

Clinicopathologic Session

Case 5/99 - Syncope in a Twenty-Three-Year-Old Male Hospital do Servidor Público Estadual - São Paulo, SP

A 23-year-old white male, clerk, born in and resident of Guarulhos, SP was hospitalized with complaints of fainting. He reported that for 3 months he had been having episodes of malaise, nausea and blurred vision followed by loss of consciousness unrelated to physical exertion in the past 3 months. According to information from family members, these episodes were not accompanied by incontinence or tonic-clonic seizures and normally lasted approximately 2min. He recovered consciousness without sequelae. During these 3 months he experienced 3 such episodes: one while bathing, another following a coughing crisis and another after rising from bed. He reported dyspnea during strenuous exertion accompanied by palpitations as well as hypertension, for which he was taking enalapril 10mg/day. He also reported being under treatment for ichthyosis. The physical examination revealed a good general health, no cyanosis, no clubbing of the fingers and no other related symptoms. He had scaling lesions and dispersed hyperkeratosis over the entire body. There was no jugular stasis and the cardiac rhythm was regular without murmurs. A fourth heart sound was present as well as hyperphonestic of the second heart sound in the pulmonary area, with physiological splitting. He had a heart rate of 108bpm and blood pressure of 100/70mmHg. Arterial pulses were present, symmetrical and normal. He was released from the hospital after 25 days and sent to another medical service. He was hospitalized again 3 months later with similar complaints, presenting with an episode of malaise, intense cyanosis and lowered level of consciousness. He was seen promptly and the electrocardiogram showed sinus tachycardia. His condition improved with the administration of oxygen via nasal catheter. Later, he presented a similar episode followed by cardiorespiratory arrest that did not respond to resuscitation attempts and died. Blood examination results showed: Hb=14.6g/%; Hct=44.8; platelets=176,000/ml; WBC=10,000/ml; neutrophils=75.5%; lymphocytes=15.9%; glucose=70mg/dl; urea=57mg/dl; Na=144mEq/L; K=4.4mEq/L; Ca=10.3mg/dl; Mg=1.9mg/dl; creatinine=1.3mg/dl; VDRL, HIV, rheumatoid factor and anti-nuclear factor were negative. Pulmonary function testing was not done due to hypoxia at the beginning of the exam. Arterial blood gas analysis revealed: pH=7.44; pO₂=51.4mmHg;

pCO₂=24.5mmHg; HCO₃=16.9mmol/L; BE=4.5mmol/L; O₂ saturation=88.6%. Chest x-ray showed normal heart size with bulging of the pulmonary artery arch, increased diameter right and left pulmonary branches (21mm and 23mm, respectively; normal=15-16mm), normal sized aortic arch and pulmonary hila and costophrenic space free of liquid (fig. 1). The electrocardiogram showed sinus rhythm, QRS axis deviated to the right and accentuated right ventricular hypertrophy (fig. 2). Transthoracic echocardiogram revealed aorta=28mm, left atria=29mm, right ventricle=34mm, left ventricle during diastole=48mm and during systole=39mm, septum=7mm and the posterior left ventricular wall=8mm. The ejection fraction was 0.65. There were signs of significant pulmonary hypertension and moderate tricuspid regurgitation. It was not possible to do a transesophageal echocardiogram because the patient had a hypoxic crisis. Hemodynamic evaluation showed pressures of 6mmHg (average) in the right atrium, 88/0/6mmHg in the right ventricle, 88/40/56mmHg in the pulmonary artery pulmonary wedge of 8mmHg (average), 105/70/81mmHg in the aorta, 105/0/10mmHg in the left ventricle and the pulmonary-systemic resistance ratio was 0.64 (Fick technique). Oxygen measurement revealed: superior vena cava=62.1%; right atrium=71.4%; right ventricle=70%; pulmonary artery=69.3%; left ventricle=98.3%; left atrium=98.6%; aorta=97.5%. Coronary angiography was considered normal.

Discussion

This young patient had a 3-month history of syncope, normal physical examination with no murmurs or other warning signs, leading to the hypotheses of tachycardia or a cerebral anomaly such as aneurysm. However, subsidiary findings clearly pointed to the diagnosis of pulmonary vascular disease, which was supported by the electrocardiogram that showed systemic-level right ventricular hypertrophy and by the chest x-ray that revealed an enlarged pulmonary artery and the branches. The echocardiogram suggested primary pulmonary hypertension. In the absence of any type of congenital defect like ventricular or atrial septal defects, all left-side obstructive defects must be ruled out (e.g. *cor triatriatum*, aortic stenosis, mitral stenosis, pulmonary venous stenosis, coarctation of the aorta, etc.). Except for coarctation of the aorta, all these defects could lead to pulmonary vascular disease but they cause increased pulmonary capillary pressure. Coarctation of the aorta with post-coarctation arterial canal could cause pulmonary hypertension with normal wedge pressure but it was ruled out by the angiography. Other causes should be remembered: thromboembolic disease of unknown origin (microembolism); hemolytic anemia (ruled out

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Fig. 1 - Chest x-ray - Note bulging of the pulmonary artery arch and increased size of right and left branches

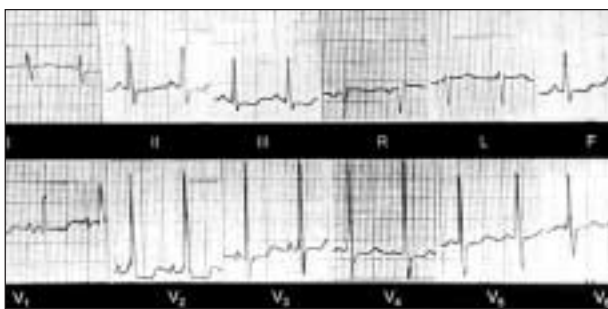


Fig. 2 - Electrocardiogram Sinus rhythm and accentuated right ventricular hypertrophy

by laboratory results); parasitosis, particularly mansonic schistosomiasis, a frequent cause that is difficult to exclude; hepatic cirrhosis and obstructive pulmonary disease. The presence of a very small interventricular septal defect would not explain the pulmonary hypertension, however, even small increases in flow could cause pulmonary hypertension, including very small interventricular septal defects of 2-3mm that remain unnoticed even by hemodynamic analysis. This patient was well, acyanotic with normal oxygen saturation and no signs of congestive heart failure, traits of pulmonary hypertension that progresses to syncopal episodes. In pulmonary hypertension, syncope occurs due to low cardiac output caused by the sudden elevation of the pulmonary artery pressure in reaction to sudden arteriolar reaction. This occurs in approximately 30% of pulmonary vascular diseases, while 30% are characterized by pain, 15% by hemoptysis and 30% by congestive heart failure.

(Dr. Edmar Atik)

Diagnostic hypotheses – a) Primary pulmonary hypertension; b) schistosomiasis

Necropsy

The heart weighed 450 grams and had a mild increase in volume. Epicardial petechiae were seen on the right

atrium, which are considered indirect signs of anoxia. There was also slight enlargement of the right atrium and right ventricle. The right ventricle had increased wall thickness: 0.9cm (twice the normal thickness of the right side) and hypertrophy of the trabeculae. The valves were unremarkable. The left ventricle was normal with wall thickness of 1.2cm. A ventricular septal defect (0.8cm by 0.3cm) was seen at the heart apex. Microscopically, the lungs showed vascular lesions in the arterioles and muscular arteries, characterized by concentric and hyaline wall hypertrophy with partial or total lumen occlusion (fig. 3-A). Other types of vascular lesions were present and were characterized by intimal fibrosis of the muscular arteries that at times showed signs of revascularization (fig. 3-B and C), besides vascular ramifications and mild dilation of some arterioles that led to plexiform vascular lesions. Arteriosclerosis was observed in the large hilar artery. Thrombosis was not documented. The observed vascular alterations were compatible with the third and fourth grades described by Heath¹. Macroscopically, nodules and fibrotic septa were seen in the liver. Microscopically, there were degenerative nodules and fibrotic septa that connected the portal spaces, forming bridges that gave the appearance of hepatic cirrhosis. This was not secondary to cardiac disease and possibly had viral etiology (hepatitis C). Data was insufficient to determine etiology and viral serology was negative. Therefore, based on micro and macroscopic findings, the diagnostic conclusions are:

Anatomicopathological diagnoses – 1) apical ventricular muscular septal defect; 2) secondary pulmonary hypertension with adaptative lesions in pulmonary vessels; 3) slight arterial hypertension; 4) hepatic cirrhosis; 5) lamellar ichthyosis; 6) systemic repercussions of anoxia

(Dr. Maria Isete F. Franco)

Comments

Certain aspects of this case deserve special discussion. Although it was not possible to characterize primary pulmonary hypertension in the presence of ventricular septal defect, the real role of such defect throughout the patient's life in the development of pulmonary vascular disease is unknown. Ventricular septal defects in children are usually accompanied by intense murmur, which was not cited in this patient. Therefore it is possible to infer that the manifestation of pulmonary hypertension was independent of the septal defect; they were two distinct elements, the defect and the syndrome. From a practical point of view, the role played by the ventricular septal defect over time, causing a right-to-left shunt, was negligible since pulmonary disease was present since birth and the ventricular septal defect was just an additional finding. Even so, the classification of the pulmonary hypertension as primary is not possible.

(Dr. Edmar Atik)

Pulmonary hypertension is the abnormal elevation of the pulmonary artery pressure, the average pressure reaching

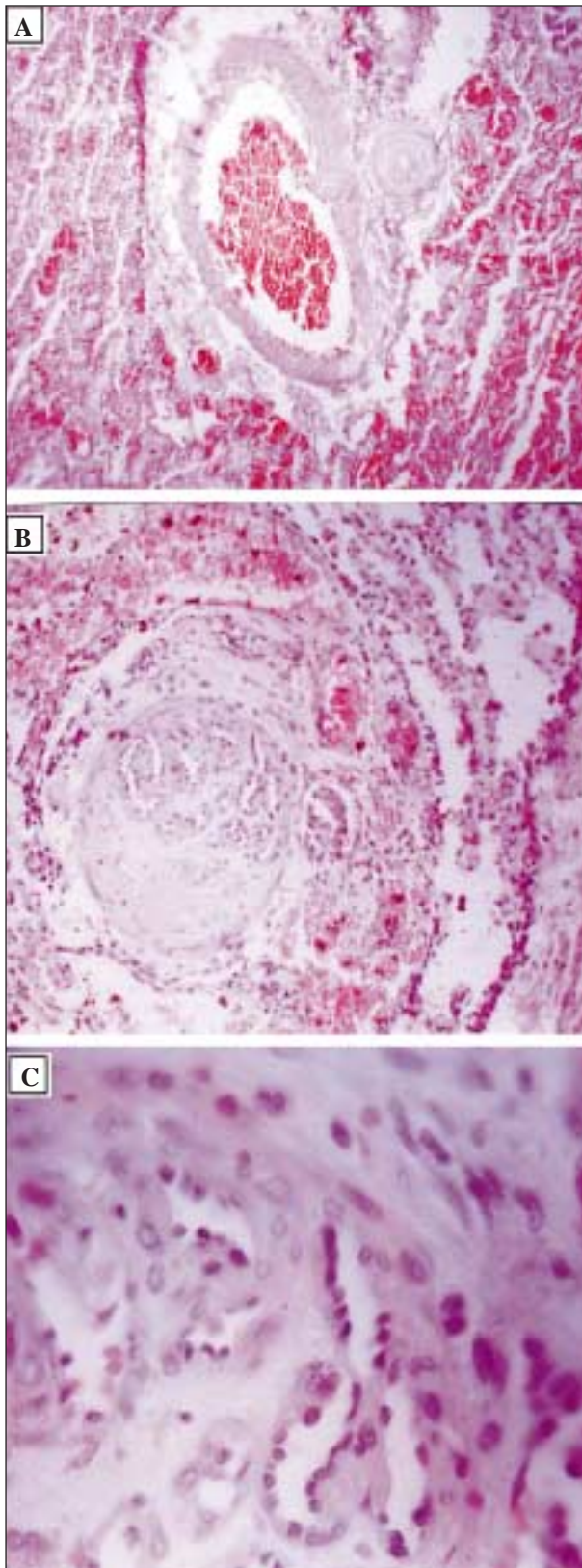


Fig. 3 – Pathological study - Microscopy: A) slight dilation of the pulmonary artery and thickening of the adjacent arteriolar wall, with hemorrhagic alveolar foci around. HE, original magnification 100X; B) thickening of the pulmonary muscular artery wall with revascularization. HE, original magnification 100X; C) thickening of the pulmonary muscular arteriole wall with revascularization. HE, original magnification 100X. Revascularization - detail. HE, original magnification 400X.

levels above 25mmHg at rest and 30mmHg on exertion². Regarding etiology, it can be primary (idiopathic) or secondary to pulmonary and cardiac problems, pulmonary thromboembolism, ingestion of exogenous substances like anorexigenics (phentermine, fenfluramine), L-tryptophan, cocaine, crack, or else HIV infection and portal hypertension^{2,3}. Histopathologically, primary pulmonary hypertension can be determined by pulmonary arteriography involving muscular arteries associated with plexiform lesions and angiomas, by pulmonary veno-occlusive disease or by pulmonary capillary hemangiomatosis⁴.

The pathogenesis of primary pulmonary hypertension remains obscure. There seems to be individual susceptibility, wherein various stimuli may initiate the development of vascular alterations. There is mainly endothelial dysfunction that creates an imbalance in favor of vasoconstrictive substances (e.g. thromboxane, endothelium-derived factors) that may or may not be associated with coagulation abnormalities².

Diagnosis is made on average two years after the onset of the disease because of multi-symptomatic clinical findings. Dyspnea is usually the first symptom and occurs due to the increase in dead space and/or low cardiac output with inadequate oxygenation. Fatigue and syncope may occur and are probably the result of the inability to increase cardiac output. Angina and hemoptysis are less common⁵.

The diagnosis of pulmonary hypertension can be made with the following exams: chest x-ray, electrocardiogram, measurement of arterial gases, pulmonary function tests, scintigraphy, ventilation-perfusion scans, Doppler echocardiogram, cardiac catheterization with oxygen measurement, angiography and lung biopsy. Cardiac catheterization is essential to confirm and define physiopathology as well as to classify the pulmonary hypertension as pre- or post-capillary⁶, thus aiding in the etiologic diagnosis. Pulmonary angiography is an essential procedure in diseases like pulmonary thromboembolism, fistulas and arteriovenous shunts. Lung biopsy is a risky procedure when pulmonary artery pressure is very high but it is important if vasculitis and pulmonary veno-occlusive disease are suspected⁵.

Treatment depends on etiology. Surgical correction is indicated for left-to-right shunt in the absence of irreversible pulmonary hypertension. Atrial septectomy may be an acceptable treatment option for patients with severe pulmonary hypertension and untreatable right heart failure². Patients with primary pulmonary hypertension present a higher incidence of *in situ* thrombosis as a result of endothelial injury and abnormal flow in the pulmonary microvasculature⁷. Because of this, the use of anticoagulants can increase life expectancy in patients with primary pulmonary hypertension^{2,3}, but caution should be taken in patients who have a history of syncope or hemoptysis. Supplemental oxygen is indicated for patients with oxygen saturation <90% or arterial oxygen tension <60mmHg at rest, during sleep or on exertion. This therapy eliminates the hypoxic vasoconstrictive stimuli and decreases erythropoiesis, right ventricular hypertrophy and the risk of cardiac arrhythmia⁸.

Medication should be prescribed to treat heart failure. Digitalis glycosides should be used with caution in patients with signs of right heart failure, but are indicated when this is associated with left heart failure. Diuretics are indicated for patients with signs of systemic venous congestion they should, however, be used with caution since they can result in metabolic alkalosis, which could worsen arterial and alveolar hypoxia^{2,8}.

Therapy with vasodilators is based on the theory that vasoconstriction is the primary cause of elevated pulmonary vascular pressure. However, response to this class of drugs seems to depend on the individual and therefore their use should be preceded by hemodynamic analysis. During the exam, prostacyclin, acetylcholine, nitric oxide or adenosine are infused. Results are considered favorable when there is a >20% decrease in pulmonary vascular pressure; >20% decrease in systemic vascular pressure (associated with a drop in the pulmonary vascular-systemic pressure ratio), >10% increase in the cardiac output together with a drop in the average pulmonary artery pressure; >30% decrease in the pulmonary vascular pressure and >30% de-

crease in the pulmonary vascular pressure combined with a drop of >10% in the average pulmonary artery pressure⁹. A positive response to vasodilators is associated with improved survival. Recommended drugs include nifedipine (30-240mg/day), diltiazem (120-900mg/day), IV prostacyclin (2-24g/kg/min) and IV prostaglandin E (5-30g/kg/min). Prostacyclin has shown the best results but deep venous puncture and daily application are required. This method has been used for patients awaiting transplantation^{2,8}.

Heart-lung transplantation has limitations because a specialized surgical center is required, besides the occurrence of bronchiolitis, rejection and opportunistic infections^{2,8}.

The survival prognosis at one year is 68-77% and at five years it is 22-38%. The main causes of mortality are right heart failure, pneumonia and sudden death. The predictive factors of low survival are elevated pulmonary vascular resistance and elevated pulmonary artery pressure, negative response to vasodilators, low functional class, right atrium pressure >20mmHg, cardiac index <2.0 and low oxygen saturation in the pulmonary artery².

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