structural degeneration.

In 2006, the most recent American guideline on valvular heart diseases was published, demonstrating that anticoagulation in mechanical mitral valve, regardless of the type of prosthesis, should have a target INR between 2.5 and 3.5. Additionally, this guideline recommended the routine use of acetylsalicylic acid at a dose of 75-100mg in all patients, regardless of the presence of risk factors (class I).On the other hand, according to the guideline of the Brazilian Society of Cardiology, the use of aspirin is only recommended as class I if the patient presents risk factors for embolic events such as atrial fibrillation and ventricular dysfunction, or in the cases of thromboembolic event during adequate anticoagulation[7,10].

When we consider the history of atrial fibrilation, left ventricular dysfunction and the intraoperative finding of a large amount of thrombi, surgery could be considered of high risk for thromboembolic events and, therefore, aspirin in combination with warfarin would be indicated.

The first follow-up evaluation was made one month after hospital discharge due to bleeding events, which are the most frequently expected complication in the follow-up of these individuals. The risk of bleeding depends on several factors, the main of which are: intensity and duration of anticoagulation; combined use of aspirin; age greater than 65 years; and history of previous bleeding. Bleeding is classified as major if it is fatal, requires surgery or invasive procedures, blood transfusion, or when it involves the nervous system, eyes, joints or retroperitoneum. Any other bleeding is considered minor. The patient presented hematuria and intestinal bleeding which are considered minor forms of bleeding.

Three months after surgery, the patient presented excessive anticoagulation with INR of 8.8, however without hemorrhagic manifestations, and only the warfarin dose was adjusted. It is important to point out that the attempt to correct INR to therapeutic levels may bring INR to inadequately low levels and, thus, induce a transient state of hypercoagulability, which increases the risk of thromboembolic events. Therefore, as long as the patient does not present major bleedings, the use of intravenous vitamin K1 should be avoided. In this case, it would be correct to simply discontinue the medication in use for one to two days and then reduce its dose. Another possibility would be discontinuation of the drug for one day and administration of oral vitamin K1 at the dose of 1-2.5mg.

The events previously reported show how difficult it is to achieve proper anticoagulation in our population. In a previously mentioned study conducted in the French population, Remadi et al[9] found that the main complications were related to anticoagulation, both excessive and subtherapeutic. They demonstrated that 20% of the patients had persistently low levels of INR. A study conducted in Brazil in patients with heart valve disease showed that only 51.3% of the patients presented INR within the desirable range, and 37% had subtherapeutic levels[11].

Approximately seven months after surgery, the patient developed rapidly progressive dyspnea on minimal exertion and was admitted in the emergency department with hypotension (BP 80 X 60mmHg), tachycardia (HR of 136bpm) and pulmonary rales. Heart auscultation was significant for the presence of a systolic and diastolic murmur in the mitral area with no hepatomegaly or splenomegaly and no reference to fever or signs of endocarditis. Baseline laboratory tests showed hemoglobin of 12.5g/dL, leukocytosis without left shift (14500), mild alteration of renal function (creatinine 1.3 mg/dL), normal LDH and bilirubins, urinalysis showing a great amount of hyaline casts, and subtherapeutic INR, in addition to ECG with rapid response AF.

The relatively sudden onset of dyspnea associated with hypotension (shock) should lead to a presumptive diagnosis of complications related to the heart valve prosthesis. Prosthesis degeneration could be one of the causes of decompensation. However, the rapid progression of the symptoms and the excellent durability of the prosthesis tell against this diagnosis.

A second hypothesis is acute infective endocarditis with prosthesis damage and dysfunction. Endocarditis is a possible complication in the follow-up of patients with prosthesis and should be considered, mainly because of the heterogeneity of its manifestations and high mortality rate (around 40%). Approximately 25% of the cases occur in prostheses, and the incidence is especially higher within the first three months post-implantation, with an estimated risk of infection of 1% in twelve months and 3% in five years. In the present case, the symptoms occurred in the seventh month post-surgery, a period when the patient is subject to a phase of transition of the most frequent microbes, with predominance of coagulase negative *Staphylococcus* (30%-35%) and *Staphylococcus aureus* (10%-15%), followed by enterococci, fungi and streptococci. In view of the sudden onset of the manifestations, in the absence of symptoms of toxemia such as fever, malaise, anorexia, weakness, absence of signs of endocarditis and of consistent laboratory abnormalities, except for leukocytosis, this diagnosis was less probable[12].

A third hypothesis to be made is prosthetic valve thrombosis. The presence of risk factors for thromboembolic events

associated with the history of inadequate anticoagulation, as confirmed by the baseline INR of 1.3 (which is present in 70% of these cases), and the rapid onset of symptoms makes the diagnosis of prosthetic valve thrombosis more feasible for the present case. The test of choice for the case is transesophageal echocardiogram, which helps in the differential diagnosis and therapeutic management.

Approximately 36 hours after admission, a transesophageal echocardiogram was performed, and showed enlarged left atrium, right ventricular dilation and hypokinesia with increased systolic pressure and significant tricuspid regurgitation. Additionally, the study showed a mean transmitral gradient of 30mmHg, decreased hemidisc excursion and thrombus all over the left atrium.

Therapy with inotropic agents, diuretics and heparin anticoagulation was started unsuccessfully, and the patient had a progressive clinical deterioration and eventually died on the third day of hospitalization.

The incidence of prosthetic valve thrombosis ranges from 0.03% to 5.7% and depends on prosthesis type and location, and mainly on adequate anticoagulation[13]. The incidence in St. Jude metallic prosthesis is of 0.2% in the international literature. However, it is accompanied by high morbidity and mortality, thus requiring accurate diagnosis and early treatment.

Obstruction is more frequent within the first year after surgery, with a quite heterogeneous clinical presentation going from asymptomatic patients to extreme manifestations of cardiogenic shock. Most of the cases present with dyspnea on minimum exertion (46%). Frequently, systemic embolic events and acute pulmonary edema may be the first manifestations of the condition. Physical examination reveals a change in the pattern of murmur, and a characteristic muffled metallic sound, which is frequently noticed by the patients themselves[14].

The best ancillary test to confirm the diagnosis is transesophageal echocardiogram, which may show the presence of an obstructive mass and its characteristics (thrombus vs. pannus), evaluate their dimensions and quantify the hemodynamic effects of the obstruction.

The treatment of prosthetic valve thrombosis remains controversial, mainly due to the small number of cases in the literature and to the impossibility of conducting a prospective randomized study comparing surgical therapy with thrombolysis. In the American guideline published in 2006, surgery is the treatment of choice in patients with involvement of the left heart valves. Although thrombolysis is not contraindicated, recommendations for this treatment modality are still limited (class IIb)[15].

Surgery is indicated as the initial therapy of patients with left-sided prosthetic valve thrombosis in functional class III-IV or with large left atrial thrombi (class IIa). However, although considered the optimal treatment for these cases, surgery has frequently a high mortality rate. The main predictor of mortality is the patient's functional class at admission and the presence or absence of cardiogenic shock, with mortality rates ranging from 4.7% in patient in FC I-II, 17.5% in patients in CF IV, and up to 35% in patients critically ill as was the case of our patient[15].

Thrombolytic therapy is the alternative to surgical treatment. Thrombolysis in heart valve prosthesis was first reported by Luluaga et al[16] in, with the use of streptokinase in tricuspid valve prosthesis. Later, several reports of thrombolysis were made with varying success and complication rates.

The first review with approximately 200 cases of thrombolysis in left-sided prosthetic valves showed a success rate of 82%, embolic events in 12% (5%-10% stroke), mortality in 6%, and major bleeding in 5%[15]. In 2000, Gupta et al[17] published a series of 110 patients with prosthetic valve thrombosis with a success rate of 81.8%, partial improvement in 10% and failure in 8.2%. Embolic events occurred in 19.1% of the cases.

Roudaut et al's study[15] with 127 cases found full success in 70.9%, incomplete success in 17.3% and failure in 11.8% of the cases. Approximately 25% of complications were observed, with embolism rate of 15%, mortality of 12%, and major bleeding of 4.7%.

There is still no well-established indication for thrombolysis in left-sided prosthetic valves. According to the latest American guideline, it is considered class IIb therapy in patients with left-sided prosthetic valve thrombosis in FC I-II and small thrombus (there is no specification as to the size of the thrombus); in patients in class III-IV and small thrombus if surgery is considered of very high risk or is unavailable; and in patients in FC II-IV with large thrombus if surgery is of very high risk or unavailable. Conversely, thrombolysis is the treatment of choice in right-sided thrombosis (IIA)[13].

The major problem of thrombolysis is the lack of significant elements predictive of success and complication rates. More recent studies have attempted to find elements that could facilitate the optimal selection of patients eligible for thrombolysis. In 2004, Tong et al[18] published a study showing that performance of transesophageal echocardiogram for quantification of thrombus is an important predictor of post-thrombolysis success. For every 1-cm increase in thrombus size there was a 2.4-fold increase in the complication rate. Their study also showed that prior history of stroke was also an independent predictor of events, with a 4.5-fold increase in complication rates. The statistical analysis could establish a cut-off point of 0.8 cm for thrombus size, that is, thrombolysis was successful in patients with a thrombus smaller than this value[18]. The thrombolytic agents approved for prosthetic valve thrombosis are streptokinase (larger number of cases), rTPA, and urokinase, with a slight superiority of streptokinase and rTPA over urokinase. The recommended dose of streptokinase is 250000 IU intravenous bolus for 30 minutes, followed by 100000 IU/h. The infusion should be interrupted if hemodynamic improvement is not verified in 24 hours or when full improvement is observed, or else when the gradients return to baseline patterns, or when 72 hours of infusion are completed. After thrombolysis, the patients should be anticoagulated with heparin and later with warfarin.

Despite these consensus recommendations, it is up to the physician to analyze each case and define the best treatment for any given patient, considering the health service where they are being treated. In the case reported, both treatment options would be feasible, since cardiogenic shock could interfere with the surgical management due to the high perioperative risk, and thrombolysis could have high rates of embolism from the

large left atrial thrombus. Heparin use in these cases would have a IIb evidence if the patients were in functional class I/II and had small thrombus.

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• *Presumptive diagnoses*: prosthetic valve thrombosis with cardiogenic shock and, less likely, infective endocarditis with prosthetic valve dysfunction or degeneration.

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Coment on the echocardiogram

The transthoracic echocardiographic studies performed from 1981 to 1982 (there is no record of studies between 1982 and 1993, period in which the first cardiac surgery was performed) describe the natural progression over time of rheumatic heart valve disease with predominance of valve stenosis. These studies showed the rheumatic damage to the mitral valve, as echocardiographically demonstrated by images of mitral commissural fusion and thickening, increased mean transmitral gradient (16 mmHg), decreased valve area (1,4 cm^2) and hemodynamic implication of the heart valve disease (mild increase of the left atrial antero-posterior diameter: 42 mm). Disturbance of the atrial electrical activity was also observed, as demonstrated by the evidence of atrial fibrillation. The intraoperative findings in 1993 were consistent with the preoperative echocardiographic findings. An important finding was the presence of a great amount of thrombi in the left atrium.

During the follow-up, degeneration of the mitral bioprosthesis was observed, as demonstrated in the transthoracic echocardiogram of 2004, which revealed an image of prosthesis calcification, reduced leaflet motion, and mild central and periprosthetic regurgitation. Significant pulmonary hypertension (systolic pulmonary pressure of 70 mmHg), increased mean transprosthetic gradient (17 mmHg), mild left ventricular dysfunction (ejection fraction measured by the Teichholz method of 44%, normal value > 55%), and moderate left atrial enlargement (46 mm) were also demonstrated. The intraoperative finding of 2004 showed rupture of the leaflets of the mitral bioprosthesis, and the pathological study showed "dense" calcification of the prosthesis leaflets and the presence of "newly formed fragments of mixed thrombi". During the follow-up after implantation of the mechanical prosthesis, the patient developed hemodynamic instability, and the transthoracic echocardiogram of June 2005 demonstrated right ventricular hypokinesia and right ventricular systolic pressure of 60 mmHg. She underwent transesophageal echocardiography which showed the image of a large left atrial thrombus, decreased excursion of the prosthetic discs, and very high mean transprosthetic gradient (30 mmHg). These findings are consistent with prosthetic valve thrombosis, despite the description of non visualization of "images typical of thrombi on the prosthesis". Right ventricular dysfunction also translates into the possibility of the occurrence of pulmonary embolism within the anatomic and clinical context of mechanical prosthetic mitral valve thrombosis, atrial fibrillation, presence of a large left atrial thrombus, and inadequate anticoagulation.

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Necropsy

At necropsy, the heart weighed 694g and had a large thrombus adhered to the left atrial lateral wall and roof (Figure 4). Small peripheral thrombi on the hemidiscs of the mechanical prosthesis were also found, but they apparently did not cause hemidisc motion restriction, based on the test performed at necropsy. The thrombus entered into the left pulmonary vein ostia (Figure 5). A small orifice on the atrial endocardial surface was also observed, communicating the atrial cavity with the remainder of the left atrial appendage. No thrombosis was found inside this atrial appendage. The aortic valve showed mild commissural fusion between the non-coronary leaflet and the right coronary leaflet, in addition to mild diffuse thickening. The right ventricle was enlarged, and a 1-cm fibrous scar with mild tapering was observed in the left ventricular diaphragmatic wall (Figure 6). Histological study showed that the major part of the thrombus was recent. However there were signs of organization (newly-formed vessels) on its base; therefore, the thrombosis was old (at least more than four weeks of onset) (Figure 7).

Histologically, the lungs showed marked chronic passive congestion, mainly on the left, where thrombi were observed into the vein ostium. Hemosiderin-laden macrophages were observed inside the alveoli (heart failure cells). Interlobar veins and venulae had thickened walls and sometimes their lumens were occluded by fibrosis (Figure 8). The vascular involvement extended to the arterial territory, with marked hypertrophy of the tunica media of the intra and pre-acinar vessels and intimal fibrosis (Figure 9).

No signs of recent or previous systemic embolism were found in the other organs. Hepatic steatosis and chronic

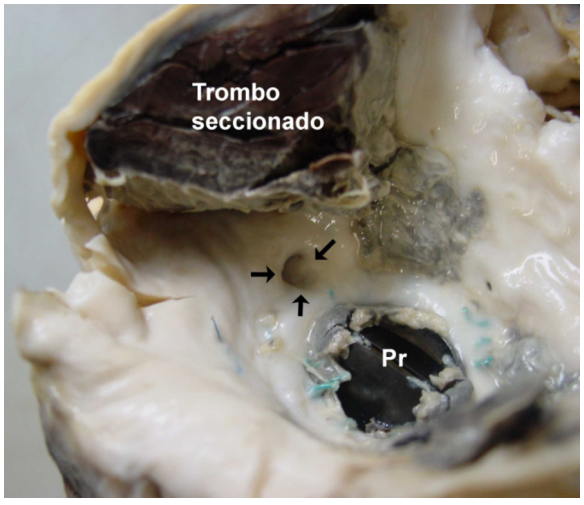

Figure 4 - Open left atrium showing thrombus (sectioned) occupying a large part of the cavity. Small thrombi are observed in the periphery of the mechanical prosthesis (Pr) discs. Arrows indicate the orifice communicating the atrial cavity with the partially ligated atrial appendage.

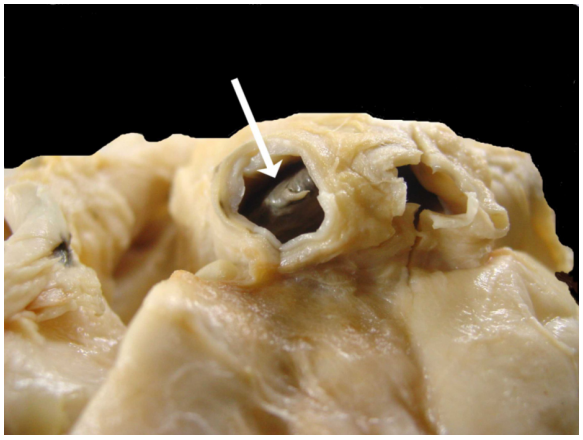

Figure 5 - *External view of the left atrial roof with upper pulmonary vein ostium partially occluded by thrombus (arrow).*

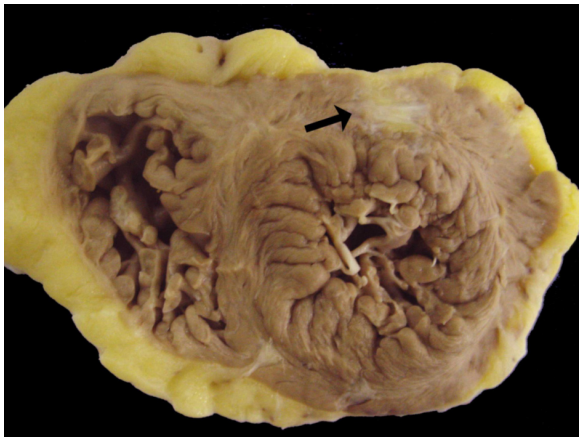

Figure 6 - *Cross section of the ventricles showing fibrosis at the left ventricular diaphragmatic wall (arrow).*

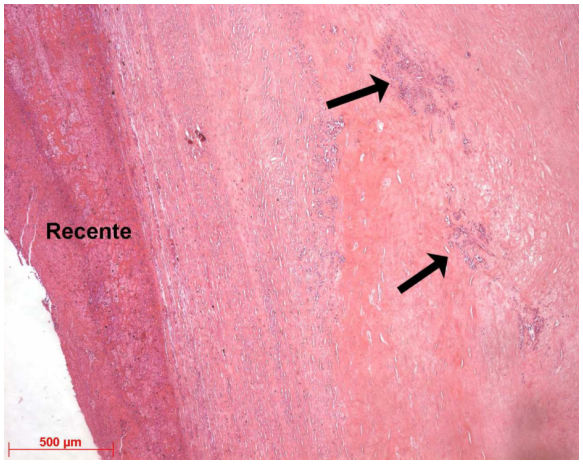

Figure 7 - *Microphotography of the base of the atrial thrombus implantation. On the surface, a recent thrombus (recente) can be observed and, deeper, there are signs of organization (newly-formed vessels – arrows). Hematoxylin and eosin staining, 5X magnification.*

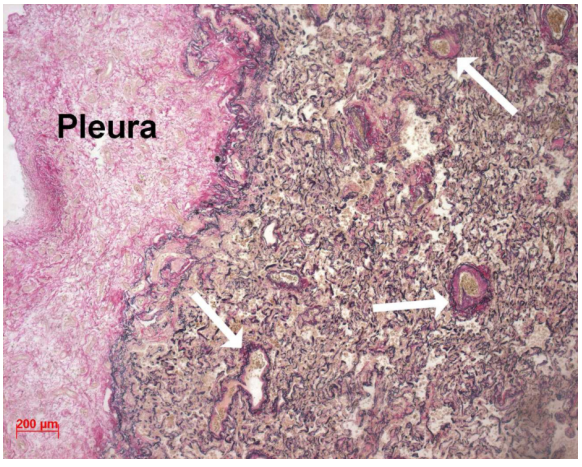

Figure 8 - *Microphotography of the lung showing venulae with thickened walls due to chronic passive congestion. The pleura shows fibrous thickening. Miller's staining for elastic fibers, objective magnification- 5X.*

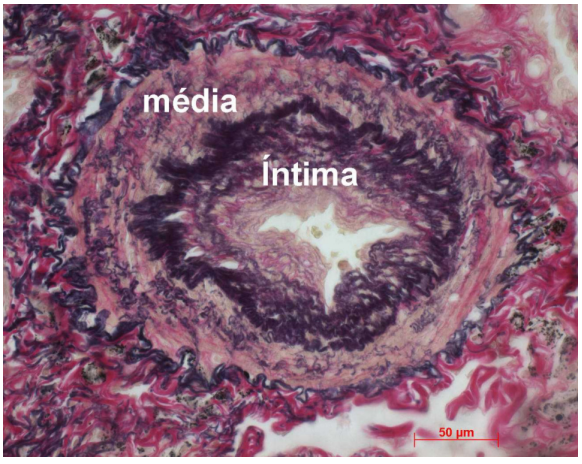

Figure 9 - *Microphotography of a pre-acinar pulmonary artery with marked hypertrophy of the medial layer and fibrous thickening of the intima. Miller's staining for elastic fibers, objective magnification- 40X.*

calculous cholecystitis were present.

Dra. Vera Demarchi Aiello

• *Pathological diagnosis*: cardiogenic shock due to extensive left atrial and pulmonary vein thrombosis.

Comments

The role of atrial appendage exclusion in the prevention of thrombotic events in patients with mitral valve disease is controversial in the literature. Some statistical data demonstrate that the patency rate of the communication between the atrial cavity and the appendage reaches more than one third of the cases. These communications would produce a turbulent blood flow which would increase the likelihood of local thrombosis[19]. In the present case, thrombosis was not

related to the communication described. Additionally, in a case series with a mean follow-up of 3.6 years of 136 patients undergoing atrial appendage exclusion during mitral valve surgery, some authors demonstrated that the rate of atrial thrombosis was 12.3%, and was higher in patients who did not receive warfarin[20].

Our attention was drawn to the fact that the patient presented atrial thromboses in different periods of the follow-up but nevertheless did not present systemic thromboembolism. The myocardial scar in the diaphragmatic wall may have been a consequence of embolism. However, we cannot fully rule out the possibility of ischemia secondary to an obstructive lesion of the distal circumflex coronary artery.

Another aspect to be discussed is the intensity of the morphological abnormalities resulting from passive pulmonary hypertension. They tend to be more severe in younger patients[21], and are seldom irreversible from the histological point of view (plexiform or dilated lesions). In the present case, the vascular lesions were qualitatively severe and undoubtedly contributed to the progression of the case.

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