

Clinicopathologic Session

Case 3/2001 – Twenty-year-old woman with pulmonary hypertension, syncope, and severe headache (Instituto do Coração do Hospital das Clínicas – FMUSP - São Paulo)

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A 20-year-old woman sought medical care due to headache and vomiting following syncope (9/22/95).

The patient was born from an uneventful normal delivery at the end of a full-term pregnancy. Up to the age of 1 year and 6 months, the patient had fatigue when being fed. At the age of 7 years, she began to have fatigue on strenuous exertion and palpitations during tense situations. At the age of 8 years, she had 2 episodes of cyanosis and dyspnea on exertion accompanied by the sensation of imminent loss of consciousness. She also complained of arthralgia in her knees and ankles, and pain in her thoracic and lumbar spine. At the age of 9 years, the patient was referred to our hospital (11/26/84).

The physical examination at that time (11/26/84) showed an eupneic and acyanotic child, with a regular and symmetric pulse. The heart rate was 72bpm and blood pressure was 120/90mmHg. The lung examination was normal. The heart examination showed an increased intensity of the second cardiac sound, which was palpable in the pulmonary area, where a systolic murmur could also be heard. The liver was palpated in the right costal margin, and no edema of the lower limbs was observed.

The electrocardiogram (11/23/84) showed sinus rhythm, a heart rate of 79bpm, QRS axis of +110° forward, and right ventricular hypertrophy (fig. 1). The chest X-ray showed enlargement of the right ventricle and bulging of the pulmonary trunk. Laboratory tests are shown in table I. The search for lupus erythematosus cells, antinuclear factor, and rheumatoid factor was negative.

The echocardiogram (10/3/85) disclosed an aneurysm

of the membranous part of the ventricular septum and a ventricular septal defect of small hemodynamic repercussion. The heart had normal dimensions and contractility (Table II).

The patient underwent hemodynamic and angiographic studies (November '85) which evidenced severe pulmonary hypertension, a mild increase in the end-diastolic volume, normal left ventricular contractility, and aneurysm of the membranous septum through which blood flow into the left ventricle was detected (Table III). New studies carried out in October '86 showed severe pulmonary hypertension (Table III).

The radionuclide ventriculography (May '86) showed a mild global reduction in left ventricular function and bulging of the pulmonary trunk (Table IV).

On the exercise test (November '87), the patient showed a low physical capacity and no signs of myocardial ischemia (Table V). New assessments were performed on 8/18/88 and 5/23/91 (Table V).

The definitive diagnoses were primary pulmonary hypertension, and, after rheumatologic assessment, juvenile rheumatoid arthritis. Nifedipine, prednisone, and chloroquine were then started.

Cardiac scintigraphy with gallium-67 (November '93) showed no concentration of the radiotracer in the cardiac area not suggestive of myocardial inflammation.

The patient evolved with fatigue on major exertion up to September '95.

A new echocardiogram (April '94) showed severe pulmonary hypertension and mild tricuspid insufficiency (Table II). The radionuclide ventriculography (April '94) was almost unaltered with dilation of the pulmonary trunk and mild dilation of the ventricles (Table IV).

In March '94, the patient had syncope after emotional stress.

In April '95, the patient underwent a left tympanoplasty due to repetitive episodes of otitis.

In September '95, a new episode of syncope occurred

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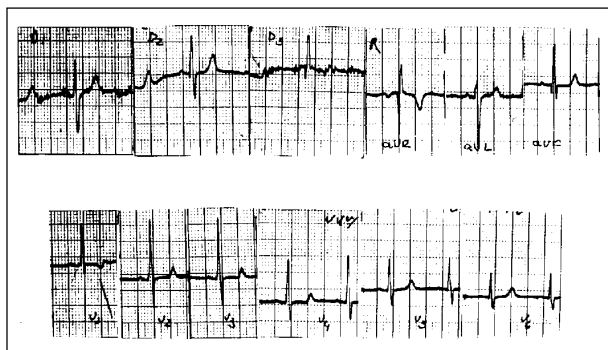


Fig. 1 – Electrocardiogram – Sinus rhythm and right ventricular hypertrophy.

| Tests/dates | April '85 | May '88 | Dec '89 | Sept '95 |
|---------------------------------|-------------|---------|-----------|-----------|
| Red blood cells/mm ³ | 5.200.000 | | 4.200.000 | 4.800.000 |
| Hemoglobin (g/dL) | 14.5 | | 12.4 | 16.4 |
| Hematocrit | 0.42 | | 0.38 | 0.48 |
| MCV (m ³) | 81 | | 90 | 100 |
| MCHC (g/dL) | 35 | | 33 | 34 |
| Leukocytes/mm ³ | 5.800 | | 6.200 | 14.900 |
| Band neutrophils (%) | 1 | | 6 | 3 |
| Segmented neutrophils | 49 | | 65 | 84 |
| Eosinophils (%) | 4 | | 2 | 0 |
| Lymphocytes (%) | 42 | | 25 | 10 |
| Monocytes (%) | 3 | | 2 | 3 |
| Platelets/mm ³ | 228.000 | | | 237.000 |
| Platelet aggregation | Normal | | | |
| Prothrombin time (s) | 14 | | | 13.4 |
| Observed/control ratio | 1.01 | | | 1.05 |
| APTT (s) | 50.4 | | | 21.8 |
| Observed/control ratio | 1.01 | | | 0.72 |
| Thrombin time (s) | 11.3 (10.5) | | | - |
| Urea (mg/dL) | | | | 49 |
| Creatinine (mg/dL) | | | | 1 |
| Glycemia (mg/dL) | | | | 97 |
| Sodium (mEq/L) | | | | 137 |
| Potassium (mEq/L) | | | | 4.3 |

| Measures/dates | October '85 | April '94 |
|---|-------------|-----------|
| Ventricular septal thickness (mm) | 6 | 8 |
| Posterior wall thickness (mm) | 6 | 8 |
| Aortic diameter (mm) | 26 | 27 |
| Left atrial diameter (mm) | 26 | 28 |
| Left ventricle | | |
| Diastolic diameter (mm) | 40 | 36 |
| Systolic diameter (mm) | 23 | 21 |
| Ejection fraction | - | 0.42 |
| Right ventricular diastolic diameter (mm) | 14 | 28 |
| Ventricular septal defect (mm) | 8 | Absent |
| Mean pulmonary artery pressure (mmHg) | Normal | 77 |

with falling and facial trauma. Four days later, the patient had intense pulsatile headache accompanied by nausea, vomiting, and dizziness, but with no eyesight changes.

On physical examination (September '95), the patient had a regular pulse, a heart rate of 100 bpm, and a blood pressure of 140/95mmHg. Her lung examination was normal. Her heart examination showed increased intensity of the

| Measures/dates | November '85 | October '86 | |
|---|--------------|-------------|------------|
| Pressures (mm Hg) | Basal | Nifedipina | |
| Right atrial mean | 9 | 6 | 2 |
| Right V. | 128/15/15 | 94/7/7 | 67/3/4 |
| (syst/initial diast/end-diast) | | | |
| Pulmonary artery | 127/96/111 | 95/68/81 | 67/49/59 |
| (syst/diast/mean) | | | |
| Pulmonary wedge (mean) | 12 | 8 | 11 |
| Left V. | 136/0/14 | 120/0/17 | 136/5/12 |
| (syst/initial diast/end-diast) | | | |
| Aorta | 135/96/114 | 118/75/94 | 130/95/111 |
| (systolic/diastolic/mean) | | | |
| Vascular resistance (dyn.seg.cm ⁻⁵) | | | |
| Pulmonary | 587 | 481 | - |
| Systemic | 1624 | 1455 | - |
| Cardiac index (L/min/m ²) | 2.3 | 3.9 | - |

| Measures/dates | 9/5/86 | 18/4/94 |
|----------------------------|-------------------------------|---------------|
| Radiocardiography | | |
| Pulmonary transit time (s) | 6 | 7 |
| Pulmonary trunk | Dilated | Dilated |
| Ventriculographies | | |
| Left ventricle | | |
| Volumes | Mild increase | Mild increase |
| Kinetics | Septal and apical hypokinesia | Normal |
| Ejection fraction | 0.49 | 0.62 |
| Right ventricle | | |
| Volumes | Mild/moderate increase | Mild increase |
| Kinetics | Normal | Normal |
| Ejection fraction | - | 0.60 |

second cardiac sound in the pulmonary area, a systolic murmur (++) in the tricuspid area, and an aspirating diastolic murmur (+/4) in the high left sternal margin. The abdominal examination was normal. The neurological examination showed an oriented patient with mild neck stiffness and no motor deficit. On ophthalmoscopy, bilateral papillary edema was present.

The diagnosis of endocranial hypertension secondary to an expansive process in the posterior cranial fossa was established.

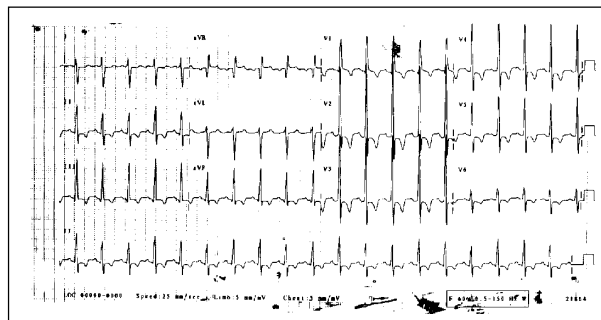


Fig. 2 - Electrocardiogram – Sinus tachycardia and right ventricular hypertrophy more marked than in the initial electrocardiogram.

Table V – Assessment through exercise test

| Variables/dates | 11/20/87 | | 8/18/88 | | 5/23/91 | |
|---------------------------|----------|----------|---------|----------|---------|----------|
| | Basal | Exertion | Basal | Exertion | Basal | Exertion |
| Condition | | | | | | |
| Velocity (mph) | | 2 | | 2 | | 2 |
| Exercise duration (min) | | 11 | | 15 | | 14 |
| Heart rate (bpm) | 111 | 180 | 86 | 145 | 92 | 157 |
| Systolic pressure (mmHg) | 150 | 140 | 130 | 140 | 169 | 119 |
| Diastolic pressure (mmHg) | 120 | 90 | 90 | 80 | 60 | 83 |
| End of test | | Rate* | | - | | Dyspnea |

* reached maximum rate expected.

The test for detecting the IgG class antibody to the hepatitis A virus was positive. Blood cultures showed no growth of microorganisms.

The electrocardiography (10/9/95) showed sinus rhythm, a heart rate of 125bpm, QRS axis of +150° forward, and right ventricular hypertrophy (fig. 2).

The cranial radiography was normal.

The computerized tomography revealed a lesion with reduced density and a ring contrast in the right cerebellar hemisphere, with no fourth ventricular deviation and no ventricular dilation. The image was considered suggestive of an abscess.

The patient was prescribed 2g of vancomycin, 1,500mg of metronidazole, 4g of ceftriaxone, and 12mg of dexamethasone, daily. In the following days, the patient remained on ceftriaxone, metronidazole, and dexamethasone. On the 6th day of hospitalization, the dose of ceftriaxone was reduced to 2g daily, vancomycin and metronidazole were suspended, and 2,400mg of clindamycin were introduced.

The patient's neurological condition and the papillary edema improved. On the 18th day of hospitalization, she complained of pain and paresthesia in the lower limbs with no signs of inflammation or blood hypoperfusion. The neurological examination showed no reduction in strength or abnormal reflexes. A global reduction in neuromuscular reflexes existed.

On the 19th day of hospitalization, the patient underwent left suboccipital trepanation for stereotaxic drainage of a cerebellar abscess. A dense and chocolate-like material suggestive of an abscess collection was drained.

Five hours after the procedure, the patient had intense cyanosis and prolonged hypotension, followed by cardiopulmonary arrest and death (10/10/95).

Discussion

Clinical considerations – Our patient is a young woman with antecedents suggesting pneumopathy since her birth and rheumatologic findings during childhood. During the clinical investigation, the diagnostic hypotheses of primary pulmonary hypertension and juvenile rheumatoid arthritis were formulated. During a hemodynamic study at the age of 10 years, a ventricular septal defect was observed, but it was no longer reported at the age of 20 years. After repetitive episodes of otitis, the patient underwent tympano-

plasty. Five months after the procedure, a diagnostic hypothesis of cerebellar abscess was made and the patient was treated with antibiotics and corticoids. On the 19th day of hospitalization, the patient underwent trepanation and stereotaxic drainage, evolving to death in 5 hours. We will focus on the diagnoses of pulmonary hypertension and cerebral abscess.

Pulmonary hypertension is defined as systolic pulmonary pressure above 30mmHg and mean pulmonary pressure above 20mmHg. The diagnosis of primary pulmonary hypertension is established only when, after appropriate investigation, no secondary cause is found¹⁻³.

On anamnesis, the patient complained of fatigue, dyspnea and cyanosis on exertion, presyncope, and syncope. On physical examination, the patient had an increased intensity of the second cardiac sound, in pulmonary area. The electrocardiogram showed deviation of the axis to the right and right ventricular hypertrophy. The chest X-ray showed enlargement of the right ventricle and bulging of the pulmonary trunk. These findings are very suggestive of pulmonary hypertension.

Rheumatoid disease may be a cause of pulmonary hypertension. If the diagnosis of juvenile rheumatoid arthritis made during the rheumatologic investigation of our patient is considered true, it may constitute a possible secondary cause of pulmonary hypertension. Juvenile rheumatoid arthritis may be classified into 3 types depending on the degree of involvement observed: systemic, in many joints, or in few joints. Systemic involvement manifests as high fever, rash, general lymphadenopathy, hepatosplenomegaly, and cardiopulmonary involvement. Articular involvement manifestation varies. Regarding pulmonary involvement, the most common finding is pleuritis, followed by pulmonary nodules, and, more rarely, by pulmonary fibrosis^{4,5}. In some cases of pulmonary fibrosis, the chest X-ray shows a diffuse reticulonodular infiltrate. However, it is worth noting that even in patients with a normal chest X-ray, alterations in pulmonary function have been found with a reduction in vital capacity, which suggests the existence of a higher incidence than expected of cases of pulmonary fibrosis with no radiographic alterations. Some patients with pulmonary fibrosis will develop pulmonary hypertension⁶⁻⁸. We conclude that regarding the clinical case in question, the hypothesis of pulmonary hypertension secondary to rheumatoid disease may not be eliminated; however, examinations such as pulmonary function tests and pulmonary biopsy, which

were not performed, would be important for establishing the diagnosis.

The echocardiogram, which is an important complementary test in investigating pulmonary hypertension, showed ventricular septal defect and eliminated mitral valve disease or cardiomyopathy, which are other possible causes of pulmonary hypertension⁹.

The hemodynamic and angiographic studies performed in November '85 confirmed the severe pulmonary hypertension, increased vascular pulmonary resistance, and ventricular septal defect, leading to right-to-left reverse shunt, which are findings reported in Eisenmenger's syndrome⁸. Data reported in the anamnesis, physical examination, electrocardiogram, and chest X-ray are compatible with this hypothesis supported by the fact that patients with Eisenmenger's syndrome may have transient bacteremia, which may enter the cerebral circulation through the shunt without being filtered in the pulmonary circulation, leading to a cerebral abscess^{10,11}. The hypothesis of Eisenmenger's syndrome can be questioned due to the presence of the small size of the ventricular septal defect (8mm in diameter), which, even though present, may not have been the cause of pulmonary hypertension. Other discordant points are the absence of an elevated hematocrit in our patient and the fact that on the echocardiogram of November '94 the ventricular septal defect was no longer detected.

Regarding the investigation of pulmonary hypertension, we have to consider the possibility of pulmonary thromboembolism as an important cause of pulmonary hypertension. Therefore, ventilation-perfusion mapping or pulmonary angiography, which were not performed, is required so the diagnosis of primary pulmonary hypertension may be established^{12,13}.

Regarding the hypothesis of pulmonary thromboembolism, we could argue that no clinical data suggestive of this diagnosis exist, and if no cause for pulmonary hypertension is identified, it should be considered primary. The current theories about the causes of primary pulmonary hypertension are as follows: 1) recurring occult systemic venous thrombosis with thromboembolism: patients with recurring thromboembolism develop pulmonary hypertension and cor pulmonale slowly, with no clinical manifestations of thromboembolism, and characteristic angiographic findings may only be present in an early phase, disappearing later¹⁴; 2) development of pulmonary hypertension due to in situ thromboses in smaller pulmonary arteries resulting in diffuse vascular pulmonary obstruction. This theory is based on the existence of defects in coagulation, including abnormalities in platelet function and defective fibrinolysis¹².

Other less probable causes of pulmonary hypertension in our case are the following: chronic obstructive pulmonary disease, to be investigated with a pulmonary function test; Takayasu's disease, which involves the peripheral pulmonary arteries (our patient, however, showed no involvement of the large arteries, as would be expected in this disease); thrombosis of the portal vein, in which the hepatic function tests would be very useful; and sickle cell disease,

which could be confirmed with erythrocytic morphology and electrophoresis of hemoglobin.

In the hemodynamic study in '85, a good response to nifedipine occurred with a reduction in the pressure in the pulmonary artery and in the right atrium, an increase in cardiac output, and a slight change in systemic blood pressure. This test is very important to recognize which patients would benefit from the prolonged use of nifedipine to control pulmonary hypertension.

Some authors recommend the prophylactic use of anti-coagulant agents in pulmonary hypertension, even if no thromboembolism has been evidenced on complementary tests during the investigation of the cause of the disease. They state that patients have a high risk for pulmonary thromboembolism due to their sedentary lifestyle, venous insufficiency, and dilation of the right cardiac chambers. This medicamentous option is being studied to determine its efficacy.

In 1995, the patient being discussed was hospitalized and the diagnostic hypothesis of left cerebellar abscess was formulated.

According to the literature, in approximately 75% of the patients with cerebral abscess, the duration of the symptoms equals or is less than 2 weeks. Only 50% of the patients have the classic triad of fever, headache, and focal neurological deficit. Headache is usually moderate to intense, and it may be hemicrania or generalized headache. Fever occurs in 45% to 50% of the patients. Changes in mental state ranging from lethargy to coma may occur. Focal neurological findings are present in 50% of the patients and depend on the localization of the lesion and adjacent edema. Nausea and vomiting affect half the patients, probably due to intracranial hypertension. Convulsions occur in 25% to 35% of the patients, usually when the frontal lobe is impaired. Stiffness of the neck and papilledema are present in 25% of the cases each¹⁵⁻¹⁷. In regard to complementary tests, moderate leukocytosis may be found in the hemogram; however, 40% of the patients have a normal white blood cell count. The sedimentation rate is increased up to around 45-50mm/h. C-reactive protein is increased and may be used in the differential diagnosis between neoplasia and cerebral abscess. Lumbar puncture is contraindicated in cases suspected of having cerebral abscess because of the risk of herniation and because of the low specificity of this type of examination. Cranial X-ray is normal in most cases.

Cranial computerized tomography is fundamental for the diagnosis of cerebral abscess; in addition, it is far superior to other traditional imaging methods for assessing the paranasal, mastoid, and middle ear sinuses. The characteristic image of a cerebral abscess on cranial computerized tomography is that of a center of reduced density with a ring of increased density around it, and a region of reduced density due to cerebral edema may be present. Cranial computed tomography, despite its high sensitivity, does not have an equivalent specificity, and the same image may be observed in neoplasias, granulomas, cerebral infarction, or a resolving hematoma. Among the differential diagnoses, the most frequently found is neoplasia. To clarify such a diagnosis, we

may use scintigraphy with leukocytes marked with indium-111, which will accumulate in the inflammatory foci. The clinical case in question is highly suggestive of cerebellar abscess, considering the data presented.

A cerebral abscess may develop in the following conditions: 1) associated with a continuous suppurative focus (47% of the cases of cerebral abscess) such as in: a) otitis media¹⁷: the patient had repetitive episodes of otitis, which ended in a tympanoplasty. Most cerebral abscesses caused by otitis media are located in the temporal lobe, followed by the cerebellar location (it is worth noting that 85% to 89% of the cerebellar abscesses are secondary to otitis media). These processes occur more frequently when the tympanic membrane is damaged as in the case of our patient; b) sinusitis: most cases involve the frontal lobe and not the cerebellum, as is the case of our patient; c) mastoiditis: no alteration in the mastoid process was observed on cranial computed tomography; therefore, this possibility does not match our case¹⁸; d) trauma: the patient had facial trauma; however, cranial radiography and tomography showed no signs of fracture; 2) through hematogenous via: a distant infectious focus is characteristically present, usually in the thorax; abscesses occurring through hematogenous via are usually multiple. They may be associated with pulmonary abscess or bronchiectasis, which is not the case of our patient, or with localized infectious foci in other parts of the body.

It should be noted that cerebral abscess complicating bacterial endocarditis is a rare occurrence when the blood-brain barrier is intact¹⁸. Among the cases of endocarditis, the acute form predominates, which in our case is not suggested by the clinical findings, over the subacute form. The cases of endocarditis and cerebral abscess are more frequent among patients with cyanotic congenital heart diseases, as in Eisenmenger's syndrome. These cases are clinically evidenced in the pediatric age bracket. Our patient had the cerebellar abscess at the age of 20 years, and the echocardiography performed 1 year earlier did not show a ventricular septal defect; these facts are contrary to hematogenic dissemination.

Five hours after trepanation and stereotaxic drainage, the patient had intense cyanosis, hemodynamic shock, cardiopulmonary arrest, and died. In cases of pulmonary hypertension, the most common causes of death are the following: right heart failure (64%), pneumonia (7%), sudden death (7%), and other causes (7%), among which we can cite pulmonary thromboembolism, malignant arrhythmias, massive pulmonary hemorrhage, and sudden ischemia of the right ventricle¹⁹.

(Dr. Paulo Bocayuva Cauduro)

Diagnostic hypotheses – Eisenmenger's syndrome; pulmonary hypertension related to repetitive pulmonary thromboembolism, primary pulmonary hypertension, cerebral abscess, juvenile rheumatoid arthritis.

(Dr. Paulo Bocayuva Cauduro)

Rheumatoid arthritis that evolves with systemic vasculitis is usually of the classical type with impairment of the bone-joint function, joint deformities, and high levels of rheumatoid factor. It usually has rheumatoid nodules, which are the clinical expression of cutaneous vasculitis. The clinical findings of our patient comprising arthralgia, absence of cutaneous nodules and of other manifestations such as peripheral neuritis and episcleritis are very different from those expected in the vasculitis of rheumatoid arthritis.

The usual pulmonary manifestation of rheumatoid arthritis is pleural effusion, which is followed in order of frequency by pulmonary interstitial disease, characteristically non-hypertensive. Another classical pulmonary lesion of rheumatoid arthritis is the presence of a nodule in the pulmonary parenchyma similar to the subcutaneous nodule, being considered an expression of vasculitis in the lungs.

The image of selective pulmonary arteriography, which shows a reduction in the lumen of the first branch of the right pulmonary artery, as well as a reduction in the branch of the arterial tree, suggests involvement of medium- and large-caliber vessels. These findings differ from the typical impairment of the vasculitis of diffuse connective tissue diseases, which is restricted to small vessels and arterioles. The pathognomonic lesion of rheumatoid vasculitis is a perivascular inflammatory infiltrate, with a granuloma surrounded by palisaded histiocytes and a central focus of fibrinoid necrosis.

The diffuse connective tissue diseases that more commonly lead to vascular and interstitial pulmonary disease accompanied by hypertension are progressive systemic sclerosis and systemic lupus erythematosus. These diseases could be hardly considered as diagnostic hypotheses in the present case due to the lack of clinical manifestations of these diseases and the lack of antinuclear factor.

(Dr. Moacyr Roberto Cucê Nobre)

Diagnostic and evolutionary characteristics of pulmonary vascular disease are evident in the present case.

Worthy of note are the symptoms and signs of pulmonary hypertension and right heart failure with a greater expression of temporal evolution, including the electrocardiographic alterations with progressive right ventricular hypertrophy.

In regard to the major cardiovascular causes of the syndrome, there are heart diseases with left-to-right shunt and increased pulmonary flow of the ventricular septal defect type, the obstructive lesions of the left side of the heart, and primary pulmonary hypertension.

Left obstructive defects usually cause severe conditions with a rapid fatal outcome in the first months of life, and the heart diseases of the ventricular septal defect type are initially present as pulmonary venocapillary congestion. Neither situation existed in our case, despite the anatomical demonstration of the latter anomaly.

Contrary to the concept of primary pulmonary hypertension, which exists when any other associated cardiac defect is excluded, could it be considered, particularly in this case, independent of the presence of ventricular septal defect?

The above question may be appropriate to ask about other similar cases, in which signs of primary pulmonary hypertension do not depend on heart defects that are eventually discovered in the follow-up. The patient had clinical findings of pulmonary hypertension in the absence of any manifestation of ventricular septal defect. This fact may not have accounted for the alterations in the pulmonary arterial tree, which were so expressive of pulmonary hypertension.

In addition, one may consider the possibility of the pulmonary vascular alteration that may occur in rheumatoid arthritis, despite its rarity, with findings similar to those of primary pulmonary hypertension.

Angiographic images and epidemiological data exclude other causes, such as chronic pulmonary thromboembolism, Takayasu's disease, and pulmonary parenchyma lesions, among which is schistosomiasis mansoni, which, even though rare, should be remembered in discussing this syndrome.

(Dr. Edmar Atik)

Autopsy

The heart weighed 400g and grossly showed an increased volume with predominance of the right chambers. On the sections, a perimembranous ventricular septal defect in the ventricular inlet was found, measuring approximately 1.5cm in diameter. The defect was totally closed due to fibrosis of the anterior and septal leaflets of the tricuspid valve and their adhesion to the margins of the septal defect orifice (fig. 3). The tricuspid valve also had dilation of the ring and rolling of the free margin of the leaflets. The right atrium was very dilated and intense hypertrophy of the right ventricular wall existed. No intracavitary thrombi or other cardiac alterations were found.

Microscopically, plexiform lesions in pulmonary arterioles compatible with Heath-Edwards grade IV pulmonary hypertension were seen (figs. 4 and 5). A few arterioles had multiple fibrin thrombi in their lumens, and multiple small and focal recent pulmonary infarcts were seen. A moderate lymphomononuclear inflammatory infiltrate was observed around rare pulmonary arterioles, but no histological alterations compatible with active vasculitis existed. Focal and sparse areas of mild pleural fibrosis with no inflammatory infiltrate were present.

A large anemic cavitated infarct was observed in the right cerebellar hemisphere measuring 4cm of diameter, with approximately 3 weeks of evolution and no liquid content. Inside the cavitation, a drain with patent lumen and no obstruction could be seen. The histochemical search for bacteria, fungi, and alcohol-acid resistant bacilli in the fragments of the cerebellar infarct was negative. The brain had an intense and diffuse edema with herniation of the cerebellar amygdalae.

No relevant morphological alterations were observed in the remaining organs.

(Dr. Léa M. M. F. Demarchi)

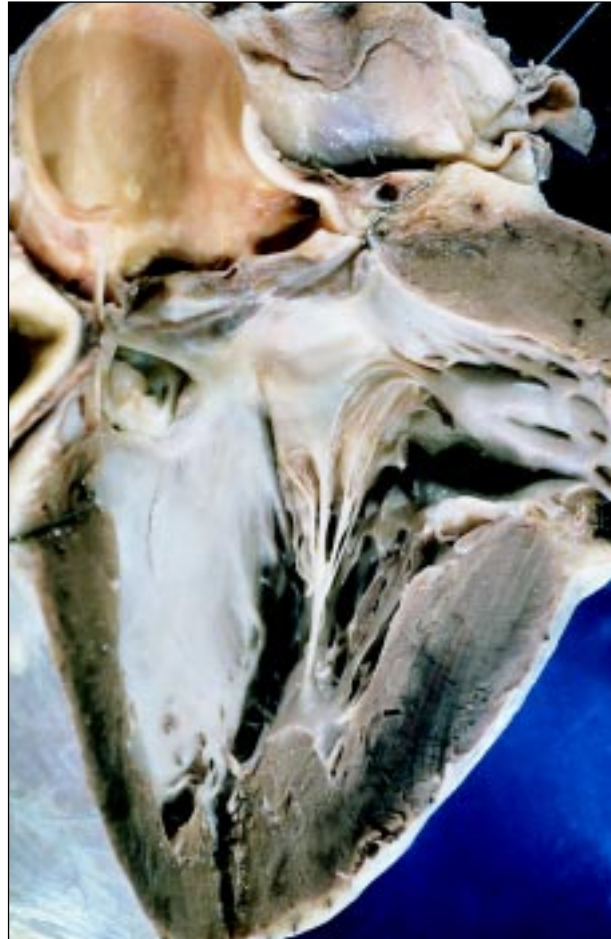


Fig. 3 – Section of the left ventricular outflow tract showing the defect of the perimembranous ventricular septum, which is totally occluded due to the adhesion and fibrosis of the anterior and septal leaflets of the tricuspid valve to the margins of the septal orifice.

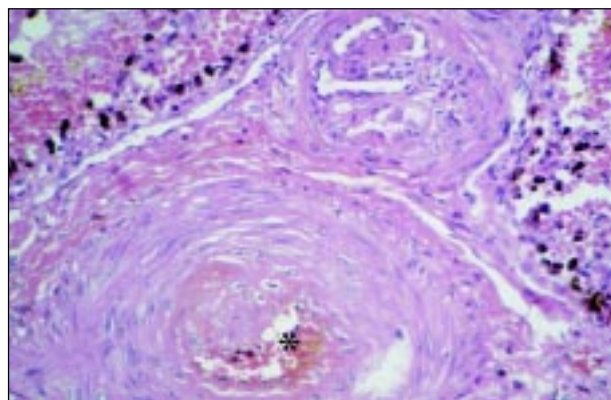


Fig. 4 – Histologic section of the lung showing a plexiform lesion of a pulmonary arteriole compatible with Heath-Edwards grade IV pulmonary hypertension. Note a fibrin thrombus in the vascular lumen (*). (Hematoxylin and eosin, original magnification x 160).

Anatomicopathological diagnoses – 1) Perimembranous ventricular septal defect in the ventricular inlet, which was naturally closed by the anterior and septal leaflets of the tricuspid valve; 2) Pulmonary vascular alterations corresponding to Heath-Edwards grade IV pulmonary hyper-

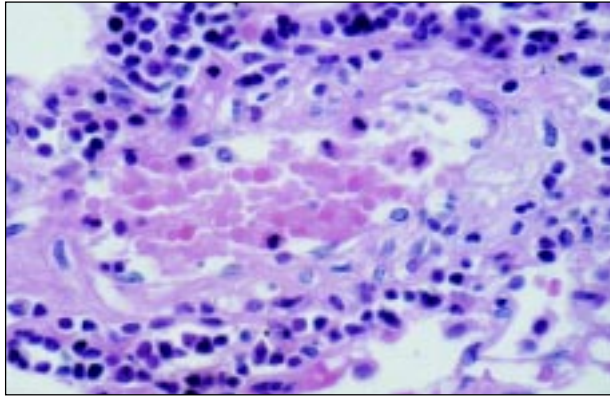


Fig. 5 - Histologic section of the lung showing moderate lymphomononuclear inflammatory infiltrate around a pulmonary arteriole. No histologic alterations compatible with active vasculitis were observed. (Hematoxylin and eosin, original magnification x160).

tension; 3) Surgically drained anemic and cavitated cerebellar infarct; 4) Cerebral edema.

(Dr. Léa M. M. F. Demarchi)

Comments

We have a case of pulmonary hypertension in a young woman with juvenile rheumatoid arthritis and naturally closed ventricular septal defect. The patient died because of alterations related to intracranial hypertension secondary to an anemic cerebellar infarct with approximately 3 weeks of evolution.

Despite the clinical suspicion of abscess, the histological cerebellar alterations are more consistent with cavitated anemic infarct. Cerebellar anemic infarcts are caused by a deficiency in irrigation of the superior or inferior cerebellar arteries, which are part of the vertebro-basilar territory. The most common causes are thrombosis, vasospasm, or arterial hypotension, and, more rarely, congenital malformations, such as the presence of rings in the walls of the cerebellar arteries, which reduce even more the lumen of these small-caliber arteries. However, on autopsy, we could not find morphological changes of cerebellar ischemia.

The major reason for discussion in this case is pulmonary hypertension, because the patient had 2 diseases that could lead to pulmonary vascular alterations: juvenile rheumatoid arthritis and ventricular septal defect. Therefore, we can not say that the patient had primary pulmonary hypertension.

Pulmonary involvement is one of the extraarticular manifestations of juvenile rheumatoid arthritis². Different pleural lesions may be found, pleural effusion being the most common. Parenchymal lesions, such as interstitial pneumonia, pulmonary fibrosis, rheumatoid nodules, and, more rarely, vasculitis and pulmonary hypertension, may also be found²⁰. In the lungs, we could not find other morphological alterations in addition to the vascular lesions of pulmonary hypertension, the moderate lymphomononu-

clear inflammatory infiltrate, and the focal areas of mild pleural fibrosis suggesting impairment due to rheumatoid arthritis. However, this does not allow us to completely eliminate the possibility of juvenile rheumatoid arthritis being the cause of or contributing to the development of pulmonary hypertension in our patient.

Ventricular septal defects represent the most frequent congenital cardiac anomaly. They are usually found in isolation, but may also be present in association with other cardiac malformations²¹.

In the case being discussed, likewise with most ventricular septal defects²², the defect was of the perimembranous type. It was located in the right ventricular inlet and was totally and naturally closed by the anterior and septal leaflets of the tricuspid valve.

Ventricular septal defects may be naturally closed by 2 mechanisms²¹: 1) by formation of fibrous tissue beginning at the fibrous or valvar structures, usually of the tricuspid valve, located in the proximities of the defect²¹. In these cases, the diagnosis of aneurysm of the membranous septum is made, which is a wrong determination, because only rarely is the fibrous tissue that closes the defect derived from the membranous septum or its remnants^{23,24}; 2) by adhesion of the septal leaflet of the tricuspid valve, which occurs only if the leaflet is adjacent to the communication orifice, ie, when the defect is located in the right ventricular inlet²¹, as is the case of our patient.

Hemodynamic alterations of a patient with ventricular septal defect are determined more by the size of the defect than by its location²². Pulmonary hypertension develops in patients with nonrestrictive defects, which comprise those defects large enough to cause no difference in pressure between the 2 sides of communication²⁵. Therefore, the flow through the defect is not determined by a pressure gradient, but by the relative resistance between the pulmonary and systemic circulations²⁵. At birth, the pulmonary vascular resistance of an individual usually decreases suddenly in regard to systemic resistance²⁵. In the presence of a nonrestrictive ventricular septal defect, blood flows from the left to the right ventricle through the ventricular communication, increasing pulmonary flow²⁵. Therefore, if the defect is not surgically corrected, the patient will develop pulmonary hypertension²⁶.

In the case being discussed, even though the assessment of the size of communication has been impaired by the natural closure, the diameter of the defect seemed to measure around 1.5cm, with a great possibility of being nonrestrictive. A few authors consider that ventricular septal defects with a diameter equal to or higher than 1.5cm are nonrestrictive²⁷.

With elevation of pulmonary resistance, blood flow through the defect becomes minimal, and reversion in the flow direction may occur. Therefore, a right-to-left ventricular blood flow may result, characterizing Eisenmenger's complex.

In most congenital cardiac anomalies, Eisenmenger's complex manifests in the first year of life, and is well established by the

age of 2 to 3 years, being observed in around 5% to 10% of the patients with large nonrestrictive ventricular septal defect²⁶.

Indications for surgical treatment comprise the following: left-to-right ventricular blood flow higher than 2:1, recurring endocarditis, and progressive aortic insufficiency. Once established, Eisenmenger's complex contraindicates the surgical repair of any intracardiac communication²⁶.

Therefore, we could prevent the pulmonary complication of pulmonary hypertension secondary to a large ventricular septal defect through surgical repair before the age of

2 years²⁶. In the case being discussed, we believe that, despite the natural closure of the ventricular septal defect, pulmonary hypertension could have resulted from an increase in pulmonary blood flow, which the patient underwent when the defect was still patent. Once more we emphasize that we have not found enough morphological data to eliminate the possibility that juvenile rheumatoid arthritis may have also contributed to the appearance of pulmonary hypertension.

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