Case 1 – 59-year-old Male Patient with Severe Obesity, Arterial Hypertension and Heart Failure Submitted to Anticoagulation Therapy for Atrial Fibrillation, Presented Cerebrovascular Accident and Septicemia

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A 59-year-old obese male patient was admitted at the hospital with left hemiplegia. He had been first admitted at the age of 54, due to intense dyspnea and arterial hypertension.

He was diagnosed with arterial hypertension at 44 years, when he presented intense dyspnea and arterial hypertension with blood pressure (BP) levels of 220/120 mm Hg. He sought emergency medical care and was medicated. The patient evolved with dyspnea, intense sudoresis and retrosternal pressure, triggered by moderate exertion. His adherence to treatment was irregular. He started to present episodes of intense snoring during sleep and a sensation of suffocation upon awakening. The patient knew he had been obese since a young age, but his weight had progressively increased since the age of 48 years.

At physical examination (March 12, 2001) his weight was 163.8 kg, height 1.74 m, body mass index was 54.1 kg/m^2, pulse of 84 bpm, BP 200/110 mm Hg. Pulmonary assessment was normal. The ictus cordis was palpable at the 6th intercostal space, out of the left hemiclavicular line and the auscultation did not disclose any extra heart sounds. There was a systolic murmur ++/4+ in the mitral area and left sternal border. The abdomen was large and he presented an "abdominal apron", without visceromegaly. He presented slight lower-limb edema and decreased pulses in the lower limbs.

The chest X-ray (March 7, 2001) showed cardiomegaly +++/4+ with global heart increase. The electrocardiogram (ECG) (March 7, 2001) showed sinus rhythm, heart rate of 77 bpm, PR interval of 172 ms, QRS duration of 96 ms, QT interval of 372 ms, a QRS axis shifted (-30^0), initial notch with QS III wave and aVF, nonprogressive R wave from V1 to V3 and loss of potential in the left leads (Figure 1).

Key words

Obesity; hypertension; heart failure; stroke; sepsis.

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Laboratory assessment (March 8, 2001) showed hemoglobin = 14.4 g/dL, hematocrit = 43%, uric acid = 9 mg/dL, creatinine = 1.6 mg/dL, potassium = 4.4 mEq/L, sodium =145 mEq/L, fasting glycemia = 148 mg/dL, total cholesterol = 121 mg/dL, triglycerides = 57 mg/dL; urinalysis showed proteinuria of 0.25 g/L, with no other alterations. TSH was 5.28 U/mL, free T4 was 1.1 ng/dL, leptin was 31 ng/mL (normal range =3.8±1.8 ng/mL), testosterone = 336 ng/mL, FSH = 2.6 UI/L, LH = 2.0 UI/L, estradiol = 40.2 pg/mL, insulin = 7.9 UI/mL, urinary cortisol = 261 g/24 h and DHEAS = 1457 ng/mL.

The echocardiogram (April 26, 2001) showed septum and posterior wall thickness of 10 mm, aortic diameter of 32 mm, left atrial diameter of 52 mm, left ventricular (LV) diastolic diameter of 70 mm and LV systolic diameter of 57 mm, with ejection fraction of 46%, due to accentuated diffuse hypokinesis. The patient presented moderate mitral regurgitation.

The kidney ultrasonography disclosed normal-sized kidneys, both with 12.1 cm in length, whereas the liver showed signs of steatosis; there were signs suggestive of cholelithiasis.

The patient was medicated with 40 mg of enalapril, 40 mg of furosemide, 25 mg of chlorthalidone, 5 mg of amlodipine, 500 mg of methyldopa, 25 mg of spironolactone, 100 mg of acetylsalicylic acid and 1,700 mg of metformin daily, in addition to dietary recommendations of a low-salt, low-calorie diet for type II diabetes. The patient's adherence to treatment, together with dietary changes, resulted in a weight loss of 28 kg, symptom improvement and BP decrease to 150/90 mm Hg.

Three years later the patient weighed 149 kg and the BP was 180/130 mm Hg.

The fundoscopy showed retinal exudates in the temporal region, abnormal arteriovenous crossings with venous stasis and arterial reflex narrowing, compatible with hypertensive retinopathy.

Laboratory assessment (February 2004) showed cholesterol = 172 mg/dL, HDL-cholesterol = 41 mg/dL, LDL-cholesterol = 114 mg/dL, triglycerides = 87 mg/dL, creatinine = 1.1 mg/dL, urea = 29 mg/dL and glycemia = 126 mg/dL.

The metformin dose was increased to 2550 mg and the furosemide dose to 80 mg/day; the patient was then referred to bariatric surgery.

The patient evolved with few symptoms until April 2006, when he presented syncope and was admitted at the hospital

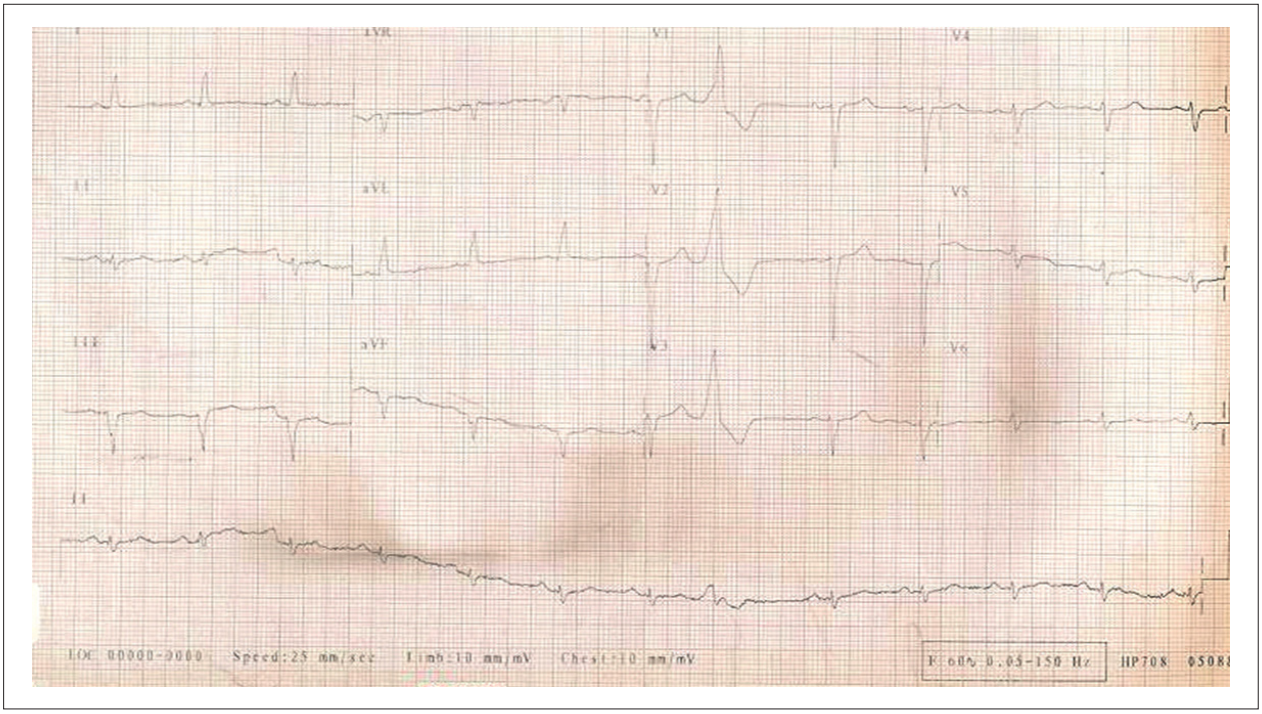

Figure 1 - ECG. Sinus rhythm, left axis deviation, electrically inactive area in the inferior wall.

close to his home; he was released with a prescription for 75 mg of captopril, 40 mg of furosemide, 0.25 mg of digoxin, 100 mg of acetylsalicylic acid and 5 mg of warfarin. One week after hospital release he started to present mental confusion, dysarthria, mouth deviation to the right and left hemiplegia and was brought to the hospital for emergency medical treatment (May 16, 2006).

The physical examination disclosed a sleepy patient, Glasgow 12/13, reactive pupils and no signs of meningeal irritation, with pulse rate of 100 bpm, BP of 130/80 mm Hg and left hemiplegia.

The ECG showed atrial fibrillation, mean heart rate of 142 bpm, with frequent ventricular extrasystoles, probable electrically inactive area on the inferior wall, decreased septal strength and left potential. The skull tomography revealed right parietooccipital hematoma and subarachnoid hemorrhage.

The prothrombin time (INR) was 12 and 5 units of fresh-frozen plasma were administered together with vitamin K (10 mg). Due to the coagulation alteration, a clinical treatment with dexamethasone and phenytoin was prescribed.

A new tomography (May 18) did not disclose significant alterations when compared to the previous examination.

On the third day of hospitalization (May 19), the patient presented worsening of the level of consciousness and the patient required orotracheal intubation for ventilator support. The neurosurgical intervention was considered once more.

The laboratory assessment (May 19) showed hemoglobin = 11.5 g/dL, leukocytes = 12000/mm3, platelets = 219000/3, creatinine = 0.8 mg/dL, INR = 1.94.

The patient was then submitted to intraparenchymatous hemorrhage drainage (May 20). The patient started to present fever and septic shock, attributed to bronchopneumonia, as a purulent secretion was drained through the endotracheal tube.

The patient presented fever (38.5°C) on May 20, 21 and 22 and received 4g of cefepime and 1 g of vancomycin daily from September 21 on.

Burkholderia cepacia was isolated from the blood culture (May 21, 2006), which was sensitive to ceftazidime, meropenem and sulfametoxazol/trimetoprim. The laboratory assessment disclosed leukocytosis and progressive worsening in renal function (Table 1). In spite of the use of vasoactive drugs and antibiotics, the patient did not improve and presented cardiorespiratory arrest in asystole, non-responsive to resuscitation maneuvers and died on May 22, 2006.

Clinical aspects

The present case reports on a 59-year-old male patient who had been obese since a young age and received a diagnosis of systemic arterial hypertension (SAH) at the age of 44 years, when he was admitted at the emergency service with intense dyspnea and BP of 220x120 mm Hg. Due to low treatment adherence, he started to present dyspnea at moderate exertion, accompanied by intense sudoresis and retrosternal pressure. At 54, when he was first admitted at the hospital, he presented a BMI of 54.1 kg/m^2, HR of 84 bpm, was once again hypertensive, with a BP of 200x110 mmHg and presented evidence of target-organ damage. He presented a dilated heart, disclosed by deviation of the ictus cordis in relation to the hemiclavicular line, palpable at the 6th intercostal space and a mitral regurgitation systolic murmur (+2/4). The cardiac area was enlarged at the chest X-ray

Table 1- Laboratory assessment

	21 May 2006	22 May 2006
Hemoglobin (g/dL)	10.7	10.8
Hematocrit (%)	33	37
Leukocytes (/mm3)	16,500	25,700
Band cells (%)		16
Segmented (%)		76
Neutrophils (%)	85	92
Eosinophils (%)	0	0
Basophils (%)	0	0
Lymphocytes (%)	9	4
Monocytes (%)	6	4
Platelets (/mm3)	129,000	232,000
Glycemia (mg/dL)	138	236
Creatinine (mg/dL)	1.3	2.4
Urea (mg/dL)		76
Potassium (mEq/L)	4.3	5.7
Sodium (mEQ/L)	142	141

(+3/4) and the transthoracic echocardiogram showed left ventricular dilatation with moderate dysfunction and diffuse hypokinesia and left atrial dilatation in addition to moderate mitral regurgitation, probably secondary to cardiac dilatation. Kidney damage was evidenced by proteinuria (0.25 g/L) and three years later the patient already presented hypertensive retinopathy characterized by retinal exudates in the temporal region, abnormal arteriovenous crossings with venous stasis and arterial reflex narrowing.

The factors that suggest that the patient's SAH was primary are: the late onset of the SAH, at 44 years and the fact that approximately 90% of the SAH cases are primary, according to the V Brazilian Guidelines of Arterial Hypertension[1] and The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure[2]. However, the patient's clinical history presents some elements that obligatorily suggest secondary causes of SAH, such as stage III arterial hypertension (characterized by systolic pressure ≥ 180 mm Hg and/or diastolic pressure ≥ 110 mm Hg) and episodes of intense snoring during sleep and a sensation of suffocation upon awakening, highly suggestive of sleep apnea/hypopnea syndrome, currently a known cause of secondary SAH. Nevertheless, an additional investigation must be carried out to confirm this diagnosis.

The patient, during his clinical history, presented a progressive dyspnea condition, until it was triggered by moderate exertion, as well as lower-limb edema and the echocardiogram showed systolic dysfunction; all of these signs suggested heart failure due to hypertensive cardiopathy. Corroborating this diagnosis, he presented stage III SAH that was difficult to control, SAH-related injuries in other target-organs, such as kidneys and retina, in addition to the absence of LV segmental involvement. However, the investigation of coronary artery disease (CAD) in this patient was quite deficient and it was not possible to rule out ischemia-related dilated cardiopathy. The reasoning for this statement is the fact that the patient presented many risk factors for CAD, among them: SAH and type II diabetes mellitus, as, according to the Consensus of the Brazilian Society of Diabetes[3] he presented two fasting glycemia levels ≥ 126 mg/dL (respectively, 148 mg/dL and 126 mg/dL); although he was not dyslipidemic, in the presence of diabetes his target-LDL should be at least ≤ 100 mg/dL, as recommended by the IV Brazilian Guideline on Dyslipidemia and Atherosclerosis Prevention of the Brazilian Society of Cardiology[4]; grade III obesity (body mass index ≥ 40 kg/m^2) and metabolic syndrome, in this case characterized by: abdominal circumference ≥ 94 cm, BP ≥ 130x85 mmHg and fasting glycemia ≥ 100 mg/dL, according to the criteria of the International Federation of Diabetes, published at the IV Brazilian Guideline on Dyslipidemia and Atherosclerosis Prevention of the Brazilian Society of Cardiology[4]. Other factors that support the reasoning for ischemic cardiopathy are the clinical history data, such as retrosternal pressure and dyspnea (ischemic equivalent), in addition to the electrocardiographic alterations, such as the electrically inactive region in the inferior wall and the poor R wave progression in the anterior wall.

The bariatric surgery was indicated during the patient's evolution. The current recommendations for this procedure, which were published at the Latin-American Obesity Consensus[5] are: BMI ≥ 40 kg/m^2 or BMI ≥ 35 kg/m^2 associated with a comorbidity, such as sleep apnea, type II diabetes mellitus, systemic arterial hypertension, dyslipidemia, difficulty in locomotion, among others. The patient must have at least 5 years of obesity evolution and the conventional methods of weight management carried out by qualified professionals must have failed. Therefore, the present case presented a solid indication for the bariatric surgery.

At 59 years, the patient had a syncope episode and needed to be hospitalized at another service. There is no report in the clinical history of the characteristics of the syncope, its investigation, or whether there was cranioencephalic trauma. Considering the medications given at the time of the hospital release, a diagnosis of a first episode of atrial fibrillation was attained during this hospitalization, as the patient was released anticoagulated on Warfarin and was also receiving digoxin for possible control of ventricular response. One week after the release he was brought back to the hospital with a neurological condition compatible with cerebrovascular accident. The ECG confirmed the finding of atrial fibrillation, in addition to a mean heart rate of 142 bpm, frequent ventricular extrasystoles, probable electrically inactive area in the inferior wall and decrease in septal strength and left potential.

The skull tomography showed parieto-occipital hematoma and subarachnoid hemorrhage. The prothrombin time at the admission was increased, with an INR of 12.

This patient, according to the Guidelines for the Management of Patients with Atrial Fibrillation of ACC/AHA[6], presented persistent atrial fibrillation (duration ≥ 7 days) and high risk for thromboembolic phenomena. There are several scores that attempt to predict the risk of thromboembolic phenomena in patients with nonvalvular atrial fibrillation.

Currently, one of the most often used is the CHADS2 score, which gives points to five risk factors for embolic events, as follows: heart failure, arterial hypertension, age ≥ 75 years, diabetes mellitus, cerebrovascular accident/ transient ischemic attack - the first four criteria receive one point each and the last criterion receives 2 points. It is accepted that patients with a score ≥ 2 must be anticoagulated.

The CHADS2 score of the present patient is 3 points and therefore, there is formal indication for the use of vitamin K antagonist. Nonetheless, it has been well documented in medical literature that anticoagulation with Warfarin presents a 2 to 5-fold increase in the risk of intracranial hemorrhage[7,8]. Half of the patients with brain hemorrhage due to Warfarin use die within 30 to 90 days of the event[9], which demonstrates the severity of this complication. High-risk factors for brain hemorrhage in anticoagulant users are: concomitant use of ASA, falls with head trauma, significant alcohol consumption, SAH, age ≥ 75 years, history of cerebrovascular disease, intensity of the anticoagulation, amyloid angiopathy, tobacco use and Mexican or Asian ethnicity[10,11]. However, according to some reports[12,13], the risk of subdural hematoma caused by falls in anticoagulated patients is so small that patients who present a 3-point CHADS2 score (risk of CVA 5%/year without anticoagulation) would have to fall 300 times during one year for the risk of anticoagulation to be higher than its benefit.

Our patient was receiving 100mg of ASA in association with Warfarin, was hypertensive, had a syncope one week before the cerebral hemorrhage and it was not clear whether there was brain trauma and presented an INR of 12 at the hospital admission. Therefore, he presented several risk factors for brain hemorrhage. Considering these aspects, which would be the mechanisms through by which the anticoagulants would increase the incidence of brain hemorrhage?

It is currently known that aging often causes small arterioles in the brain to become fragile and undergo rupture. Most ruptures form autolimited and subclinical bleeding foci, called microbleeds, which can be demonstrated in autopsies or through the use of specific sequences of magnetic resonance[14]. This phenomenon is quite prevalent in hypertensive patients and in individuals older than 75 years. Occasionally, the blood leak caused by this arteriolar weakness and rupture cannot be contained by hemostatic mechanisms and by the adjacent tissues, resulting in more severe bleeding with clinical implications. This is the physiopathology of spontaneous intracranial hemorrhage.

Anticoagulants increase the probability of these spontaneous ruptures becoming more severe bleeding episodes with clinical manifestations. In other words, anticoagulants disclose asymptomatic brain microbleeds, turning them into larger bleeds with obvious clinical signs. That is the reason why the high-risk factors for spontaneous intracranial hemorrhage are the same for bleeding due to the use of anticoagulants[15].

Another noteworthy fact regarding the patient's clinical history is the high levels of leptin in the blood. Leptin is a hormone secreted by the adipocytes, of which function is to produce the sensation of satiety, in addition to participating in the regulation of the body energy balance. In 1950, Ingalls and cols.[16] described a new species of mutant obese rats characterized by significant hyperphagia and decreased energy expenditure. Subsequently, it was described that the substance which was not produced by the ob/ob rats was leptin. It is currently known that the rise in serum leptin is common in obese humans and characterizes resistance to the leptin found in this population. This rise is associated with the syndrome of insulin resistance and thus, with cardiovascular diseases.

In 1999, Söderberg and cols[17] reported that plasma leptin is strongly associated with the increased risk of a first event of hemorrhagic cerebrovascular accident, regardless of other cardiovascular risk markers, with leptin being an important link in the development of cardiovascular diseases in obese individuals. Therefore, leptin resistance can be an interface of the metabolic deregulation with inflammation in the pathogenesis of obesity, its comorbidities and finally, of cardiovascular diseases.

After the brain hemorrhage, the patient developed intracranial hypertension syndrome, a lowering of the level of consciousness and needed orotracheal intubation. After the draining of the intraparenchymatous hemorrhage, he developed pneumonia associated with the mechanical ventilation, characterized by the purulent secretion through the cannula, fever and leukocytosis. The incidence of pneumonia associated with the mechanical ventilation described in the literature is 3%/day in the first week of intubation, 2%/day in the second week and 1%/day in the third week[18]; therefore, it is a quite common complication. On May 20, 2006, the patient was in septic shock due to pneumonia by *Burkholderia cepacia*, which rapidly developed into multiple-organ failure and death on May 22, 2006.

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Diagnostic hypothesis

Obesity grade III; primary and/or secondary SAH, due to possible apnea/hypopnea syndrome; type II diabetes mellitus; metabolic syndrome; subclinical hypothyroidism; hypertensive retinopathy; hypertensive dilated and/ or ischemic cardiomyopathy; persistent chronic atrial fibrillation; Warfarin intoxication; brain hemorrhagic syndrome; intraparenchymatous hematoma and subarachnoid hemorrhage with intracranial hypertension syndrome; and septic shock due to in-hospital pneumonia due to *B. cepacia*

Dr. Pedro Veronese

Necropsy

Cadaver of patient with severe obesity, presenting a recent surgical incision of right temporoparietal craniotomy. The heart was large and weighed 866 g, with hypertrophy and dilatation of the four chambers, with multiple small foci of interstitial fibrosis in both ventricles (Figure 2). Vegetation was found in the atrial region of the posterior cusp of the mitral valve, measuring 1.5 cm in extension, and in the semilunar cusps of the pulmonary valve (the largest measuring 0.8 cm), with the presence of numerous colonies of Gram-positive cocci (Figure 3). The heart valves did not show signs of rheumatic disease sequelae or evidence of any previous anatomopathological alterations. The epicardial coronary arteries presented slight atherosclerosis, as well as the aorta, with no obstructive lesions.

There were microabscesses and bacterial colonies in the myocardium, kidneys and spleen, with focal macroscopic infarctions in the latter two (Figure 4). The brain weighed 1,428 g and presented edema in the right hemisphere, in addition to extensive hemorrhagic infarction that affected the cortex and the white substance on this side and hemorrhage in the lateral ventricles (Figure 5).The histochemical screening for bacteria was negative in this organ. The lungs presented congestion, edema and areas of macrophage accumulation, containing hemosiderotic pigment in the alveolar spaces. The liver presented centrilobular sinusoidal dilatation, with areas of recent hemorrhagic necrosis. The kidneys presented foci of glomerular sclerosis and interstitial fibrosis. There were large greenish calculi in the gall bladder, which measured 1 to 2 cm each.

Dr. Luiz Alberto Benvenuti

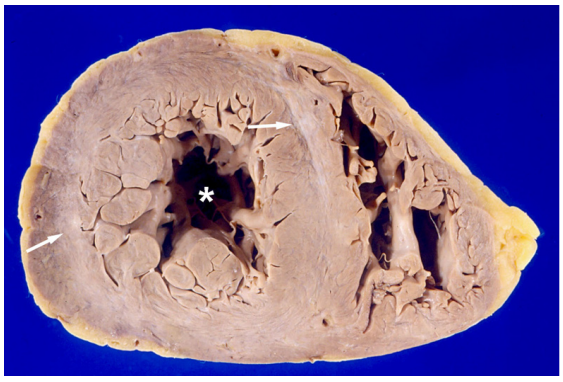

Figure 2 - Cross-section of the heart showing LV hypertrophy, with moderate dilatation of the cavity (asterisk) and areas of myocardial fibrosis, characterized by the whitish color (arrows).

Anatomopathological diagnoses

Morbid obesity; systemic arterial hypertension; diabetes mellitus; cholelithiasis; hypertensive cardiopathy at dilated phase; infectious endocarditis of the mitral and pulmonary valves; hemorrhagic brain infarction; septicemia (cause of death).

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Comments

The present case describes a 59-year-old male presenting morbid obesity as the main disease, accompanied by systemic arterial hypertension, diabetes mellitus and cholelithiasis,

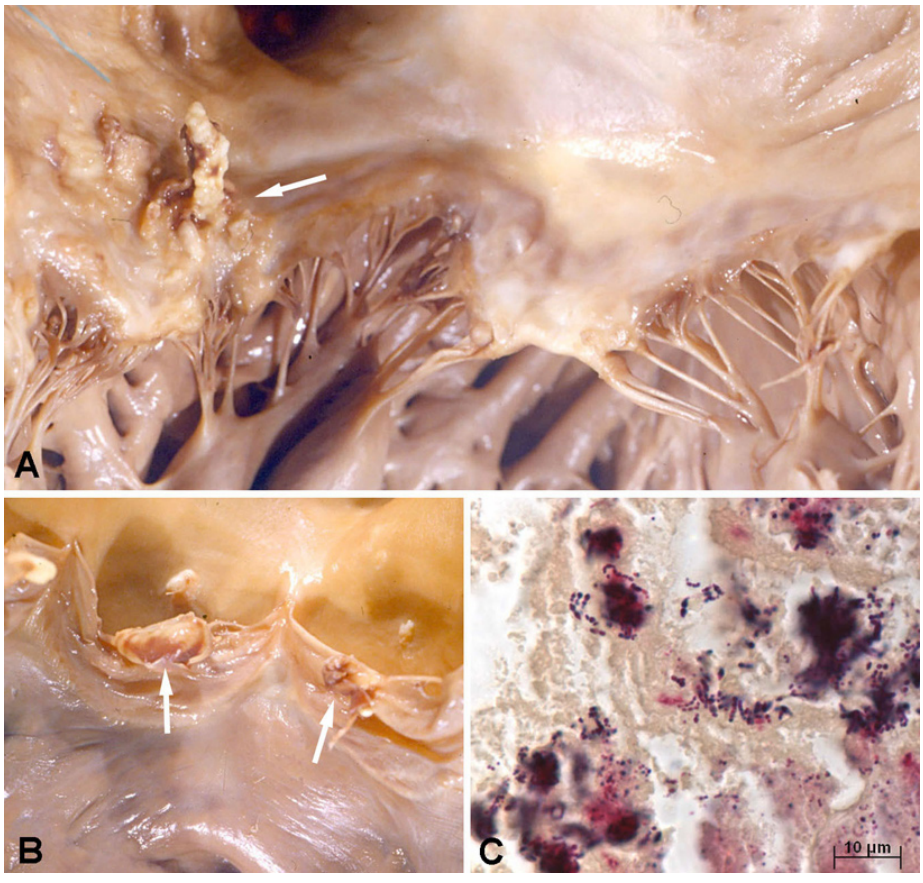

Figure 3 - Infectious endocarditis. Vegetations in the atrial region of the posterior cusp of mitral valve (panel A, arrow) and in the free border of the semilunar cusps of the pulmonary valve (panel B, arrows). It is noteworthy that the valves did not present previous disease sequelae. Histological examination showed abundant Gram-positive coccus groups, dark-blue in color, present in the vegetations (panel C, Brown-Hopps stain).

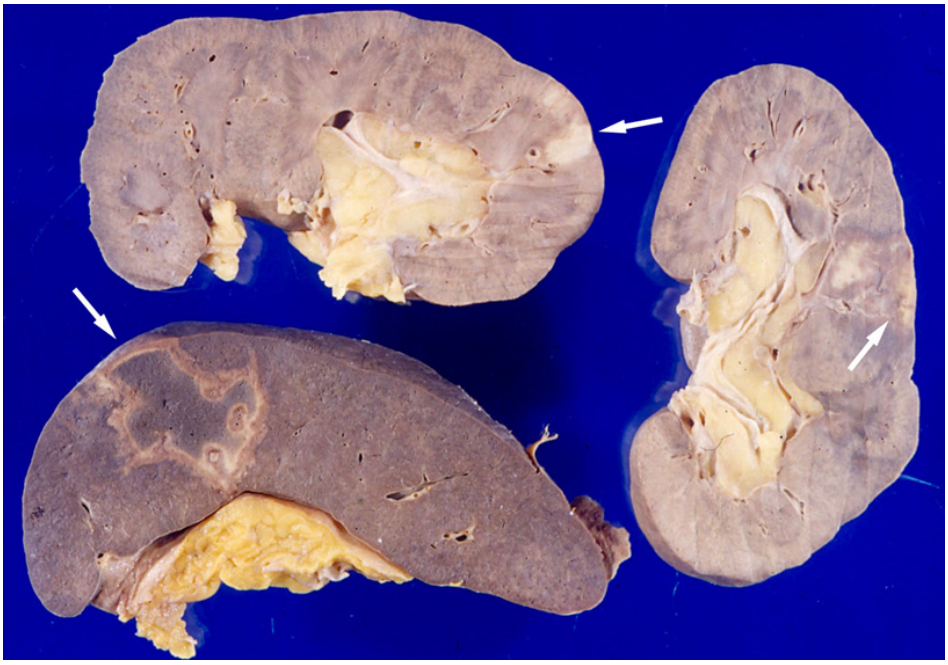

Figure 4 - Macroscopic aspect of the kidneys and spleen, demonstrating areas of recent infarction on the cross-sectional surfaces (arrows).

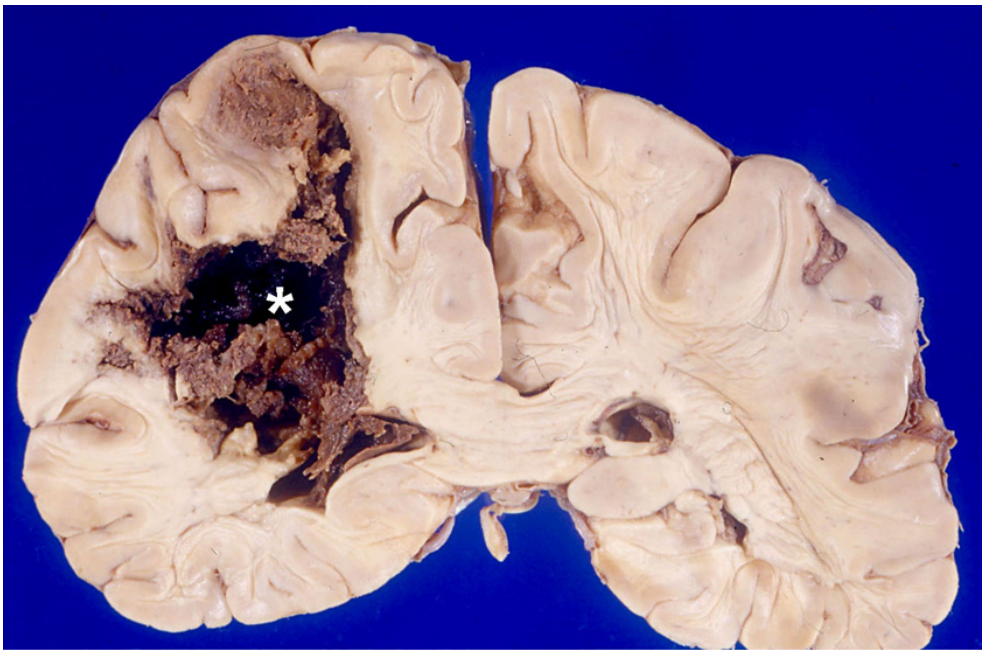

Figure 5 - Extensive hemorrhagic infarction affecting the cortex and white substance of the right brain hemisphere (asterisk).

comorbidities which are frequently associated with this disease[19]. The hypertension was difficult to control and the patient developed decompensated hypertensive cardiopathy and progressive congestive heart failure. In spite of the existence of risk factors, he did not develop significant atherosclerosis in any arterial territory and did not present coronariopathy.

The cause of death was bacterial septicemia secondary to infectious endocarditis of the mitral and pulmonary valves by Gram-positive cocci. The bacterium *Burkholderia cepacia*, identified at the blood culture shortly before the death, is a Gram-negative agent and thus, not likely to be responsible for the endocarditis. In addition to the simultaneous involvement

of the pulmonary valve, another unusual aspect is that both affected valves (mitral and pulmonary) were previously normal, that is, did not present previous disease sequelae. The initial clinical manifestation of the endocarditis was neurological, due to the extensive hemorrhagic cerebral infarction, probably due to an embolic cause. The necropsy showed indisputable evidence of septic embolization, with the presence of microabscesses and bacterial colonies in the spleen, kidneys and myocardium. Although diabetes mellitus is generally considered a predisposing factor for infection, it has not been classically considered as a risk factor for the development of infectious endocarditis. However, this concept has been recently modified due to reports of the association between these two entities, as in the present case, as well as the more severe endocarditis in insulin-dependent diabetic patients[20, 21].

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