Clinicopathologic Session

Case 2/00 – A 15-year-old male with progressive muscular dystrophy of the Becker type and severe heart failure - Instituto do Coração of the Hospital das Clínicas - FMUSP

The patient is a 15-year-old male admitted to the hospital due to abdominal pain, vomiting, dark urine, and edema.

The patient had a history of good health until the age of 10 years when progressive muscular weakness, mainly in the lower limbs, began. He sought medical assistance and was diagnosed of progressive muscular dystrophy of the Becker type. His mother, a 34-year-old woman, is considered an asymptomatic carrier of the gene for progressive muscular dystrophy, and his 4-year-old brother has signs of progressive muscular dystrophy of the Duchenne type.

The patient also had bronchial asthma.

He reported fatigue on exertion six months earlier and daily crises of tachycardic palpitations 4 months earlier with cold sweating and perioral paleness of approximately 15 minutes of duration. He denied syncope. Two months earlier, dyspnea became worse, being triggered on minimum exertion, and edema appeared. To the patient was prescribed 40mg of furosemide and 0.25mg of digoxin daily. One month earlier, the patient required hospitalization to control heart failure, and he was discharged with symptom improvement and the same medicamentous prescription. Chest X-ray at that time showed cardiomegaly (+++/4+), and the patient was then referred to InCor for medical treatment.

On physical examination (1/24/97), the patient was in a wheelchair, thin, eupneic, with a regular pulse of 92bpm, and blood pressure of 100/70mmHg. The precordium was mildly bulgy and the lung examination was normal. The ictus cordis was palpable on the 7th intercostal space, no thrill was audible, the first cardiac sound was split on the tricuspid region, the 4th cardiac sound was audible, and no murmur could be heard. The liver was palpable 1cm from the right costal margin and no edema existed. All pulses were palpable and symmetric.

Electrocardiographic assessment (1/10/97) showed sinus rhythm, heart rate of 100bpm a PR interval of variable duration 0.16s or 0.12s. Internimtent delta wave was present, QRS duration was 0.12s and the QRS axis was shifted upwards and to the left. The delta wave was positive in I, aVL, and from V2 to V6, and negative in II, III, aVF and V1 (fig. 1). The diagnosis (was preexcitation of Wolf-Parkinson-White syndrome).

A chest X-ray showed cardiomegaly (+++/4+) and a mild increase in the pulmonary trunk.

The medications being used were maintained and 12.5mg daily of captopril was added. Assessment of cardiac function and arrhythmias was started.

Three months later (4/11/97), the patient sought medical assistance due to edema, which had started in the lower limbs and had proceeded to the face in the 2 previous months, with cough and hemoptysis, reduction in appetite, and weight loss. Two weeks earlier, in addition to edema, pain in the right hypochondrium, vomiting, and dark urine appeared. The patient denied dyspnea and fecal acholia.

On physical examination (4/11/97), the patient was in regular condition, eupneic, with a regular pulse of 100bpm and blood pressure of 100/70mmHg. Lung examination showed reduction in the respiratory sounds in both bases and no rales. Heart examination showed no abnormal cardiac sounds and no murmurs. The liver was palpated 5cm from the right costal margin.

The electrocardiogram (4/12/97) showed sinus rhythm, heart rate of 125bpm, QRS axis of +140° parallel, left and right atrial hypertrophy and left and right ventricular hypertrophy.

The laboratory tests at admission are shown in table I.

The echocardiogram (4/13/97) showed left ventricular diastolic and systolic diameters of 58mm and 52mm, respectively, and a circumferential shortening fraction of 10%. The left ventricle was diffusely hypokinetic and signs of a thrombus of 23mm were detected in the left ventricular apex.

Ventilation and perfusion pulmonary scintigraphies (4/14/97) showed hypoperfusion in the right pulmonary middle 1/3 and base, and in smaller areas of the lateral segment of the middle lobe, and part of the anterior basal and posterior basal segments of the lower lobe of the same lung. In the ventilation scintigraphy as compared with the perfusion study, a concordant pattern was observed in the lateral segment of the middle lobe and a discordant pattern in the remaining segments. Those images suggested right pulmonary thromboembolism with a probable infarct in the middle lobe.

The patient evolved with clinical improvement, requiring a continuous use of dobutamine and dopamine, in addition to 80 mg of furosemide daily. On April 4th, 24,000 units of heparin through intravenous via were started.

On the night of April 20th, the patient had general tonic-clonic convulsions followed by bradycardia and cardiac arrest that did not respond to resuscitation maneuvers and died.

Muscle biopsy – A muscle biopsy was performed on

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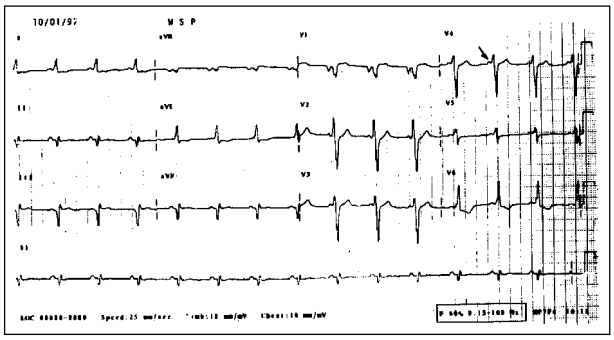

Fig. 1 - Electrocardiogram – preexcitation syndrome, intermittent delta waves.

the biceps brachii muscle and serial frozen sections were stained by hematoxylin and eosin and the modified Gomori's trichrome. The sections also underwent histochemical reactions, such as NADH, SDH, acid phosphatase, and 4.3 and 9.4 ATPase. The biopsy showed a variation in the diameter of the muscle fibers, presence of round hyaline fibers, degenerating fibers, predominance of type I fibers, and proliferation of the endo- and perimysial connective tissue.

Dystrophin analysis by immunostaining and the quantitative Western blot analysis showed a reduced amount and abnormal molecular weight of that protein.

(Dr. Sueli Kazue Nagahashi Marie)

Discussion

Clinical features – The patient is a 15-year-old male diagnosed with Becker muscular dystrophy and progressive heart failure of recent onset.

On physical examination, the cardiac silhouette was enlarged and the 4th cardiac sound was audible, indicating cardiac dilation and myocardial dysfunction. These findings were confirmed on echocardiographic analysis, which showed a low circumferential shortening fraction and diffuse hypokinesia.

Appearance of edema in the lower limbs and face in association with pain in the right hypochondrium, vomiting, and enlargement of the liver on palpation, indicate aggravation of the heart failure and visceral congestion. Because the serum levels of albumin, total proteins, and creatinine were normal, the possibility of the edema being due to hypoproteinemia or renal failure was eliminated.

Another cause of vomiting could be the patient's low cardiac output.

The facial edema could also be caused by an obstruction of the superior vena cava; however, as enlargement of the liver occurred as well as edema of the lower limbs, the most probable cause is an increase in right ventricular filling pressures.

Hemoptysis could be a consequence of pulmonary

Table I – Admission laboratory tests

Laboratory tests	4/11/97	4/14/97	4/20/97
Red blood cells/mm^3	6.500.000	-	4.700.000
Hemoglobin g/dL	15.5	-	11.5
Hematocrit %	49	-	35
MCV ((m3)	75	-	74
MCHC (g/dL)	32	-	33
Leukocytes/mm^3	11.100	-	12.200
Rod (%)	8	-	6
Segmented (%)	70	-	61
Eosinophils (%)	0	-	0
Basophils (%)	1	-	0
Lymphocytes (%)	20	-	28
Monocytes (%)	1	-	5
Platelets/mm^3	273.000	-	448.000
Prothrombin time (s)	15.3 (N=12,2)	16.9 (12.2)	15.7 (12.2)
INR	1,62	1.99	1.29
APTT(s)	29.4 (N=28)	59.4 (28)	35.1 (28)
Fibrin dimer (N <500ng/mL)	-	positivo	-
Fibrinogen (mg/dL)	-	326(200-400)	-
Activity of the factors II, VII and X (%)	-	50 (100)	-
Activity of factor V (%)	-	76 (68-150)	-
Platelet aggregation	-	normal	-
Presence of lupus anticoagulant	-	negativa	-
Urea(mg/dL)	49	-	40
Creatinine (mg/dL)	0.5	-	0.5
Total protein (g/dL)	6.9	-	-
Albumin (g/dL)	3.7	-	-
Total bilirubin (mg/dL)	1.4	-	-
Direct bilirubin (mg/dL)	0.62	-	-
GOT/AST (U/L)	23	-	-
GPT/ALT (U/L)	15	-	-
Lactic dehydrogenase (U/L)	-	341 (240)	-
Sodium (mEq/L)	134	-	130
Potassium (mEq/L)	5.4	-	4.8

Arq Bras Cardiol
volume 74, (nº 4), 2000

congestion only but pulmonary thromboembolism should always be eliminated because the patient had congestive heart failure and remained in bed, which are known factors associated with that complication. Confirming this fact, in the present case, in addition to hemoptysis, aggravation of dyspnea and electrocardiographic alterations suggesting hypertrophy of the right chambers of sudden onset occurred. These findings together with those of the ventilation and perfusion pulmonary scintigraphies and the presence of fibrin dimers strongly suggest the diagnosis of pulmonary thromboembolism.

The patient had crises of tachycardic palpitations in association with sweating and paleness. Electrocardiographic analysis showed a PR interval of variable duration; when it was short, a negative delta wave appeared in V1, II, III, and aVF, as well as a sudden transition of the QRS complex from V1 to V2, with an alteration in the QS pattern to RS. These findings suggest the presence of a preexcitation syndrome with an anomalous via of right posteroseptal location.

The convulsions preceding the cardiopulmonary arrest could have resulted from embolization of the left ventricle thrombus; the patient, however, had been under anticoagulation therapy with heparin for six days.

The patient's cause of death was a natural evolution of the cardiomyopathy of progressive Becker muscular dystrophy leading to severe and terminal heart failure. The final event might have been ventricular tachyarrhythmia or supraventricular arrhythmia with rapid conduction through the anomalous via, both causing ventricular fibrillation and death.

Considering the syndromic point of view and the pathophysiology of the cardiovascular events, those are the significant findings in this case. Now I begin to discuss the etiology and pathophysiology of the patient's underlying disease, Becker muscular dystrophy.

Muscular dystrophy belongs to a group of hereditary and progressive diseases. Cardiac involviment is an inherent part of the management[1]. The X-linked muscular dystrophy has 2 variants as follows: Duchenne muscular dystrophy and Becker muscular dystrophy.

The disease is recessive and sex-linked, being transmitted from the mother to half of her male offsprings as a manifest disease and to half of her female offsprings as gene carriers. Therefore, genetic counseling is important because of the high probability that a mother carrying the gene will give birth to a female carrier (50%) or a sick male (50%).

The gene for Duchenne muscular dystrophy was identified in the short arm of the X chromosome in the Xp21 locus and it has a high mutation rate. Cardiac involvement in Becker muscular dystrophy occurs preferentially when deletion of the gene includes a specific segment of intron located between the 48 and 49 exon [1].

That gene produces the dystrophin protein that is located in the sarcolemma of the muscle fibers and accounts for their stability [2]. In Duchenne muscular dystrophy, that protein is absent or present in small amounts, with a normal molecular weight. On the other hand, in Becker muscular dystrophy, dystrophin is present but has an abnormal molecular weight.

Clinically, it is possible to distinguish the 2 forms of muscular dystrophy. Duchenne muscular dystrophy has the onset of its manifestations at about the age of 2 years, and it is rapidly progressive with loss of strength, mainly in the muscles of the pelvic and shoulder girdles (proximal muscles of the limbs), involving rather the lower limbs than the upper limbs. Waddling gait, frequent falls, pseudohypertrophy of the calves, lumbar lordosis, kyphoscoliosis, and shortening of the Achilles tendon are commonly found. Between the 8th and the 10th year of life, walking requires the use of crutches and by the age of 12 most patients are confined to wheelchairs.

Becker muscular dystrophy is slowly progressive and usually starts around the age of 5 years (from 5 to 15 years), but it may start in the 3rd or 4th decades of life. Patients manage to walk until after the age of 15, which constitutes a clinical difference between the two forms of muscular dystrophy [3].

Cardiac involvement occurs in both forms of muscular dystrophy. In Duchenne muscular dystrophy, heart failure is rapidly progressive, but it may stabilize after some time, and the only evidence of cardiac involvement may be electrocardiographic alterations [4]. Thoracic deformities may render the clinical examination of the heart difficult. Pulmonary and systemic thromboembolism have been reported in the final stages of the disease.

Cardiac involvement is segmentary, with dystrophy of the posterobasal segment and lateral extension of the left ventricular wall. This may cause dysfunction of the posterolateral papillary muscle and mitral regurgitation [5].

Electrocardiographic alterations are present from childhood onward and consist of the following: appearance of wide R waves in the right leads, increase in the R/S relation, and Q waves in I, aVL, V5 and V6.

Inappropriate sinus tachycardia is the most common arrhythmia and, in the final phase of the disease, atrial flutter is the most common supraventricular arrhythmia. Atrial extrasystoles and ectopic atrial rhythm have also been reported. Fifty per cent of the cases have a short PR interval without delta waves, which may represent atriofascicular bands or accelerated conduction of the atrioventricular node [6].

In Becker muscular dystrophy, heart disease is severe and rapidly progressive with a frequent impairment of the heart after adolescence. Dilation of the 4 cardiac chambers occurs and cardiac involvement may be more intense than muscle incapacitation. Cardiac involvement in Becker muscular dystrophy is characterized by a precocious involvement of the right ventricle in association or not with left ventricular dysfunction [1]. Yet, abnormality in infranodal conduction may occur, which may be expressed through fascicular and atrioventricular blocks.

(Dr. José Leão de Sousa Jr)

Diagnostic hypotheses – Cardiomyopathy of Becker muscular dystrophy, preexcitation syndrome, and pulmonary thromboembolism.

Neurologist comments – Anatomicopathological findings of muscular dystrophy in skeletal muscles are characterized by the presence of excessively stained necrotic or degenerating hyaline fibers, with a marked variation in the diameter of the muscle fibers and replacement of these fibers by adipose tissue and connective tissue, which proliferates in the endomysium and perimysium.

Dystrophin, which is usually distributed in the subsarcolemmal zone of skeletal muscle fibers, is absent in Duchenne muscular dystrophy (DMD) and present in variable amounts with a discontinuous marking in Becker muscular dystrophy (BMD). Usually, the amount of dystrophin present in BMD is inversely proportional to the severity of clinical findings [7,8].

Dystrophin production depends on the maintenance of the mutation ability of protein transcription and synthesis. Usually, out-of-frame deletions, which rupture the reading frame of the mRNA of dystrophin, lead to the formation of a very abnormal protein, which is rapidly destroyed by the cell. This happens in DMD. If the deletion preserves the reading frame of the mRNA (in-frame mutation), a qualitatively or quantitatively altered protein is formed, which is partially functional. This occurs in more moderate and varied cases, such as BMD [9].

Diagnosis of dystrophy linked to the X chromosome is made by the following methods: 1) dosage of CK – elevated levels up to 300 times the normal value, even in preclinical stages; 2) detection of deletion in the gene of dystrophin in DNA of peripheral lymphocytes; 3) muscle biopsy, which is considered the gold standard for diagnosis in cases where deletion is not detected. Immunostaining and quantification of dystrophin by Western blot are performed in the biopsy [10,11].

Prenatal diagnosis may be made in pregnant women carriers or those at risk through the demonstration of deletion on the Xp21 in DNA extracted from cells of the chorionic villi obtained through biopsy performed by the 10th gestational week [12].

Detection of a female carrier is the most important way of preventing new cases of DMD/BMD. CK level helps in this detection because it is increased in about 80% of female carriers. Among the most recent techniques used in detecting female carriers, we can cite the following: restriction fragment length polymorphism study (RFLP), the use of probe linkage for determining polymorphic DNA sequences; identification of the mutation through analysis of DNA dosage; detection of the junction of fragments through in situ hybridization; DNA sequencing and mRNA amplification in lymphocytes. If the mutation of the family is known, the carrier condition may be determined with 100% of accuracy [13,14]. Immunohistochemical analysis of dystrophin in female carriers shows mosaic staining with positive and negative fibers [15]. Usually, asymptomatic female carriers have the stain of normal dystrophin.

(Dr. Sueli Kazue Nagahashi Marie)

Autopsy

The heart showed dilation of the 4 chambers and biventricular cavitary thrombosis (fig. 2). The left ventricular wall was not thickened (7mm). Microscopically, narrowing of the myocardial fibers occurred as well as scarce foci of fibrosis (fig. 3) and a mononuclear inflammatory cell infiltration, with no aggression to the cardiomyocytes. Despite focal disarrangement of myocardial fibers, the amount was not enough to characterize hypertrophic cardiomyopathy. Thromboembolism with recent hemorrhagic infarct in the lower lobe of the left lung and in the middle and lower lobes of the right lung (fig. 4) was observed. Death resulted from

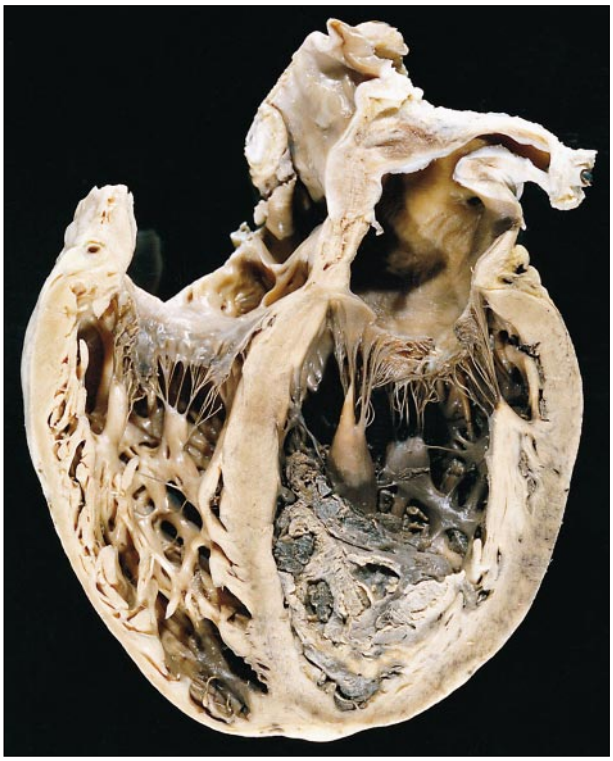

Fig. 2 – Section showing dilation of the 4 cardiac chambers and biventricular thrombosis.

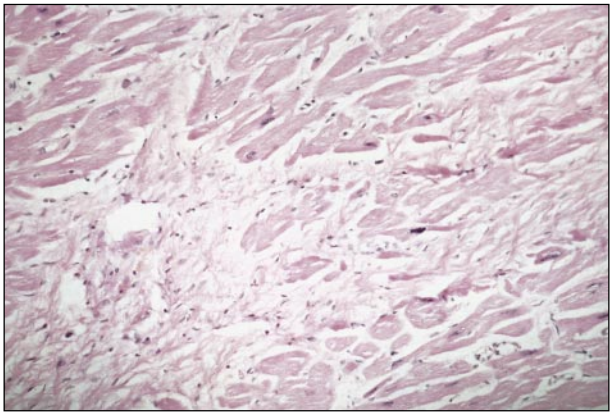

Fig. 3 – Photomicrography of the myocardium showing atrophic cardiac fibers and focal fibrosis (H&E, original magnification 160x).

Arq Bras Cardiol
volume 74, (nº 4), 2000

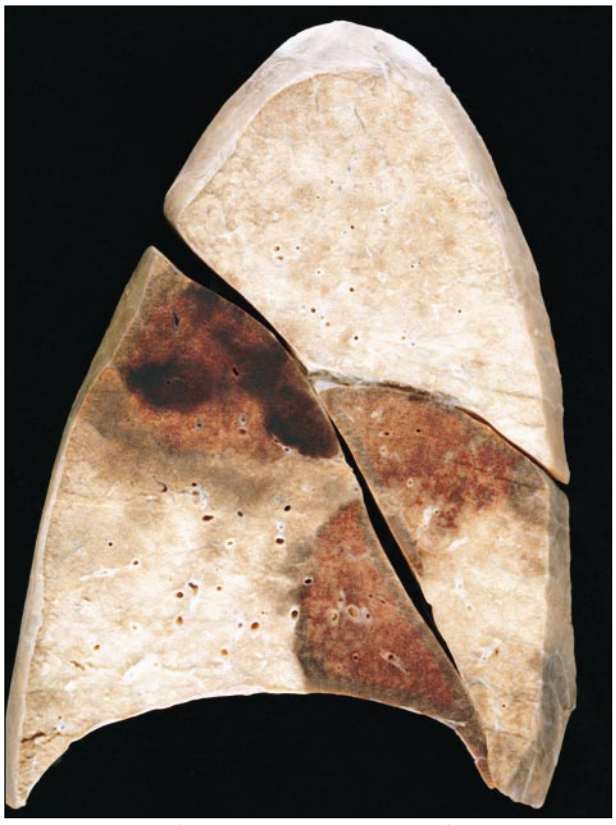

Fig. 4 - Hemorrhagic infarcts in the middle and lower lobes of the right lung.

the aggravation of heart failure due to the pulmonary lesions. The rectus abdominis muscle showed mild atrophy. Muscle changes might have been more exuberant if a muscle of the lower limbs had been examined.

(Dr. Paulo Sampaio Gutierrez)

Anatomicopathological diagnoses – Cardiomyopathy of Becker muscular dystrophy; biventricular thrombosis; bilateral pulmonary thromboembolism.

Comments

Becker muscular dystrophy, like the Duchenne variant, is related to a defect in the short arm of the X chromosome in the Xp21 locus [1]. Both may show cardiac involvement, which is characterized by arrhythmia or congestive heart failure with dilated cardiomyopathy, or both. Absence of cardiac symptoms in some patients is believed to result from a limitation in physical activities directly caused by the skeletal muscle disease. In some series of patients with Becker muscular dystrophy, cardiac changes are found in 60% to 70% of cases [15]. No study exists of the incidence of muscle disease among patients with dilated cardiomyopathy or with arrhythmias, who probably constitute a small fraction of patients. Therefore, the neurologist managing a patient with muscle disease should proceed to the appropriate and careful cardiac evaluation. In the same way, the cardiologist examining a patient with dilated cardiomyopathy or arrhythmias with no demonstrable cause should investigate, including genetic counseling, whether a di–sease of that type exists or not. For this purpose, dosage of creatine kinase should be performed, or as a last resource, the immunohistochemical analysis of the myocardial biopsy, once the material is frozen and not fixed in formalin [16, 17].

(Dr. Paulo Sampaio Gutierrez)

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