Case 2/2008 – A 43-year-old man with hallucinations, nuchal rigidity, seizures, and severe aortic valve dysfunction

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A 43-year-old black male patient from Campinas, São Paulo, was admitted in a state of lethargy, presenting hallucinations and seizures for approximately 12 hours and a past history of systemic hypertension and rheumatoid arthritis.

On physical examination he was dehydrated, febrile, sweaty, and pale. His blood pressure was 90x60 mm Hg, heart rate 120 bpm, respiratory rate 34 brpm, and capillary blood glucose 93 mg/dl. Cardiac auscultation revealed a harsh, systolic murmur +++ over the aortic area radiating to the neck and a blowing diastolic murmur ++, also over the aortic area. Neurological examination showed nuchal rigidity but was otherwise normal, and the hands had deformities suggestive of rheumatoid arthritis.

The patient's fever persisted, and on the 5th day he progressed with worsening hypotension refractory to vasoactive drugs. The cause of death was attributed to septic shock.

Laboratory tests are shown in tables 1 and 4. Both blood and cerebrospinal fluid (CSF) cultures were positive for *Staphylococcus aureus*. Cerebrospinal fluid was xanthochromic and clear, with RBC of 145/mm^3, WBC of 75/mm^3 (40% neutrophils and 60% lymphocytes), chlorine 134 mEq/l, glucose 25 mg/dl, and protein level 89.6 mg/dl.

A plain chest X-ray showed mediastinal widening (Fig. 1) consistent with thoracic aortic aneurysm. A chest CT scan was performed, revealing ascending aortic aneurysm, with aortic dissection from the origin of the ascending segment to the lower third of the descending segment (Fig.2). No ECG changes were found. Echocardiograms were not performed due to technical difficulties.

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Clinical features

In addition to hypertension and autoimmune disease, namely rheumatoid arthritis (RA), this patient had valvular heart disease and aortic wall abnormalities, features associated with acute neurological condition.

This may be attributed to a rheumatic aortic valve disease, with a completely dysfunctional aortic valve, in addition to bacterial endocarditis and septic embolism, which could explain the neurological condition.

Table 1 - Platelet count, complete blood count, and platelet count

Analysis	Result	Unit of measurement	Normal range
Prothrombin time (PT)	18.0	sec	
INR	1.59		1.0 to 1.25
Testemunho (TPAP)	12.6	sec	
APTT ratio,pac/test	0.86		1.00 to 1.25
RBC	4.29	mil/mm^3	4.3 to 5.9
Hemoglobin	12.2	g/dl	13.3 to 17.7
Hematocrit	35.8	%	40 to 52
WBC	17.30	K/mm^3	4 to 10
Band neutrophils	2768	/mm^3	Up to 1,000
Band neutrophils (%)	16	%	
Segmented neutrophils	12110	/mm^3	1,800 to 7,000
Segmented neutrophils (%)	70	%	
Eosinophils (%)	00	%	
Basophils (%)	00	%	
Lymphocytes (%)	12	%	
Monocytes (%)	02	%	
Platelets	57	K/mm^3	140 to 400

Table 2 - Blood gas analysis

Analysis	Result	Unit of measurement	Normal range
pH	7.405		7.39 to 7.44
pCO_2	16.4	mm Hg	35 to 40
pO_2	74.1	mm Hg	95 to 100
HCO_3	10	mmol/L	19 to 24
O^2 total content	10.5	mmol/L	8 – 11
Base excess	-12	mmol/L	-3.3 to +1.2
SaO_2	94.2	%	94 to 100

Key words

Arthritis, rheumatoid; autoimmune diseases; aortic valve/abnormalities.

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Table 3 - Biochemistry

Analysis	Result	Unit of measurement	Normal range
Creatinine	2.2	mg/dl	0.7 to 1.2
Potassium	3.4	mEq/l	3.6 to 5.2
Sodium	153	mEq/l	136.0 to 142.0
Urea	135	mg/dl	10 to 50

Yet, how to explain the aortic dissecting aneurysm? It is known that some patients may develop dilation of the ascending aorta due to the aortic valve stenosis itself, particularly in the presence of wall abnormalities. As this patient has an autoimmune disease, there may be a change in collagen content of the aortic media, thereby favoring its dilation and delamination, a process that can be aggravated by high blood pressure.

Another hypothesis to be considered is that the primary disease was that of the aorta, with the presence of a dissecting aneurysm and thrombosis of the false lumen. Accordingly, aortic dilation would account for the diastolic murmur, while thrombosis would account for the systolic murmur. The most likely diagnosis in this case is cystic medial degeneration (CMD), since few cases of aortitis have been reported as an extra-articular manifestation of rheumatoid arthritis (RA). It is noteworthy that, in some cases, computed tomography (CT) does not allow discrimination between isolated dissection and that with thrombosis.

CMD, or Erdheim disease, is characterized by a noninflammatory process with loss of smooth muscle cells, fragmentation of elastic fibers, basophilic collagen degeneration, and accumulation of mucoid material within the aortic media. However, infectious diseases, atherosclerosis, and connective tissue disorders, such as Marfan and Ehlers-Danlos syndromes, may result in the same histological changes described earlier.

The diagnosis of Marfan syndrome is unlikely, because this is an autosomal dominant disorder of connective tissue that affects not only the cardiovascular system (aortic aneurysm and mitral valve prolapse) but also the eyes, muscles, and skin.

Echocardiogram is a valuable tool in the differential diagnosis of valvular heart disease, because although rheumatic disease is a common cause of valvular disease in Brazil, it is essential to bear in mind congenital diseases,

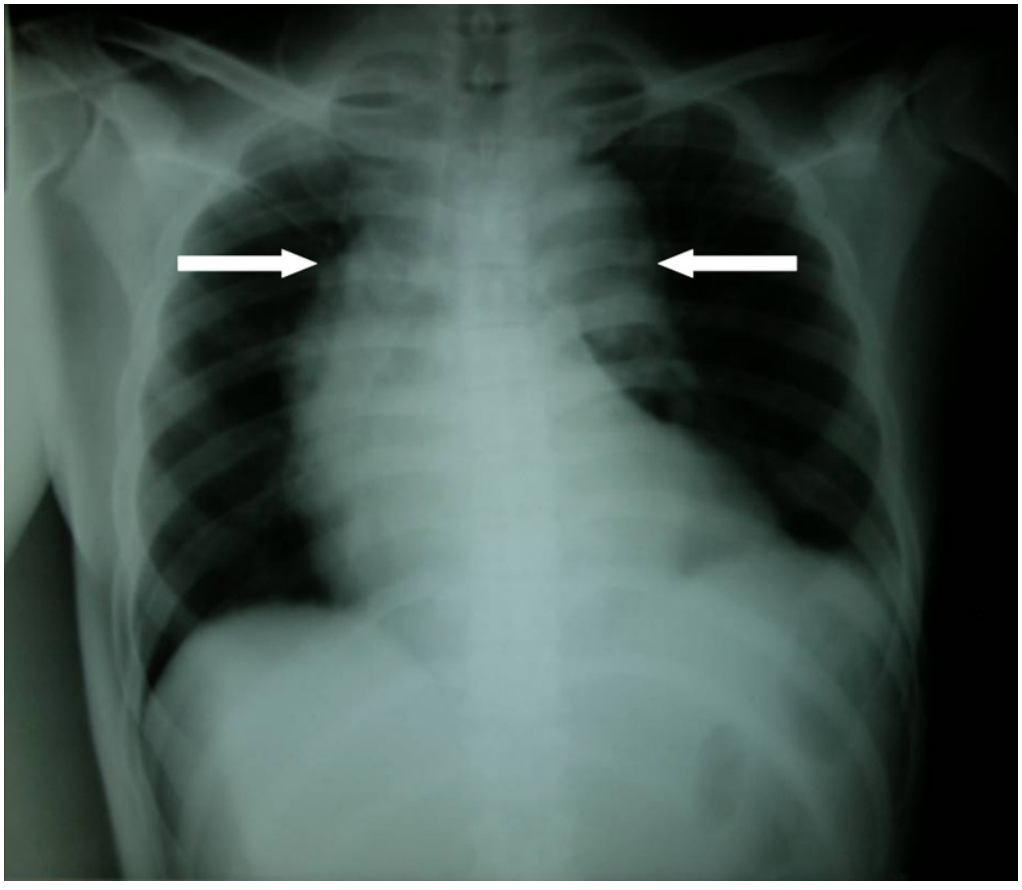

Fig. 1 - Plain chest X-ray showing mediastinal widening (arrow) suggestive of thoracic aortic aneurysm.

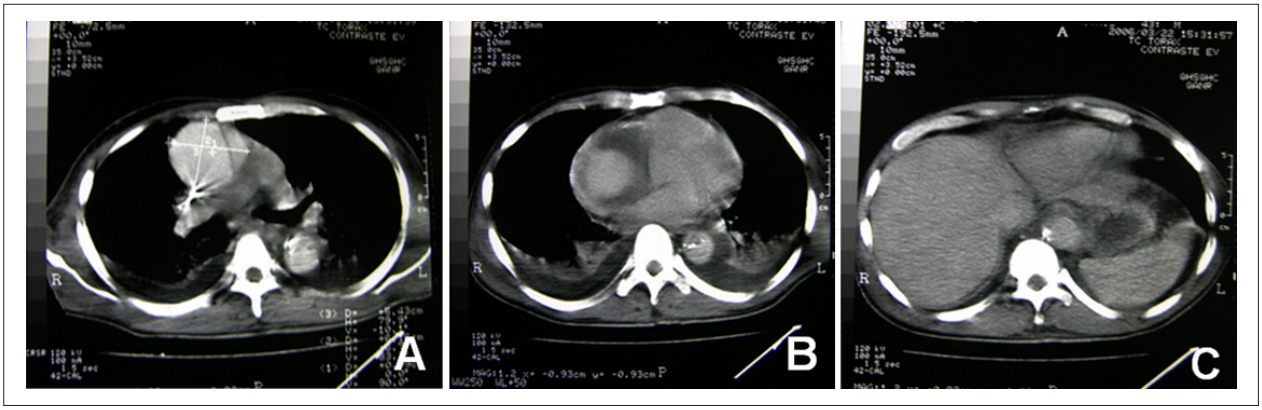

Fig. 2 - Chest CT scan revealing (A) ascending thoracic aortic aneurysm, with aortic dissection extending from the origin of the ascending segment to the thoracic aorta (B) to the lower third of the descending segment (C).

such as a bicuspid aortic valve, which is the most frequent congenital heart disease in adults, infective endocarditis and aortic dilation and dissection.

As stated previously, the neurological condition may be explained by septic emboli to the meninge and, thereby, nuchal rigidity from meningitis, since cerebrospinal fluid culture was positive for *S. aureus*, even with 60% of lymphocytes, and this could occur in a later phase of such infection.

Impaired consciousness could be secondary to the association of several factors, such as septic embolism, in addition to the toxic-infectious condition and metabolic acidosis.

Both blood and cerebrospinal fluid cultures were positive for *S. aureus*, a microorganism found in 10% to 27% of native-valve bacterial endocarditis that, most frequently, progress to sepsis, which may contribute to increased systemic inflammatory response and its complications.

This patient's death, therefore, may be attributed to septic shock and intracranial hypertension.

Diagnostic hypotheses: 1. bacterial endocarditis; 2. rheumatic aortic insufficiency; 3. bicuspid aortic valve; 4. aortic aneurysm and dissection; 5. cystic medial degeneration of the aorta; 6. acute meningitis; 7. systemic hypertension; 8. rheumatoid arthritis.

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Autopsy studies

After rib cage removal, the ascending aorta was found to be markedly dilated (Fig. 3). The right atrial cavity was reduced due to a bulging caused by the thrombosis in the ascending aorta, and a thrombus was adherent to the left atrial wall (Fig. 4). This thrombus, measuring approximately 4 x 3 cm, was not very friable and had a surface containing bacterial colonies on optical microscopy. The ventricles were sectioned into five slices, 175 g each, from the apex to the insertion of tricuspid and mitral valves. Histologically, myocyte nuclei were enlarged and hyperchromic, changes that are characteristic of cellular hypertrophy.

The aortic valve was bicuspid (fig. 5), and the coronary ostia were in the same Valsalsa sinus. Histological examination of this valve showed foci of predominantly neutrophilic inflammatory infiltrate, consistent with subacute infective endocarditis.

The aorta was opened, revealing the presence of two lumen it its ascending portion, which communicated with each other through an orifice of about 1,5 cm in its largest diameter, approximately 2 cm from the leaflets of the aortic valve (fig. 5). The ascending aorta was 6 cm in diameter and was adherent to both the right and left atrium by fibrosis. The false lumen was completely occluded by thrombosis, and the wall between both lumens was thickened.

Although no enlargement was found from the aortic arch, there was delamination, and the false lumen wall was also thickened, with thrombosis from the brachiocephalic trunk to the celiac trunk, sparing the mesenteric and renal arteries. Approximately 4 cm from the bifurcation of the iliac arteries, there was roughness, suggestive of inflammatory process, which was confirmed by microscopy. Histopathological examination of the aortic walls, both of the delaminated and non-delaminated regions, showed intimal thickening, in addition to fragmentation and tortuosity of elastic fibers, basophilic degeneration of collagen, and accumulation of mucoid material within the media (Fig. 6).

Postmortem studies also revealed septic emboli to the kidneys, spleen, brain, and meninge. Histopathological examination of several organs revealed changes typical of disseminated intravascular coagulation (DIC).

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Clinical comments

Bicuspid aortic valve (BAV) is one of the most common congenital heart diseases, affecting 1% to 2% of the population according to autopsy studies. However, prospective studies using echocardiography in children have shown an *in-vivo* prevalence of 0.5%, the prevalence in the general population being similar to that found in studies based on autopsy[1-8].

The earliest description of BAV was credited to Leonardo da Vinci, over 400 years ago, but the precise mechanism underlying its development has not yet been determined. Nevertheless, many authors believe that this malformation

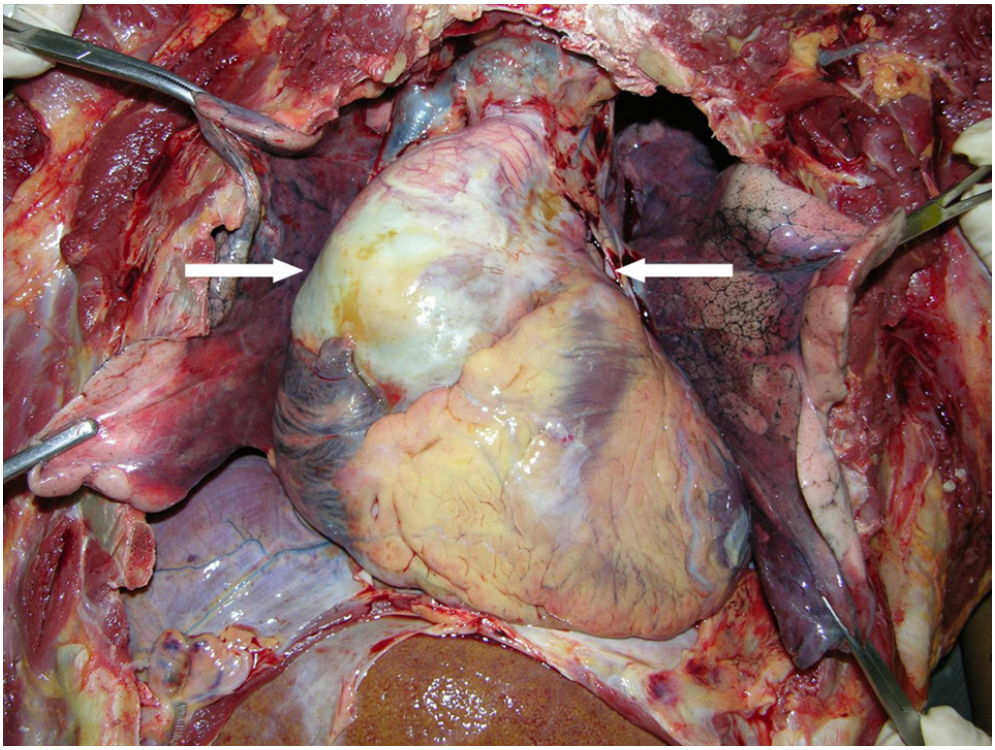

Fig. 3 - View of the corpse after removal of the rib cage and pericardium showing a markedly dilated ascending aorta (arrow).

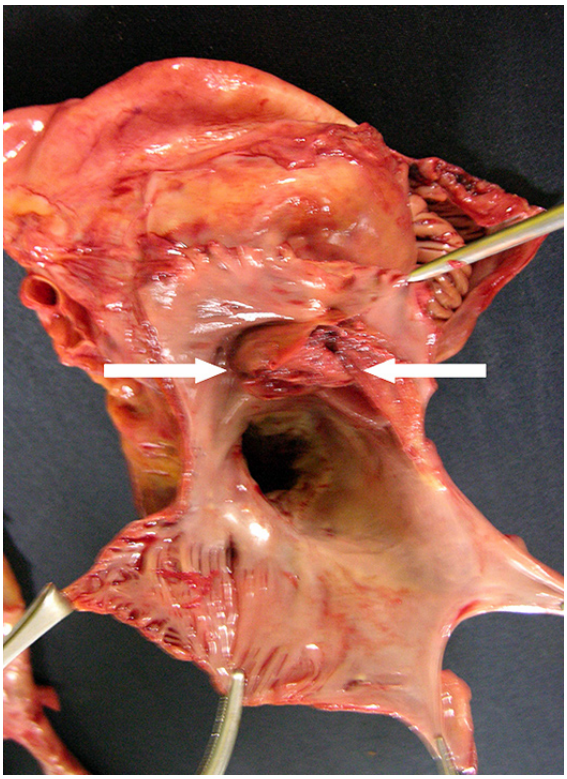

Fig. 4 - Left atrium with a friable thrombus measuring approximately 4 x 3 cm adherent to its wall (arrow).

results from a defect in neural crest-derived cells, since they are present in the aortic and pulmonary valve leaflets of the developing embryos[1,5,7].

Other authors suggest that BAV is a genetic disorder and describe cases in monozygotic twins or members of the same family. Among the latter, BAV prevalence ranges from 1% to 24% (mean 9%), showing an autosomal dominance inheritance with reduced penetrance[1].

Bicuspid aortic valve may be related or not to valvular heart disease (25%) with a high risk of developing bacterial endocarditis; in addition, it may be associated with aortic wall abnormalities, such as ascending aorta coarctation, dissection and dilation and aneurysm formation[1-3,5,6,8].

Aortic insufficiency is the most frequent dysfunction in BAV, and it is usually related to infective endocarditis (50%), while stenosis is associated with calcification. Aortic regurgitation in the absence of endocarditis occurs in 15% to 20% of BAV patients, 32% of whom have normal opening and closing of this valve, with this rate remaining relatively constant with increasing age[1].

Aortic dilation is the most common complication in BAV patients and may occur regardless of the valve functional status, despite being significantly more common in those with severe aortic regurgitation. In autopsy studies and surgical pathology specimens, the presence of dilation or aneurysm of the proximal thoracic aorta was found in 10% to 35% of the patients. Echocardiographic examinations, however, show dilation in 50% to 70% of adult BAV patients without valvular dysfunction[1,2,6,8].

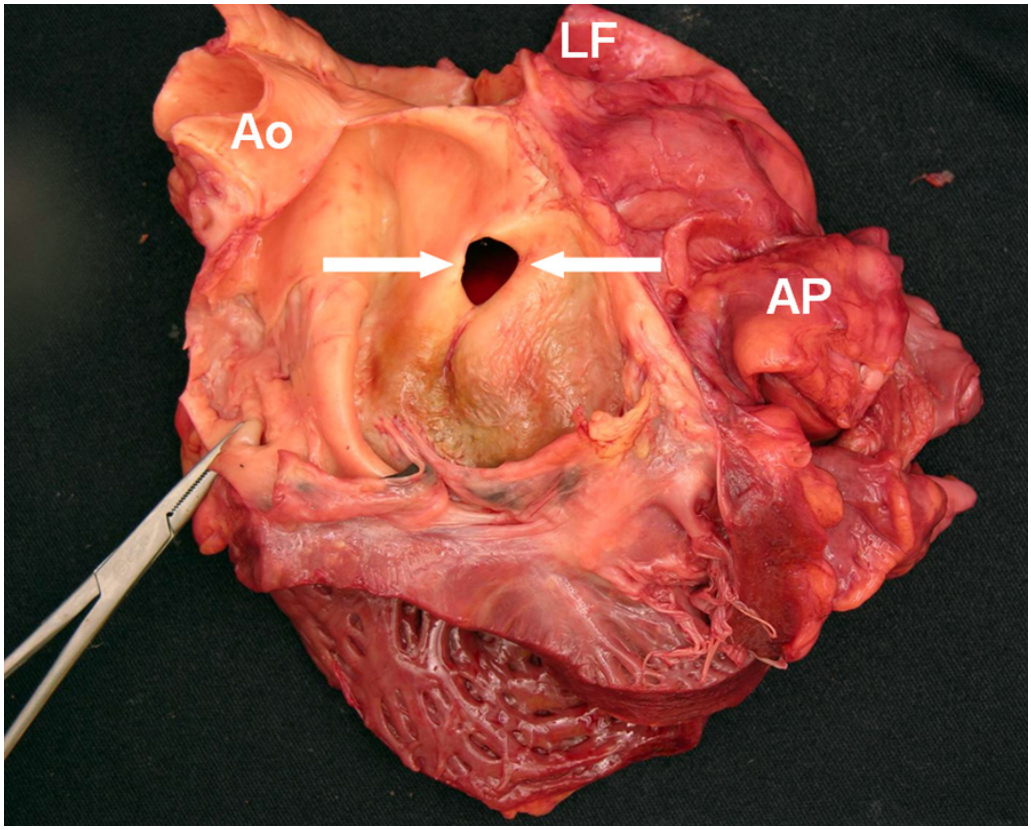

Fig. 5 - Aorta (Ao) and left ventricle showing a bicuspid aortic valve and an orifice of 1.5 cm (arrow) communicating with the false lumen (FL).

Aortic dissection may be a complication of BAV, regardless of the association with coarctation of the aorta and arterial hypertension. It was first described by Abott, in 1927 apud Braverman e cols.[1]. In 1984, Larson and Edwards apud Braverman e cols.[1], identified BAV as an important risk factor for dissection, based on clinicopathological studies. In the International Registry of Aortic Dissection, BAV accounts for 9% of the cases, and only 1% of the patients were older than 40 years. In clinical and autopsy studies, aortic dissection as a complication of BAV may represent 7% to 28% of the cases[1,4,7-9].

The literature is controversial as to whether aortic dilation, dissection and aneurysm are hemodynamic complications of BAV or associated changes, because of the presence of the same congenital and/or genetic defect[2,3,6,7,10].

A number of studies show aortic wall abnormalities, regardless of BAV function and whether or not dilation is present, and this may be explained by the aortic arch and aortic medial layer having the same embryological origin: the "conotruncus". An abnormal migration of neural crest cells may be responsible for the combined changes in the ascending aorta and aortic valve[1,3].

The histopathological changes in the media of the ascending aorta that may be present are as follows: cystic medial necrosis; elastic fiber fragmentation; medionecrosis; fibrosis; changes in smooth muscle cell orientation; loss of smooth muscle cells; basophilic degeneration of collagen; and accumulation of mucoid material between its fibers. Depending on the populations studied and also on whether the study was performed using necropsy or surgical specimens, these changes may show a varying degree of involvement[1-3,5,7,10].

Two mechanisms are involved in these changes: (1) an increase in the apoptotic index of smooth muscle cells, and (2) vascular matrix remodeling: increased activity of matrix metalloproteinase leads to protein degradation in the aortic wall, reducing fibrillin-1 microfibrils[1,5,10].

Our patient was asymptomatic, as are most cases found in the literature, and, in addition to the aneurysm, he had chronic aortic dissection with thrombosis of the false lumen. Such an association has not been described in the researched literature. The etiological agent of infective endocarditis was *Staphylococcus aureus*, which is present in 30% of the cases reported in the literature[1-10].

Histopathological changes found in the aortic wall were less severe than expected, namely, fiber fragmentation, basophilic degeneration of collagen, and small areas of deposition of mucoid material in the tunica media. The literature shows that no correlation exists between the magnitude of dilation and the presence of dissection with the number and degree of histopathological changes in the aortic media[7].

As our patient had hypertension and RA, the possibility that these conditions may have contributed to the aortic wall

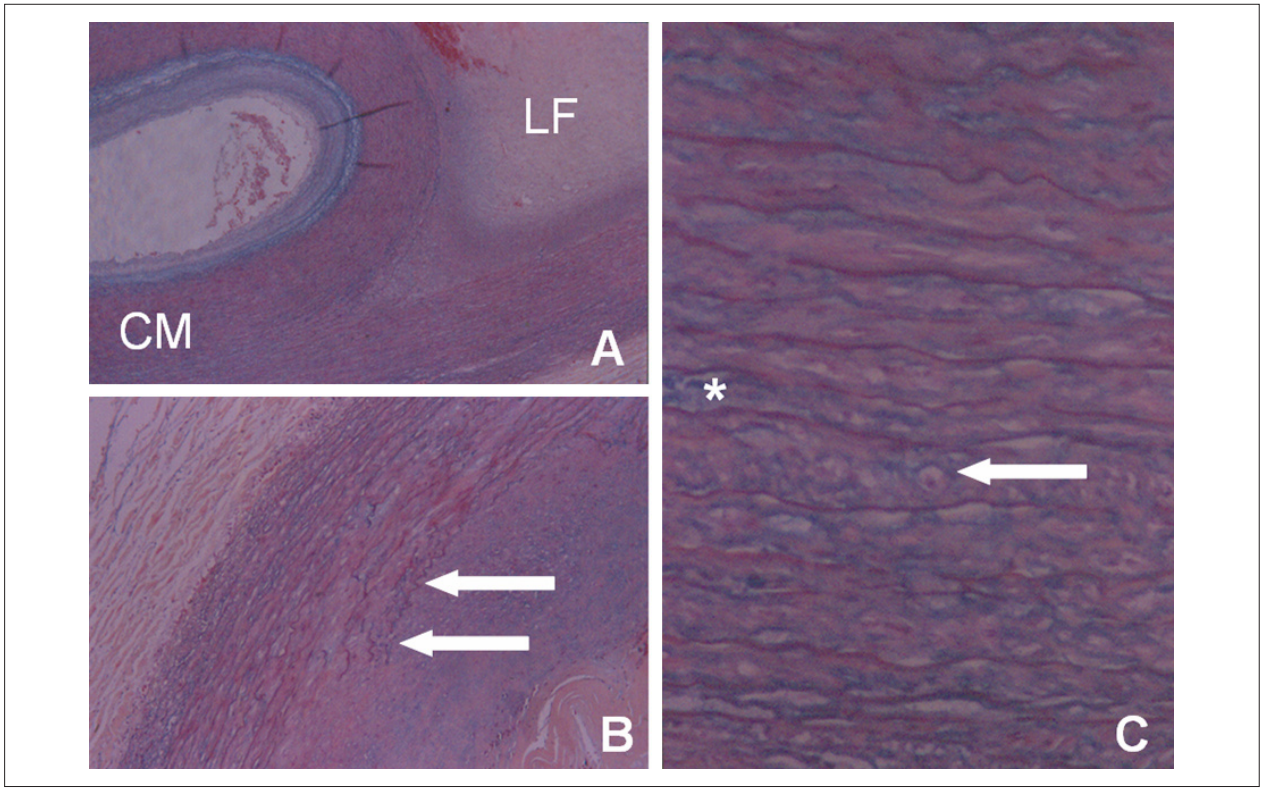

Fig. 6 - Photomicrograph (PMG) of the aortic wall using MOVAT staining: A - delamination and thickening of the medial layer (ML) in the false lumen, (x40); B - tortuosity and fiber fragmentation (arrow) in the medial layer (x100); C - basophilic degeneration of collagen (*), and small areas of accumulated mucoid material (arrow) (x400).

abnormalities cannot be discarded; however, as discussed earlier, these changes occur regardless of the presence of arterial hypertension, and there is no report in the researched literature about an association with RA, although there are cases of aortitis secondary to RA[11].

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Comments

Once again, autopsy studies not only enabled us to explain the patient's signs and symptoms, but also to check the accuracy of additional examinations. This would be an unnecessary comment were it not for the purpose of redeeming the value of *post-mortem* studies.

In regard to the BAV finding, the literature shows that two-dimensional echocardiogram has a sensibility of 78%, specificity of 96%, and predictive value of 93% for diagnosing this abnormality. Transesophageal echocardiogram is indicated when endocarditis and dissection are suspected[1,2]. It was not possible to demonstrate this correlation, since echocardiogram was not performed on our patient.

The absence of murmurs on cardiac auscultation of patients with BAV is common[9]. In our patient, the anatomical substrate for the systolic murmur was an orifice of approximately 1.5 cm in its largest diameter, located about 2 cm from aortic valve leaflets, since BAV was not stenotic. As for the diastolic murmur, it may have been caused by the dilation and inflammatory process found by microscopy, which may have contributed to the valvular insufficiency. The possibility of the patient already having aortic regurgitation cannot be discarded, since there was no knowledge of previous cardiac auscultation.

The diagnostic imaging modalities performed, namely plain chest X-ray and CT scan, adequately showed the presence of aortic dilation. CT scanning was interpreted as acute dissection, based on the different densities between the true and false lumen. This finding, however, contrasted with that of the autopsy study, which found chronic dissection by thickening of the false lumen wall. Microscopic examination revealed endothelization of the false lumen and calcified areas and fibrosis.

Left atrial thrombosis, an autopsy finding, may have been caused by aortic wall rupture into this chamber, since both structures were firmly and contiguously adhered. An acute inflammatory process with bacterial colonization was found in this thrombus, demonstrating that infective endocarditis extended to the atrial thrombosis. However, whether the primary focus was in the aortic valve or atrial endocardium is not known. Septic emboli to the myocardium, kidneys, spleen, meninge, and brain probably originated from this atrial thrombosis.

The patient's seizures and hallucinations may be explained by the brain involvement, as well as by metabolic acidosis

and sepsis caused by *S. aureus*, as stated previously.

There was no electrocardiographic substrate for the myocardial hypertrophy found at autopsy, since on microscopic examination this was detected only by nuclear enlargement and hyperchromatism.

The patient died of metabolic acidosis, sepsis, and disseminated intravascular coagulation, found in his kidneys and lungs, where the presence of hyaline membrane was also detected.

(Carlos Osvaldo Teixeira, M.D; Luciana Sacilotto, M.D)

Conclusion

Bicuspid aortic valve is recognized as a multifaceted congenital heart disease, since it is an autosomal dominant condition with incomplete penetrance and variable expression, therefore the family members should be investigated.

It is clear that BAV is an independent risk factor for ascending aortic aneurysm and dissection in young adults; thus the use of beta-blockers and serial echocardiograms is recommended for these patients[1,2,9]. Surgical correction should be tailored to each patient and discussed according to the degree of dilation, valve dysfunction, and the presence of acute dissection[1,2].

References

1. Braverman AC, Guven H, Beardslee MA, Makan M, Kates AM, Moon MR. The bicuspid aortic valve. Curr Probl Cardiol. 2005; 30: 470-522.
2. Cecconi M, Nistri S, Quarti A, Manfrin M, Colonna PL, Molini E, et al. Aortic dilatation in patients with bicuspid aortic. J Cardiovasc Med. 2006; 7: 11-20.
3. de Sa M, Moshkovitz Y, Butany J, David TE. Histologic abnormalities of the ascending aorta and pulmonary trunk in patients with bicuspid aortic valve disease: clinical relevance to the Ross procedure. J Thorac Cardiovasc Surg. 1999; 118: 588-96.
4. Roberts CS, Roberts WC. Dissection of the aorta associated with congenital malformation of the aortic valve. J Am Coll Cardiol. 1991; 17: 712-6.
5. Bonderman D, Gharehbaghi-Schenell E, Wollenek G, Maurer G, Baumgartner H, Lang IM. Mechanisms underlying aortic dilatation in congenital aortic valve malformation. Circulation. 1999; 99: 2138-43.
6. Nkomo VT, Enriquez-Sarano M, Ammash NM, Melton LJ3rd, Bailey KR, Desjardins V, et al. Bicuspid aortic valve associated with aortic dilatation. Arterioscler Thromb Vasc Biol. 2003; 23: 351-6.
7. Parai JL, Masters RG, Walley VM, Stinson WA, Veinot PG. Aortic medial changes associated with bicuspid aortic valve: myth or reality? Can J Cardiol. 1999; 15: 1233-8.
8. Keane MG, Wiegers SE, Plappert T, Pochettino A, Bavaria JE, Sutton MG. Bicuspid aortic valves are associated with aortic dilatation out of proportion to coexistent valvular lesions. Circulation. 2000; 102: III-35-9.
9. Burks JM, Illes RW, Keating EC, Lubbe WJ. Ascending aortic aneurysm and dissection in young adults with bicuspid aortic valve: implications for echocardiographic surveillance. Clin Cardiol. 1998; 2: 439-43.
10. Niwa K, Perloff JK, Bhuta SM, Laks H, Drinkwater DC, Child JS, et al. Structural abnormalities of great arterial walls in congenital heart disease. Circulation. 2001; 103: 393-405.
11. Hachulla E, Beregi JP. Diagnosis of aortitis. J Mal Vasc. 2001; 26: 223-7.