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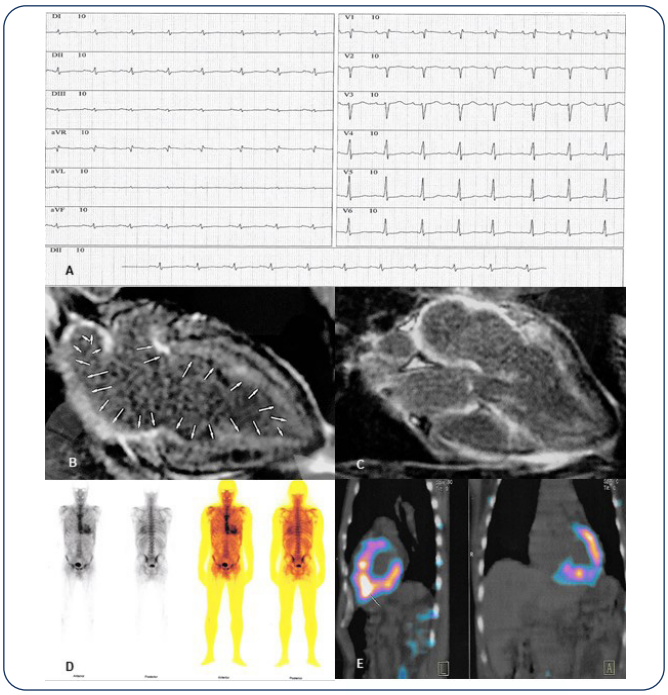

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Syncope as a Phenotypic Expression of Hereditary Transthyretin Amyloidosis Val142Ile (Val122Ile)

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Introduction

Transthyretin amyloidosis (ATTR) is a familial disease caused by one of more than 100 described mutations, where there is production of amyloids that are deposited in tissues.[1] Phenocopies include neuropathy (autonomic and peripheral), cardiomyopathy, renal, gastrointestinal, vitreous and meningeal involvement, which vary according to the genetic mutation, ethnicity and geographical origin, even among individuals with the same mutation or within the same family.[2]

Syncope (transient loss of consciousness caused by global cerebral hypoperfusion) in the presence of heart disease confers risk of fatal events.[3] The Val142Ile mutation has heart failure with preserved ejection fraction (HFpEF) as the predominant clinical phenotype, with syncope being an uncommon symptom.[4,5]

Case Report

The patient was male, 64 years old, of white ethnicity, engineer, born in Rio de Janeiro. He reported an isolated episode of syncope when he quickly got up from a sitting position after running. There was a history of sudden death in the family (uncle at 60). He used to take escitalopram 10 mg/day and finasteride 5 mg/day.

At physical examination: BMI of 21.8 kg/m^2 and jugular turgency at 45º. BP: 140x80 mmHg, HR: 85 bpm, RR: 18 breaths per minute, fourth heart sound, sustained and palpable apex beat in the 6º intercostal space at the hemiclavicular line, clear lungs and ankle edema. He was in NYHA FC I. Blood: BNP: 233 pg/mL (NV: up to 100 pg/mL) and ultra-sensitive Troponin: 0.135 ng/mL (NV: up to 0.01 ng/mL).

The electrocardiogram (EKG) (Fig.1) showed sinus rhythm, HR: 84bpm, right bundle branch block, low voltage in frontal leads, and an pseudo-infarct pattern in precordial leads.

Keywords

Syncope; Amyloidosis, Familial/genetics; Amyloid Neuropathies, Familial; Cardiomyopathies/diagnosis; Diagnostic, Imaging/methods; Prevalence.

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The transthoracic Echocardiogram (TTE) showed left ventricular hypertrophy (LVH) - septum = 16 mm and posterior wall = 13 mm - mitral flow with type II relaxation deficit and LA indexed volume: 87 mL/m^2 (Figure 2). 24-h Holter and Exercise Test (ET) showed short and asymptomatic polymorphic ventricular tachycardia (PVT) outbreaks.

Cardiac magnetic resonance imaging (CMRI) at rest and after stress with dipyridamole requested after TTE showed diffuse LVH and absence of myocardial ischemia, with areas of lateral and anterior mesocardial late enhancement (LE) and diffuse subendocardial LE in the LV, atria and interatrial septum (Figure 1). Evaluation of global longitudinal strain (GLS) after CMRI showed marked alterations in the basal and medial portions of all myocardial walls, sparing the LV apical regions, which was consistent with the described cardiac amyloidosis (CA) pattern.

Abdominal fat and rectal biopsies confirmed the diagnosis of amyloidosis with Congo red staining. Immunofixation in blood and 24-h urine and measurement of light chains Imunoglobulins in the blood ruled out monoclonal gammopathy, after which cardiac technetium-99m pyrophosphate scintigraphy (99mTc-PYP) (Figure 1) was requested, witch showed intense radiotracer uptake in the myocardium (grade 3), suggesting Transthyretin CA (ATTR-CA) etiology.

Finally, the patient underwent genetic testing, which confirmed a heterozygous Val142Ile mutation for the TTR gene.

Discussion

When evaluating a syncope patient, it is a priority to stratify the risk of fatal events,[3] which take into account electro and echocardiographic alterations, which were present in this patient. The low voltage pattern found in the EKG (Figure 1), in the presence of LVH, are already warning signs for the diagnosis of CA.[1,4,6]

Elevated BNP and troponin levels reflected increased intracavitary pressures and ongoing myocardial injury, which was indicative of heart disease.

The TTE confirmed the suspected heart disease. The (Figure 2), family history of sudden death and the presence of PVT on exertion raised the suspicion of cardiac syncope and the main differential diagnoses would be hypertrophic cardiomyopathy (HCM), coronary artery disease (CAD) and CA.[3]

The CMRI, which was subsequently requested, provided evidence that was strongly suggestive of CA, given the characteristic LE pattern, ruling out the hypotheses of HCM and

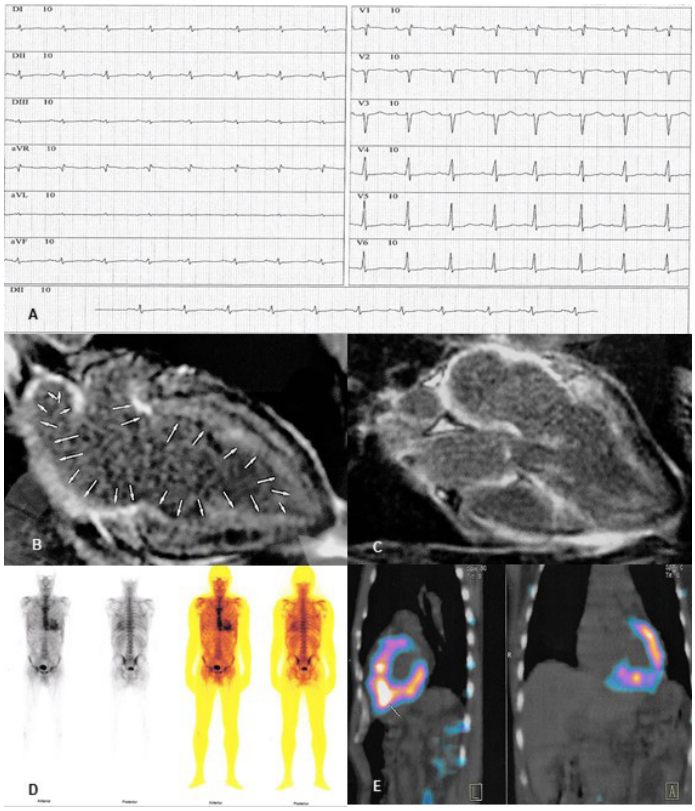

Figure 1 – *A) Electrocardiogram: Sinus rhythm, HR: 88 bpm, indeterminate QRS axis. P-wave in the frontal plane with increased duration (160 ms), with partial Bachmann's bundle block and tricuspid P wave in D2, D3 and aVF; qR pattern in V1 and Morris index are observed in the horizontal plane, which means right and left atrial enlargement. Pseudo-infarct pattern in precordial leads and presence of low voltage in the frontal plane are also observed. B and C) Resting Cardiac MRI shows diffuse LVH, with areas of diffuse subendocardial late enhancement in the LV (arrows), atria, and interatrial septum. D and E) 99mTc-PYP myocardial scintigraphy showing intense radiotracer uptake in the myocardium (Grade 3).*

CAD. Because gadolinium is a purely extracellular agent and does not penetrate the intact cardiomyocyte, the characteristic appearance of LE (Figure1) in non-coronary territory is extremely suggestive of CA and this was decisive in this case.[1,4,7]

The evaluation of myocardial deformity by the GLS technique, performed after the CMRI, demonstrated a typical pattern of CA (Figure 2), which ruled out other causes of LVH and corroborated the diagnosis, which has been very useful in this scenario.[8]

Among the CA types, the one caused by light chains Imunoglobulins (AL) is the one that most commonly affects the heart; therefore, we began with the search for hematological disease.[1,4,6] Since the definitive diagnosis of CA required tissue biopsy at that time, this was performed. More recent diagnostic algorithms reserve tissue biopsy only for suspected cases of AL, as the 99m-Tc-PYP myocardial scintigraphy replaced myocardial biopsy in ATTR-CA.[1,9]

This technique has been used for a long time to diagnose bone diseases, of which radiotracer has a strong affinity for calcium, that is almost only present in ATTR deposits. Positive and negative predictive values for ATTR diagnosis by 99mTc-PYP myocardial scintigraphy with a score ≥ 2 are 88 and 100%, respectively. Diagnostic certainty is proposed when the score is ≥ 2 in the absence of an immunoglobulin monoclonal peak, which would be equivalent to a positive endomyocardial biopsy,[9] as in the case described (Figure1), witch was confirmed latter by the genetic testing.

The most frequent cardiac symptoms in Val142Ile ATTR are: heart failure, dyspnea, arrhythmias and dizziness. Syncope, most frequently found in AL (20%), is unusual in ATTR (8%), and when it occurs on exertion it represents the inability to increase cardiac output, which confers high mortality.[5,10] Moreover, sensitivity to intravascular fluid depletion combined with autonomic neuropathy, depressed myocardial reserve, atrial dysfunction and stiffness, and the presence of arrhythmias contribute to the occurrence of syncope.[6] All these possibilities make syncope a multifactorial presentation in CA, as it may have occurred in the case described herein.

THAOS, an open worldwid registry to all patients with ATTR, shows that the Val142Ile, also known as Val122Ile mutation, is the second most common genotype worldwide and the most common in the USA, accounting for 23% of the total mutations in the country and 1% in the rest of the world. The carriers of this mutation are mostly of African descent and males, being prevalent in 3 to 4% of African-Americans at birth, with a penetrance of approximately 20%.[5]

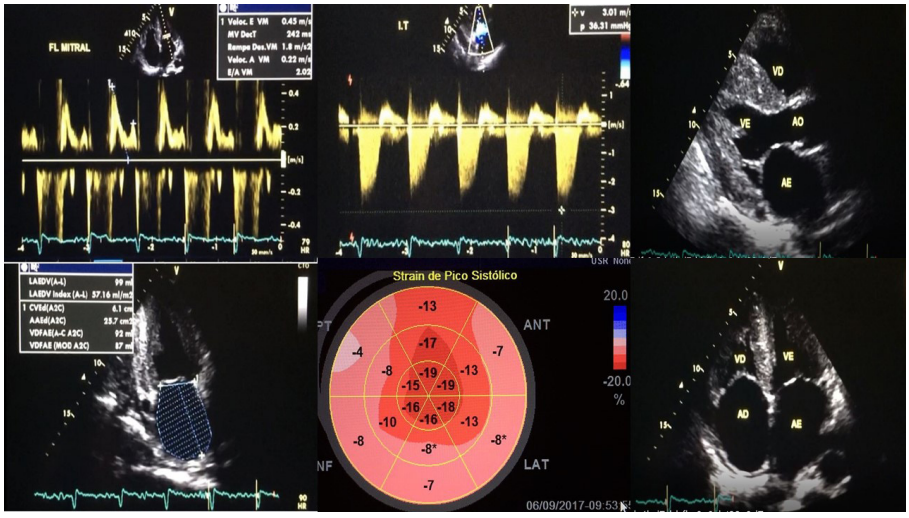

Figure 2 – *Transthoracic echocardiogram showing pseudonormal mitral Doppler pattern (type II diastolic dysfunction), tricuspid regurgitation peak velocity >2.8 m/s and biatrial enlargement with indexed LA volume of 87 mL/m². Parasternal longitudinal apical-4 chamber projections showing increased myocardial brightness, interatrial septum and valve thickening, and LVH. Global Longitudinal Strain showing typical amyloidosis pattern – "relative preservation of the apical regions" and longitudinal strain reduction in the basal and middle myocardial segments.*

ATTR is an underdiagnosed cause of HFpEF, although TTR deposits are identified in up to 30% of elderly patients referred for autopsy.[1,2,5] Syncope, although uncommon in the presentation of this phenotype, may be the first symptom of this disease.

Author contributions

Conception and design of the research and Acquisition of data: Nunes NSV, Mesquita CT, Mesquita ET; Analysis and interpretation of the data: Nunes NSV, Carvalho JPM, Costa FS, Nacif MS, Dominato J, Mesquita CT, Mesquita ET; Writing of the manuscript: Nunes NSV, Carvalho JPM, Costa FS, Nacif MS, Dominato J; Critical revision of the manuscript for intellectual content: Mesquita CT, Mesquita ET.

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Image Diagnosis: An Anomalous Origin of Left Coronary Artery from the Pulmonary Artery

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Introduction

Anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) is a rare congenital anomaly with a mortality of 90% by 1 year of age without surgical intervention.[1] Nowadays the procedure of choice for correction of ALCAPA depends on the establishment of a dual coronary artery system by direct reimplantation of the anomalous left coronary artery (LCA) into the ascending aorta. However, anatomic variations of the origin of the anomalous LCA often make this aim difficult to achieve, especially in patients undergoing reoperation.

Chronic ischemic mitral regurgitation (MR) develops as a consequence of coronary artery disease in the absence of primary leaflet abnormalities or chordal pathology:[2] ischemic cardiopathy causes remodeling of left ventricular geometry, displacement of papillary muscles, leaflet tethering and annular dilatation, leading to functional mitral insufficiency. The outcome of these patients represents a challenging problem for both cardiologists and cardiac surgeons. In fact, the role of mitral valve surgery (MVS) associated with coronary artery revascularization is still debated.

Case report 1

11-year-old boy from a remote village in southern China, s/p mitral valvuloplasty without significant symptomatic improvement. Transthoracic echocardiography (TTE) showed an enlarged left atrium of 61 mm, moderate MR (Figure 1A), and an ejection fraction of 60%. The right coronary artery (RCA) diameter was increased to 7 mm at the proximal end (Figure 1B), and the LCA was not from a left coronary sinus (Figure 1C) and inserted into the pulmonary artery through a 5-mm fistula (Figure 1D). Three-dimensional coronary artery computed tomography angiography (CTA) showed an ALCAPA (Figure 2B and D) with a giant and twisted RCA (Figure 2A and C). Ascending aorta angiography showed dilated and twisted RCA (Figure 3A and B) and ALCAPA. The direction of coronary blood flow was RCA-communicating branch-LCA-pulmonary artery (Figure 3C and D) and hence there was a coronary steal.

Case report 2

A 9-year-old Chinese boy status post mitral valve replacement for about seven years presented with repeated fever and exertional dyspnea and referred to our department. TTE showed an enlarged left atrium of 58mm, moderate mitral parabasilar leak, and an ejection fraction of 62%. The RCA diameter was increased to 5 mm at the proximal end, and the LCA was not from left crown sinus. Three-dimensional coronary artery CTA showed an ALCARPA (Figure 4B and C) with a giant RCA (Figure 4A, B and C). Ascending aorta angiography showed dilated and twisted RCA (Figure 4D). There was a phenomenon of stealing blood. The direction of coronary blood flow was from RCA-communicating branch-LCA-pulmonary artery (Figure 4E and F).

Result and conclusion

ALCAPA is a rare congenital anomaly with a mortality of 90% by 1 year of age without surgical intervention. Ninety percent of patients present in the first year of life with signs and symptoms of heart failure or sudden cardiac death secondary to chronic myocardial ischemia.[3] Adult survivors, however, are either asymptomatic or present with dyspnea, angina, MR, myocardial ischemia, or ventricular arrhythmia, pulmonary hypertension, and sudden death. This contrasts with the clinical presentation of myocardial ischemia and infarction (palpitations, angina and fatigue) in children, and failure to thrive, irritability, excessive sweating, and listlessness in babies.[4,5]

During the infancy phase, there is a decrease in pulmonary pressures and decline in oxygen levels leading to decreased coronary perfusion and ischemia, especially during feeding or crying when myocardial oxygen demand is increased. Chronic mycardial ischemia leads to impaired function not only of the myocardium, but often also of the mitral valve apparatus with cardiac failure and mitral valve regurgitation following. If this phase is tolerated, then compensatory changes occur over time and the myocardium remodels during in children. Due to the development of intercoronary collaterals from the increasingly large RCA providing collateral supply to the LCA leads to a reversal of flow from the anomalous left coronary into the pulmonary artery.[3] Finally, there are excessive collateral vessels that lead to the shunting of blood from the RCA via collaterals to the LCA and into pulmonary artery during in adults.[3,5] This is seen as an example of a phenomenon of stealing blood.

Keywords

Heart Defects,Congenital/surgery; Insufficiency Mitral Valve/surgery; Myocardial Ischemia; Diagnostic Imaging; Magnetic Resonance Imaging/methods; Pulmonary Artery/abnormalities; Echocardiography/methods.

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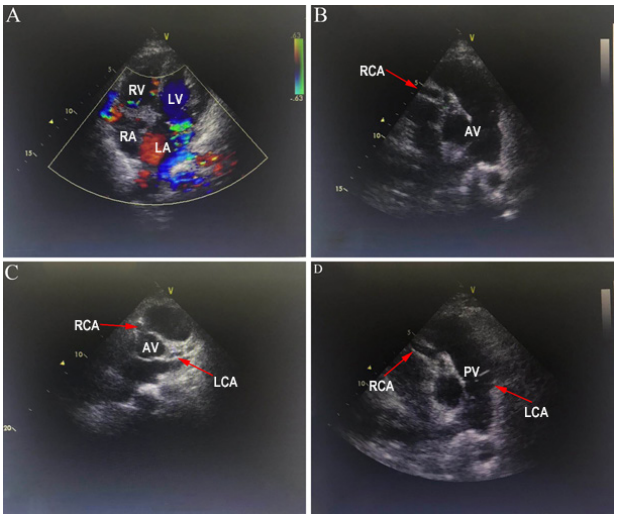

Figure 1 – *Transthoracic echocardiography showed moderate mitral regurgitation (A) and the RCA diameter was increased at the proximal end (B, arrows), and the LCA was not from left crown sinus (C, arrows) and inserted into the pulmonary artery (D, arrows). RV: right ventricle; RA: right atrium; LV: left ventricle; LA: left atrium; AV: aortic valve; RCA: right coronary artery; LCA: left coronary artery; PV: pulmonary valve.*

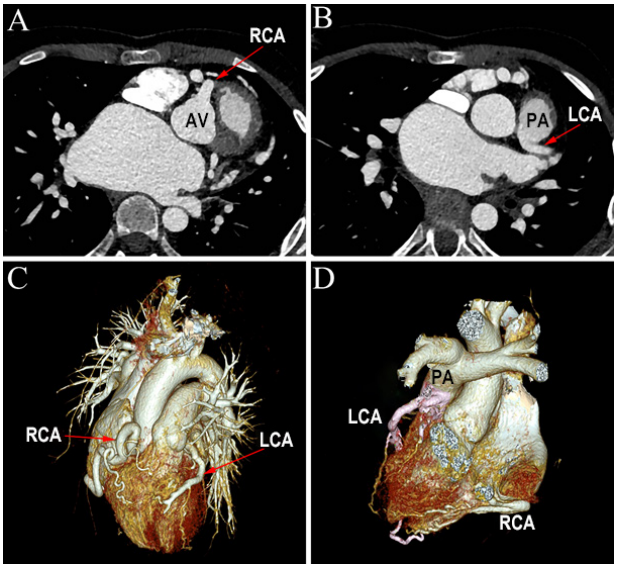

Figure 2 – *Computed tomography angiography scan image showed a giant and twisted RCA (A and C, arrows) and ALCAPA (B and D, arrows). AV: aortic valve; RCA: right coronary artery; LCA: left coronary artery; PA: pulmonary artery.*

Echocardiography is the mainstay of non-invasive diagnostic tool during early screening that depicts the abnormal origin of the LCA with an abnormal jet, left ventricular dilatation, dilated RCA, retrograde filling, the mild hypokinesis of the anterior wall, presence of hyperechogenicity of the endocardium and/or papillary muscles, the RCA diameter as a ratio of the aorta ring diameter, etc.[4]

The diagnosis of ALCAPA has traditionally been made by coronary angiography. In recent years, coronary computed tomographic angiography (CCTA) has emerged as the standard of reference for identification and characterization of coronary artery anomalies. CCTA allows a non-invasive accurate diagnosis, depicting the origin and course of the coronary arteries. Additionally, it offers a three-dimensional assessment of the anatomic relations between coronary arteries and adjacent structures,[6] and it provides sectional views of cardiac structures from various angles. Hence, it could be considered as the imaging modality of choice to noninvasively delineate coronary vessel anatomy. Moreover, it plays an important role in surgical intervention planning, and it may be a valuable postoperative follow-up tool for patients.[7]

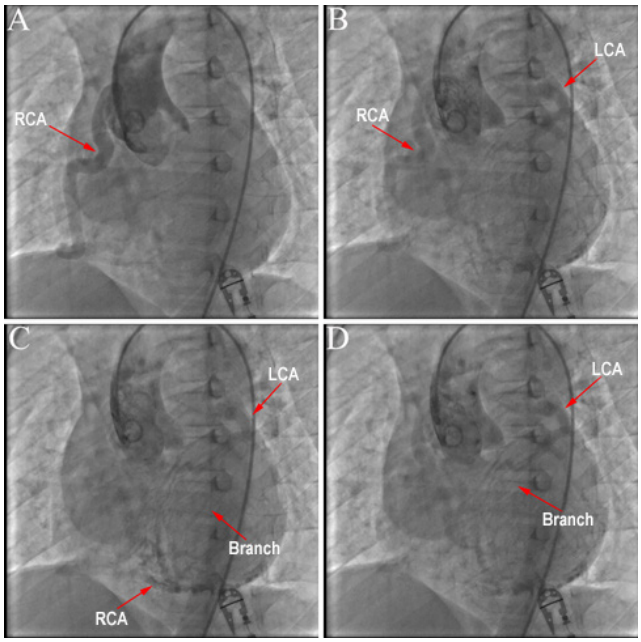

Figure 3 – *Ascending aorta angiography showed dilated and twisted RCA and ALCAPA (A and B, arrows) as well as a phenomenon of stealing blood (C and D, arrows). RCA: right coronary artery; LCA: left coronary artery.*

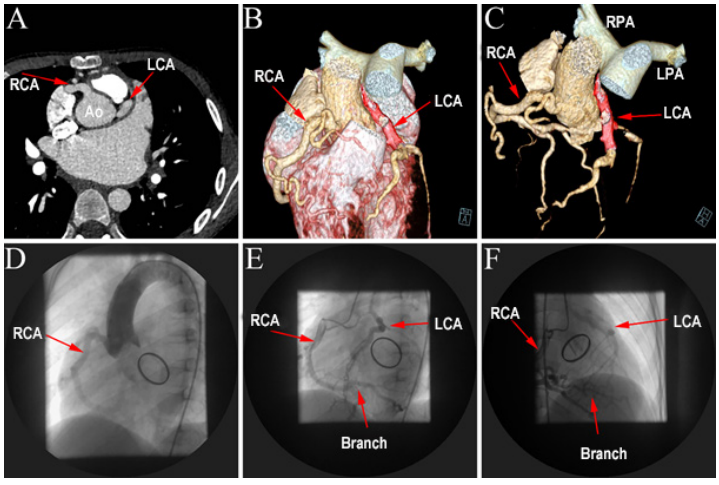

Figure 4 – *Computed tomography angiography scan image showed a giant RCA (A, B and C, arrows) and ALCARPA (C, arrows); Ascending aorta angiography only showed dilated and twisted RCA (D, arrows) and a phenomenon of stealing blood (E and F, arrows). Ao: aorta; RCA: right coronary artery; LCA: left coronary artery; LPA: left pulmonary artery; RPA: right pulmonary artery.*

The increasing use of cardiac magnetic resonance imaging (MRI) has not only increased the diagnostic yield but also enabled a better assessment of the consequences of myocardial hypoperfusion and associated congenital defects. The presence of left ventricular dilatation, subendocardial scarring, and regional wall motion abnormalities are indicators of chronic ischemia. And the presence of delayed subendocardial enhancement may be seen on cardiac MRI images, which suggests chronic subendocardial ischemia and is considered as a very important sign, particularly in asymptomatic patients.[3] Surgical correction should be strongly considered if this finding is present. Cardiac MRI has been increasingly utilized in multiple other studies to guide both diagnostic and therapeutic decisions in patients with ALCAPA.

Reimplantation into the aorta is the only true anatomical repair, but the benefits of MVS at the time of ALCAPA operation should be weighed against the effects of prolonged bypass in the setting of an already ischemic left ventricle.[3] After mitral

valvuloplasty/valve replacement and LCA transplantation, they had no symptoms of blood flow steal phenomenon, and myocardial perfusion scintigraphy did not show any ischemic changes. Postoperative echocardiography 7 days after the procedure showed that LCA originates from the aorta with good visualization of the coronary ostia, left atrium and left ventricle became smaller, no MR and ventricular ejection fraction increased to 72%.

Hence, their exercise-induced dyspnea and MR were likely due to coronary artery steal phenomenon from their abnormal origin of a coronary artery. This report highlights the essence of increasing the preoperative diagnosis rate in China remote village. For patients with moderate or significant mitral insufficiency without other apparent causes, with left ventricular dilatation and the possible presence of hyperechogenicity of the endocardium and/or papillary muscles, without good visualization of the coronary ostia (or with suspicion of the anomalous origin or dilation of the coronary artery) were submitted to CTA or cardiac angiotomography.

Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Statistical analysis, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Bu H, Zhao T; Obtaining financing: Zhao T.

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No potential conflict of interest relevant to this article was reported.

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Xiangya Second Hospital under the protocol number XYEYXW-2018-986. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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Transthyretin Amyloidosis (ATTR) - The Role of Multimodality in the Definitive Diagnosis

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Introduction

Transthyretin amyloidosis (ATTR) is a rare cause of restrictive cardiomyopathy and/or peripheral polyneuropathy, of a progressive, irreversible and fatal nature, underdiagnosed and with its definitive diagnosis performed late.[1] Early diagnosis, characterization of the type of amyloidosis and subsequent establishment of specific therapy are fundamental for a better prognosis of this disease.[1] We present a case of ATTR where clinical suspicion associated with multimodality diagnosis — nuclear medicine — was able to safely deliver diagnosis, without the need for biopsy.[2]

Case Report

Male patient, 75 years old, previously diagnosed with stage 1 systemic arterial hypertension (SAH), reporting dyspnea on moderate exertion for 2 months. He was regularly taking Losartan 50 mg a day, with proper blood pressure control. Physical examination with no relevant finding, electrocardiogram (ECG) showing sinus rhythm of 64 bpm and isolated ventricular extrasystoles. Echocardiography revealed mild biatrial dilation, mild left ventricular systolic dysfunction, ejection fraction = 49% (Simpson), grade II diastolic dysfunction and severe concentric hypertrophy of the left ventricle disproportionate to his history of SAH, which led to the suspicion of cardiac amyloidosis. Magnetic resonance imaging of the heart (figure 1-B) showed ventricular hypertrophy with diffuse heterogeneous subendocardial late enhancement. Two-dimensional speckle tracking echocardiography showed reduced global longitudinal strain (GLS = -10%), ejection fraction/GLS ratio = 4.9, with diffuse impairment of the subendocardial strain, but with preserved apex (figure 1-A), which reinforced the initial clinical suspicion.

Immunofixation of proteins in blood and urine associated with blood search for light chains, all negative, was requested. Still without a conclusive diagnosis and in view of the clinical findings and suggestive imaging findings, a rarer type of amyloidosis, ATTR, was suspected. In this type of amyloidosis, laboratory tests do not help and biopsies may not be conclusive.[1,2] Pyrophosphate scintigraphy was then requested because of its high diagnostic accuracy for this type of amyloidosis.[2,3] The scintigraphy findings were compatible with ATTR (Figure 2).

The patient underwent genetic study to differentiate ATTRw (wild) x ATTRm (mutant), through DNA testing using saliva swab, confirming it is ATTRm, with valine to isoleucine mutation (figure 1-C). He had also been diagnosed with bilateral carpal tunnel syndrome with no clear cause. Electroneuromyography was performed and showed distal axonal polyneuropathy (characteristic of amyloid neuropathy).[1,5] Treatment started with Tafamidis, a drug that stabilizes transthyretin, decreasing progression of neurological disease and, more recently, showing an important benefit in hospitalizations and mortality.[1,4]

Discussion

Amyloidosis is a localized or systemic infiltrative disease, where the degree of cardiac involvement can define its prognosis. It is a recognized cause of restrictive cardiomyopathy, heart failure and polyneuropathy.[1] There are more than twenty types of amyloid protein, most notably two: Light chain (AL) and transthyretin-related (ATTR).[1] In the AL type, which is more prevalent, more common in the elderly and in males, fibrillar proteins are formed by light chains (Kappa and Lambda) produced by plasma cells in the bone marrow. Mutant or hereditary ATTRm is caused by an autosomal dominant mutation, similarly affecting both sexes, with the onset of symptoms above 60 years of age. However, this will depend on the type of mutation found.[1] As for ATTRw, known as a "wild" or senile type, there is no associated mutation and it is more prevalent in men >70 years of age.[1] The two organs most frequently affected by amyloidosis are the heart and the kidney. Severe proteinuria leading to nephrotic syndrome and renal dysfunction are the main manifestations of renal involvement of this clinical disorder. The clinical presentation of amyloid cardiomyopathy involves restrictive cardiomyopathy, right heart failure (HF), with ascites, hepatomegaly and lower limb edema, HF with preserved ejection fraction and, less frequently, a condition that is similar to that of an asymmetric hypertrophic septal cardiomyopathy.[1] Impairment of the autonomic system with orthostatic hypotension, peripheral nervous system with sensory-motor polyneuropathy, conduction system disorders and also carpal tunnel syndrome (CTS), especially if bilateral,

Keywords

Amyloidosis/complications; Prealbumin; Cardiomyopathy,Restrictive; Endomyocardial Fibrosis; Hypertension; Heart Failure; Diagnostic Imaging.

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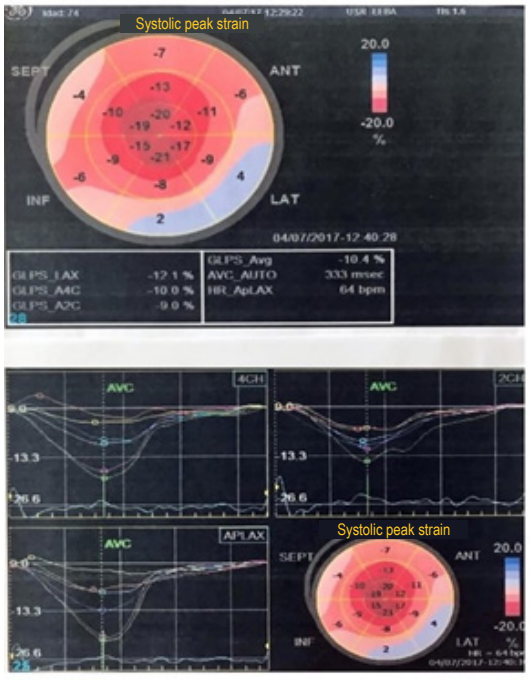


Figure 1 - A

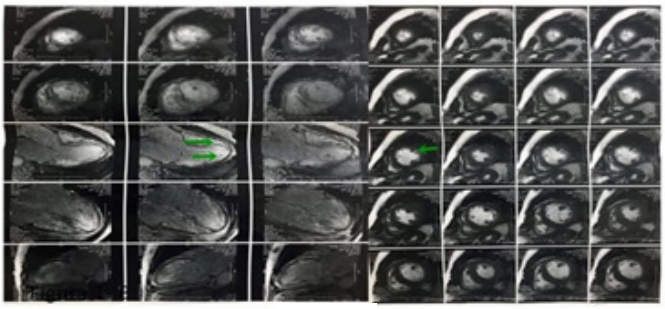


Figure 1 - B

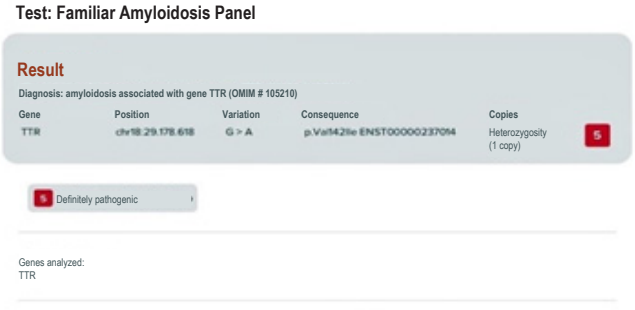


Figure 1 - C

Figure 1 – *1-A) Strain echocardiography showing classic apical sparing. 1-B) MRI with diffuse heterogeneous left ventricular late enhancement (arrows on the left) and diffuse increase in LV thickness (arrow on the right). 1-C) Result of genetic study showing valine to isoleucine mutation (VAL142Ile).*

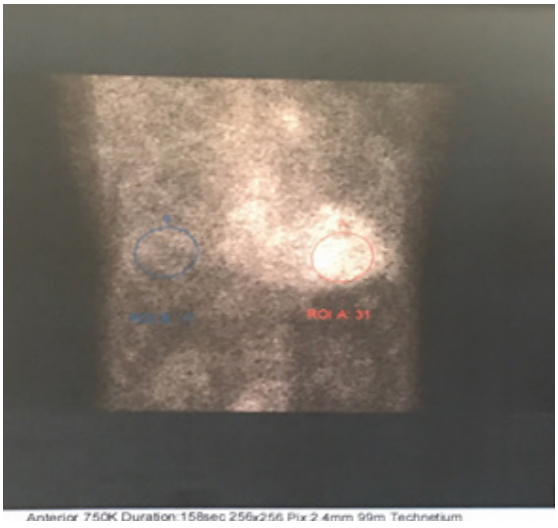
are some of the possible manifestations of systemic infiltration by amyloid material.[1,5] Regarding CTS, a recent study by Sperry BW et al. showed that some of the patients with surgical indication actually had amyloidosis as the underlying disease and, of these, 20% also had cardiac involvement.[5]

Transthyretin is a protein synthesized mainly in the liver and carries vitamin A and thyroxine. There are more than one hundred mutations of the genes that encode this protein, ultimately leading to the formation of proteins with incorrect folding and extra-cellular deposition of these amyloid fibrils in the peripheral and autonomic nerves and in organs, such as the heart and kidneys.[1] AL and ATTR present differences in prognosis and have completely different therapeutic strategies.[3,5] Thus, early diagnosis and characterization of their type are crucial for the proper management of these patients.[2,3]

On clinical reasoning, the presence of LVH on the echocardiogram (especially if septal thickness >12 mm) and low voltage (LV) ECG, the diagnostic hypothesis of cardiac amyloidosis should always be considered. However, this classical finding of ECG X ECHO dissociation is very little sensitive (present in 50% of AL cases and only 25% in ATTR cases).[1,6] The echocardiogram in this clinical entity classically presents increased ventricular thickness, diastolic dysfunction and, in more advanced stages, systolic dysfunction, but these are non-specific findings. In order to deliver a diagnosis with a high probability of certainty, a more advanced workup is necessary.[2,3,7,8] Magnetic resonance imaging (MRI) of the heart and two-dimensional speckle tracking echocardiogram have good accuracy, playing an important role in the early diagnosis of this pathology.[6-8] According to a study by Austin et al.,[9] MRI with late enhancement presents 88% sensitivity (S) 95% specificity (E) 93% positive predictive value (PPV) and 90% negative predictive value (NPV).[9] Impairment is subendocardial, and may be diffuse, heterogeneous or transmural, with the latter presenting the worst prognosis.[8] Cardiac strain can be used for the differential diagnosis of causes of increased ventricular thickness, with diagnostic accuracy provided by the finding of quite satisfactory apex preservation (S = 96 %, E = 88%, in patients without coronary artery disease).[6,7] It is noteworthy that the presence of apical sparing is not exclusive to amyloid disease, and can be found in SAH, aortic stenosis and hypertrophic cardiomyopathy, for example.[7]

However, the finding of apex preservation, with RRSR (relative regional strain rate, which represents the sum of apical/basal + medium strain) >1, associated with EF/GLS ratio >4.1 (as seen in this case), are highly suggestive of amyloidosis.[6,7] Both MRI and strain echocardiogram can adequately suggest the diagnosis of cardiac amyloidosis.[2,6-8] The definition of whether it is AL or ATTR, which is essential for managing these patients, can be done accurately using nuclear medicine.[3,10] Scintigraphy with pyrophosphate-labeled technetium can differentiate, in most cases, these types.[3,10] Uptake of Perugini grade 2 or 3 radiotracer (visual evaluation) have sensitivity and specificity around 88%, with an area under the ROC curve of 0.945 (95% CI, 0.901–0.977).[10] Quantitative evaluation, done through the heart/contralateral chest area ratio, is best in terms of accuracy, since a value >1.5 presents S and E around 92%, with an area under the ROC curve of 0.960

Figure 2.1



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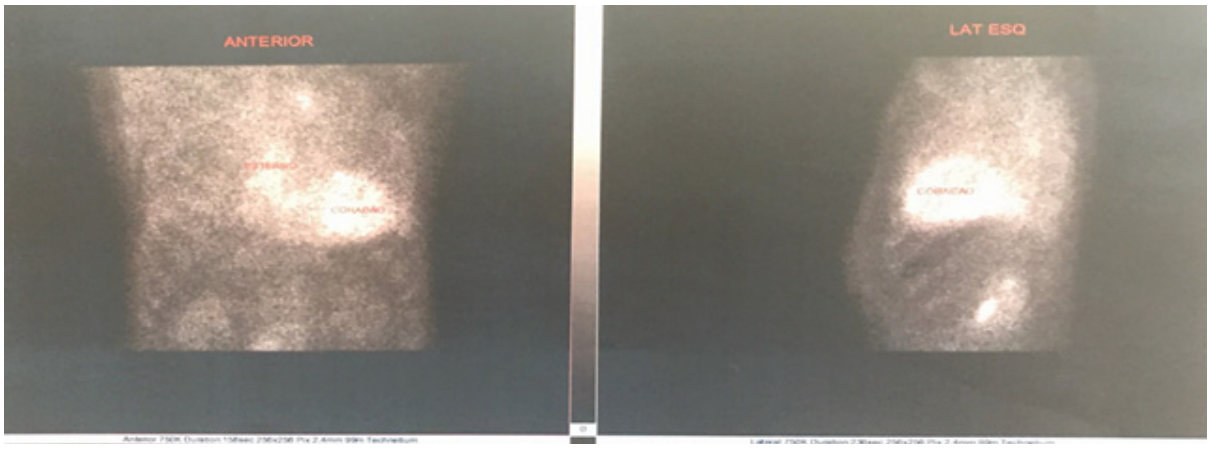

Figure 2 – *Myocardial scintigraphy with technetium-99m labelled pyrophosphate. 2.1) Counting ratio between the heart and the corresponding site in the right hemithorax = 1.8 (31/17 = 1.8). 2.2) Increased concentration of the radiotracer in the projection area of the heart against the costal margin, corresponding to score 3. Score >2 and counting ratio between the heart and the contralateral region >1.5 have a high probability of senile or hereditary transthyretin amyloidosis.*

(95% CI, 0910–0.981).[10] The largest sample in this scenario was published by Gilmore et al.[2] with a sample of 1,217 patients with suspected amyloidosis, where about 360 patients had diagnostic confirmation made through pyrophosphate scintigraphy not requiring histopathological study.[2] In this multicenter study, in those patients without monoclonal gammopathy, nuclear medicine showed specificity and PPV close to 100%.

For patients with clinical suspicion, echocardiogram or MRI suggesting the possibility of amyloidosis, there is a diagnostic sequence to be followed.[2,3,10] The flowchart begins with the request for immunofixation of proteins in the blood and urine in addition to assessment of light chains in the search for primary amyloidosis (AL). To move to the other stage of the investigation algorithm, it is essential that these initial laboratory tests be negative. This is due to the existence of a portion of cases of AL with positive scintigraphy (possibly reaching 27% false positives).[2] If no monoclonal gammopathy is found, then the next step is to request 99mTc-pyrophosphate scintigraphy, for the purposes of, this time, identifying transthyretin deposits in the myocardium.[2,3,10] (Figure 3). With multimodality, we can identify and differentiate the types of amyloidosis early, with excellent accuracy and without the need for biopsies.[2,3,6-8,10]

Conclusion

Patients with clinical suspicion of amyloidosis, in the absence of monoclonal gammopathy, should continue the investigation with pyrophosphate scintigraphy, as it may

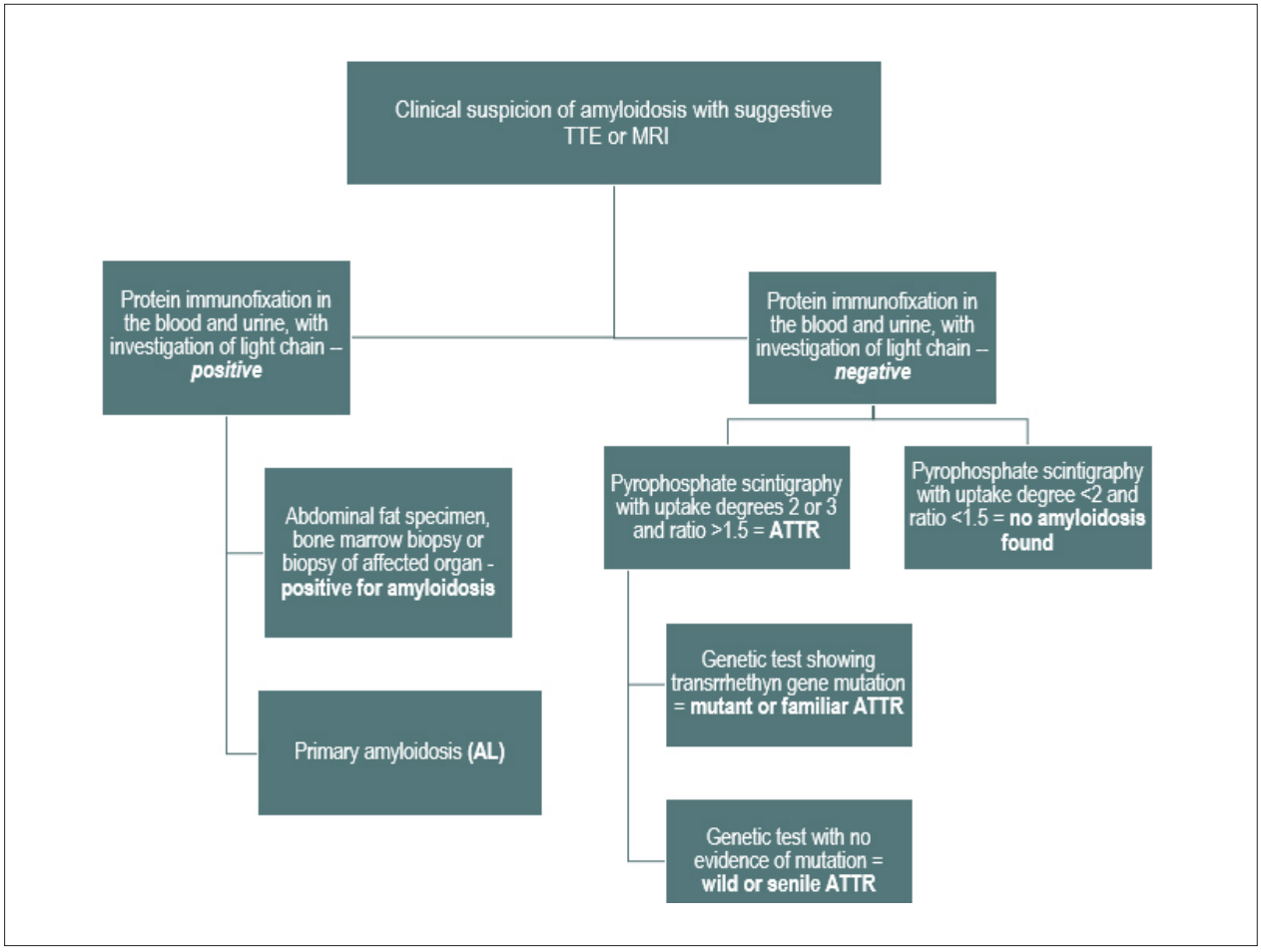

Figure 3 – *Simplified flowchart for the diagnosis of amyloidosis.*

be ATTR.[2,3,10] Amyloidosis, notably that associated with transthyretin, is a disease that requires a high degree of clinical suspicion for diagnosis. Its early diagnosis is essential, as it is a cause of polyneuropathy and/or cardiomyopathy that, if left untreated, evolves progressively to death.[1]

Author contributions

Writing of the manuscript: Silva TO; Critical revision of the manuscript for intellectual content: Silva TO, Darzé ED, Ritt LEF, Almeida ALC, Ximenes A.

Potential Conflict of Interest

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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A Life-threatening Combination: Indomethacin and Dabigatran

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Introduction

Although rare, several bleeding complications may occur in patients receiving dabigatran. The risk of bleeding is particularly high in patients with impaired kidney functions or in patients who are on concomitant nephrotoxic drugs.[1] We report a case of massive pleuropericardial effusion developed after the initiation of indomethacin treatment in a patient who was receiving dabigatran for deep venous thrombosis.

Case Report

A 50-year old male patient admitted to the emergency department with progressive dyspnea. He had a heart rate of 120 beats/min, blood pressure of 180/90 mmHg, respiration rate of 15 breaths/min, oxygen saturation of 95% (on room air) and temperature of 36.8 ºC at presentation. He had a sedentary lifestyle, obesity (body mass index: 31 kg/m^2), uncontrolled hypertension (for 5 years without medical therapy) and deep vein thrombosis (on dabigatran 150 mg twice a day for 50 days). Twenty days prior to his presentation, he started to receive indomethacin (once a day) for his leg pain. On physical examination, he had diminished heart and lung sounds. Electrocardiography showed sinus tachycardia. Cardiomegaly and bilateral pleural effusion (greater on the left lung) were noticed on chest X-ray. Chest computerized tomography confirmed bilateral pleural effusion and revealed massive pericardial effusion (Figure 1A). On admission, his blood tests were as follows: glucose: 107 mg/dL, urea: 63 mg/dL, creatinine: 1.99 mg/dL, AST: 69 U/L, ALT: 99 U/L, white blood cells: 9.73 10^9/L, hemoglobin: 9.6 mg/dL, C-reactive protein: 0.9 mg/dL, activated partial thromboplastin time (APTT): 91.4-seconds and international normalized ratio (INR): 2.5. Since his last creatinine level was 1.1 mg/dL 20 days before (just before the initiation of indomethacin treatment), acute renal failure was considered. The patient was admitted to the intensive care unit and detailed echocardiography was performed. Transthoracic echocardiography revealed normal left ventricular systolic function (EF 65%), left ventricular concentric hypertrophy (LVMI: 118 g/m^2), massive pericardial and pleural effusion (Figure 1B). There were no signs of cardiac tamponade on the first echocardiographic evaluation. However, during follow-up, his dyspnea and tachycardia were gradually increased, and right ventricular diastolic collapse was noticed on control echocardiography. We decided to perform urgent pericardiocentesis. In order to reduce the risk of bleeding, idarucizumab was administered (total 5 grams divided into two consecutive infusions of 2.5 grams) before pericardiocentesis. Two hours after administration of idarucizumab, the APTT value decreased to 44 seconds. Pericardiocentesis was performed with echocardiography guidance. Approximately 3L of blood-red, non-coagulating pericardial fluid was drained out (Figure 2). Pericardial fluid analysis was negative for gram staining, cytology, polymerase

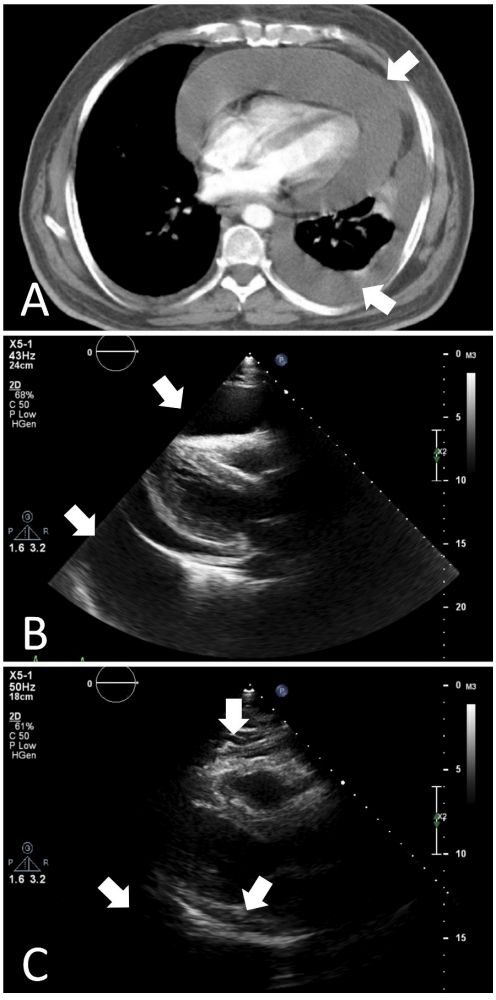

Figure 1 – *A) Massive pericardial and pleural effusion in thoracic tomography. B) Pericardial effusion surrounding the heart and pleural effusion. C) Pericardial effusion was drained completely.*

Keywords

Indomenthacin/administration & dosage; Dabigatran/administration & dosage; Cardiomegaly; Pleural Effusion; Renal Insufficiency; Echocardiography.

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chain reaction (PCR) and microorganisms (*Mycobacterium tuberculosis*). There was no pericardial effusion on repeat echocardiography performed on the following day after pericardiocentesis (Figure 1C). According to the modified Light criteria, pericardial effusion had exudative characteristics. Thoracentesis was then performed, and 2 L of pleural fluid was drained out. Biochemical tests were again consistent with exudative fluid. Inflammatory, rheumatological, infection and cancer screening markers were all negative. Renal functions improved after fluid replacement, pericardiocentesis, and discontinuation of indomethacin therapy. His overall status improved significantly, and no other complications were noticed. On the 8th day of hospitalization, he was discharged with subcutaneous enoxaparin.

Discussion

This is the first reported case of massive pleuropericardial effusion associated with concomitant use of dabigatran and indomethacin. For the following reasons, we thought that dabigatran toxicity was the most plausible cause of pleuropericardial effusion in the present case. (1) Presence of hemorrhagic pleuropericardial effusion, (2) development of effusions after development of acute renal failure, (3) high APTT (91.4 seconds) and INR (2.5) levels at presentation,[2] and, finally, (4) no other reasons to explain hemorrhagic pleuropericardial effusion.

Dabigatran is an active metabolite derived from the hydrolysis of dabigatran etexilate. It inhibits both free and clot-bound thrombin. The half-life of dabigatran is 12–14 hours and it is largely excreted via the kidneys.[3]

Current guidelines recommend regular follow-up of kidney function in these patients.[4] In the present case, the patient experienced acute renal failure after initiation of indomethacin, a nephrotoxic agent, during dabigatran therapy. We found 12 cases of hemopericardium associated with dabigatran toxicity.[1,5-9] Indication for dabigatran was stroke prevention in atrial fibrillation for all reported cases. Consistent with our findings, 7 (58%)[,7,10-13] of these cases had acute renal failure at presentation and 4 (33%)[5,7-9] experienced hemopericardium two months after initiation of dabigatran.

The absorption of dabigatran etexilate is mediated by the p-glycoprotein (P-gp). Gastrointestinal tract-based P-gb interactions may interfere with the absorption of dabigatran. Ye CG et al. reported that indomethacin may inhibit P-gp by decreasing its expression and/or direct inhibition of its activity.[14] Thus, co-administration with indomethacin may have contributed to dabigatran toxicity in our case.

Idarucizumab, a humanized monoclonal antibody fragment which binds to dabigatran with high affinity without increasing thrombotic events, is used for reversing the anticoagulant effect of dabigatran in patients with life-threatening bleeding conditions.[15] The effect of dabigatran was successfully reversed with idarucizumab in the present case. Two hours after initiating idarucizumab, the APPT value was found to fall from 91.4 seconds to 44 seconds. In addition, no bleeding or thrombotic complications occurred after pericardiocentesis.

Conclusion

Pleuropericardial effusion should be considered in patients with newly developed dyspnea who are under dabigatran treatment. The risk of major bleeding may increase when indomethacin is used concomitantly with dabigatran. When prescribing dabigatran, all patients should be informed about the potential interactions with other drugs. Potential risks of concomitant nephrotoxic medications should be considered in all patients receiving dabigatran and, if possible, these agents should be avoided, particularly in patients with multiple risk factors for bleeding. Finally, patients who develop bleeding under treatment with dabigatran should be investigated for co-medications.

Author contributions

Conception and design of the research: Adar A, Onalan O; Acquisition of data and Analysis and interpretation of the data: Adar A, Onalan O, Cakan F; Writing of the manuscript: Adar A, Cakan F; Critical revision of the manuscript for intellectual content: Onalan O.

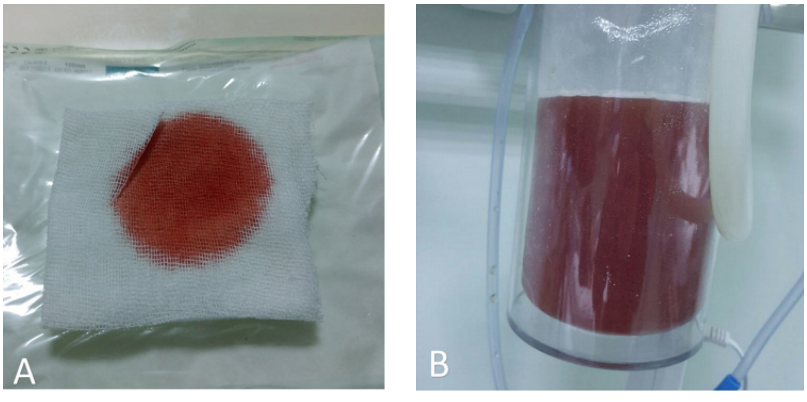

Figure 2 – *Blood-red non-coagulating pericardial fluid.*

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

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Giant Cell Arteritis with Aortic Involvement Leading to Cardio Vocal Syndrome (Ortner's Syndrome)

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Introduction

Giant cell arteritis or temporal arteritis is the most common large-vessel arteritis in Western countries, generally affecting patients over 50 years of age.[1] In most cases cranial symptoms are present, however, exclusively extracranial manifestations can occur in up to 22% of cases.[2]

The involvement of aortic and other large vessels (carotid, subclavian) is frequent in this context. The involvement of the adventitia of the artery is observed mainly by activation of dendritic cells generating a granulomatous inflammatory process in multiple foci with intense lymphocytic presence. The occurrence of thoracic aortic aneurysms is reported in about 20% of patients.[3]

The cardiovocal syndrome also known as Ortner's Syndrome is characterized by non-malignant involvement of the recurrent laryngeal nerve secondary to cardiovascular causes, mainly pathologies that lead to enlargement of the left atrium and thoracic aortic aneurysm. This is a rare condition that leads to hoarseness by compression of the aforementioned nerve.[4]

In this report, we describe an unusual case of a patient with giant-cell arteritis with extracranial manifestations due to involvement of the thoracic aorta culminating with cardiovocal syndrome. This association is rare, never described in Brazilian literature.

Case Report

At 65 years old female patient seen in outpatient cardiology with a complaint of fever started 30 days ago, hyporexia and weight loss. In the last 10 days, she started with continuous left thoracic pain without angina patterns, which is why she was referred for a cardiological appointment after an initial investigation with an infectologist. Pathological antecedents included long-standing systemic arterial hypertension and smoking history (20-year smoking load).

Keywords

Giant Cells Arteritis; Aortic Aneurysm, Thoracic/physiopathology; Vocal Cord Syndrome; Recurrent Laryngeal Nerve; Ortner's Syndrome.

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At physical examination, the patient presented regular general condition and skin pallor. Cardiac and pulmonary auscultation without abnormalities. Right carotid bruit. Left radial and brachial pulses slightly decreased in relation to the right. Blood pressure measured was 140/80 mmHg and 120/70 mmHg in the right and left upper limbs, respectively.

Laboratory tests showed normochromic and normocytic anemia (Hb:10.6 g/dl), Erythrocyte sedimentation rate (ESR) of 115 mm/1 hour, and C-reactive protein (CRP) of 48mg/L. Other laboratory tests with no significant changes. Arterial Doppler of cervical vessels was requested and showed increased thickness of the intima-medial complex and 70% obstructive plaque in the direct internal carotid artery. Retrograde flow from the left vertebral artery to the left subclavian artery (type III subclavian artery steal syndrome) was also observed.

Facing the findings of carotid and subclavian involvement in a patient with constitutional symptoms, with evidence of high inflammatory activity and chest pain, a computed tomography angiography of the thoracic aorta was requested. Examination showed aneurysmatic dilation of the thoracic aorta with significant parietal thickening soon after the emergence of the left subclavian artery with a diameter of 24x28mm (Figure 1).

Based on *American College of Rheumatology* 1990[1] diagnostic criteria, a hypothesis of giant-cell arthritis in extracranial form with aortic involvement was suggested. Corticotherapy was initiated with prednisone 60mg/day.

In the following days, the patient evolved with persistent hoarseness. Videolaryngoscopy was requested which showed paralysis of the left vocal cord (Figure 2). Due to the anatomical correlation of the aneurysm with the left recurrent laryngeal nerve, the diagnosis of cardiovocal syndrome (or Ortner's syndrome) was established.

After corticotherapy, the patient obtained a significant improvement in constitutional symptoms and chest pain. Inflammatory markers after two weeks of treatment showed a significant drop (ESR: 20mm/1 hour and PCR: 1.0 g/L) and there was an improvement in anemia (Hb: 12.4 g/dl). In the 30-day follow-up, the patient remained asymptomatic with a slight improvement of hoarseness after starting phonoaudiology treatment

Discussion

Giant-cell arteritis, even though it is a non-negligible condition in some situations, can be difficult to diagnose, especially when cranial symptoms such as temporal headache are absent. However, in the face of an appropriate epidemiological profile, associated with constitutional symptoms without clear explanation and evidence of involvement of large vessels, its diagnosis should be suggested.

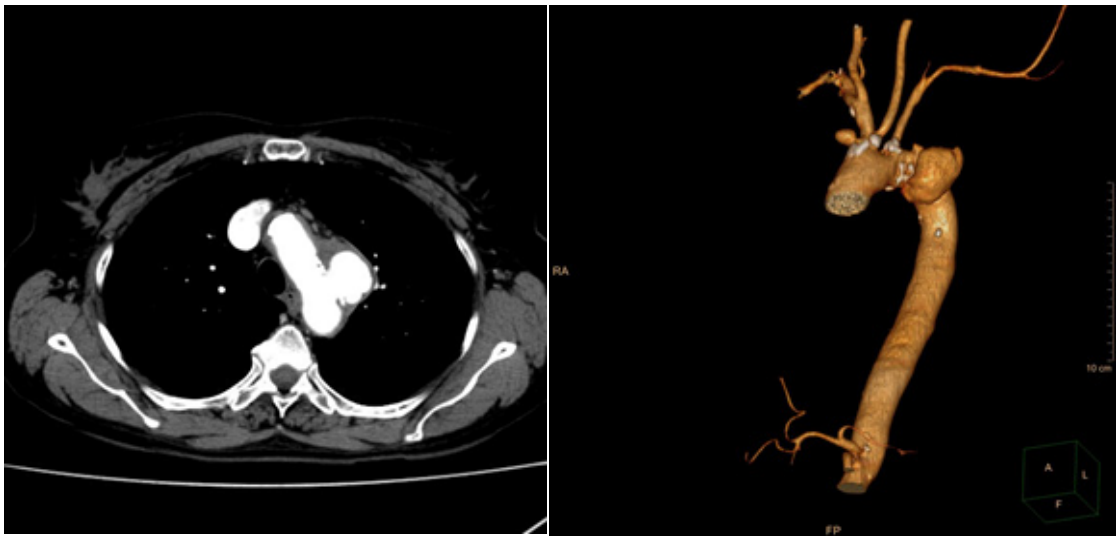

Figure 1 – *Computed tomography angiography. A) Saccular aneurysmatic dilation after the emergence of the left subclavian, partially thrombosed, measuring 4.2 cm in length and 2.4 x 2.8 cm in the largest diameters. B) Image obtained after 3D reconstruction.*

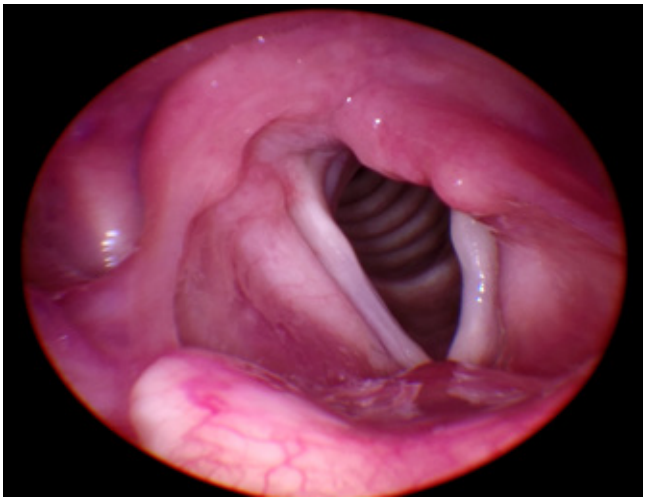

Figure 2 – *Image obtained by videolaryngoscopy shows asymmetry of the vocal cords, with signs of left vocal cord paralysis.*

Represents a condition that is more frequent in females in the proportion of 4:1. History of smoking, as in our case, increases 6-fold the risk of developing it.[5] The diagnostic criteria were established in 1990 by the American College of Rheumatology. Temporal artery biopsy showing an inflammatory granulomatous pattern is part of the criteria, but it lacks adequate sensitivity and can be avoided in the appropriate context in the presence of a suggestive clinical picture and with imaging studies compatible with the involvement of large vessels.[6]

The presence of a high erythrocyte sedimentation rate (usually over 55mm/1 hour) is a non-specific laboratory finding, but very frequently. The fast and effective response to corticotherapy strengthens the diagnostic possibility. Aortic involvement is not infrequent and early recognition, and treatment is essential to minimize acute and chronic complications.[7]

Ortner's syndrome or cardiovocal syndrome, first described in 1897, is a rare situation characterized by compression of the recurrent laryngeal nerve by cardiovascular conditions leading to hoarseness, dysphagia and dysphonia.[8] Its association with

giant cell arteritis is extremely rare and infrequent as an initial presentation likewise in our case.[9]

This case presents an unusual association whose recognition is fundamental for proper management and appropriate therapy in order to minimize adjacent complications of giant cell arteritis.

Author contributions

Conception and design of the research: Lamas ES. Acquisition of data: Lamas ES, Boroni RLJR, Reis PACA. Analysis and interpretation of the data: Lamas ES, Boroni RLJR, Reis PACA. Writing of the manuscript: Lamas ES. Critical revision of the manuscript for intellectual content: Lamas ES, Boroni RLJR, Reis PACA.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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Acute Decompensated Heart Failure due to Chikungunya Fever

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Introduction

Heart failure (HF) is a chronic condition with worldwide high and growing prevalence.[1-3]

It is extremely important to identify the cause of decompensated HF in order to manage cases correctly, given that identification makes it possible to implement specific treatment and prevent new hospitalizations. In Brazil, the main causes are poor adherence to medical treatment (30%) and infections (23%),[1] mainly pulmonary bacterial ones.[4] For this reason, patients with HF should receive the pneumococcal vaccine. Although it is less common, decompensation may occur due to viral infections, which justifies vaccination against influenza in these patients.[3]

Over the past years, diverse Brazilian cities have been affected by epidemics of arboviruses that had previously been considered rare, such as those caused by the Zika and the chikungunya viruses.[5] These epidemics have drawn the scientific community's attention, not only due to the number of patients affected, but mainly due to the common sequelae, such as microcephaly in children of pregnant women affected by the Zika virus and the disabling, chronic arthralgia secondary to chikungunya fever. Although there are case reports of myocarditis caused by arboviruses,[6-8] little is known regarding the risks of compliactions when patients previously diagnosed with heart failure are affected. The high prevalence of HF worldwide and the high incidence of arboviruses in Brazil justify the following case report.

Case Report

A 71-year-old retired male patient sought emergency service due to dyspnea during light exertion, which had progressively worsened over the past two days, evolving to resting dyspnea and paroxysmal nocturnal dyspnea after an episode of unmeasured fever the previous evening. He denied coughing, chest pain, dizziness, and syncope. The patient has previously been diagnosed with hypertensive/alcoholic cardiomyopathy, chronic non-dialytic renal failure, permanent atrial fibrillation, hyperuricemia, chronic obstructive pulmonary disease, and cholelithiasis. He suffered from alcoholism, and he was a former smoker (47 packs/year, having ceased six years before). He regularly took carvedilol (12.5 mg in the morning and 25 mg at night), hydralazine (25 mg, 3 times daily), amlodipine (5 mg daily), furosemide (40 mg, 4 times daily), digoxin (0.125 mg daily), apixaban (2.5 mg, 2 times daily), bamifylline (300 mg daily), and formoterol/budesonide (12 mcg + 400 mcg, 2 times daily). Upon admission, the patient presented blood pressure of 110/84 mmHg, heart rate of 86 bpm, respiratory rate of 26 rpm, and jugular venous distention at 30°. Pulmonary auscultation revealed universally audible vesicular murmurs, without adventitious sounds, and cardiac auscultation revealed an irregular rhythm, with normal heart sounds and no accessory sounds. The patient had lower limb edema (2+/4+), and there was no ascites on physical examination.

There was no clinical evidence of angina, new arrhythmias, or infection (Table 1). The patient and his wife denied poor adherence to medical treatment, consumption of alcohol, or excessive salt or liquid intake. It was, therefore, not possible to identify precipitating factors for the clinical picture of decompensated HF. The patient's admission electrocardiogram showed atrial fibrillation rhythm and left bundle branch block. There were no electrocardiographic alterations suggestive of myocardial ischemia. Chest radiography showed an increase in the cardiothoracic index, with slight pulmonary congestion and no pleural effusion or pulmonary consolidation. For the purpose of screening for infection, a urinary sediment test was performed, and the results were normal.

The patient was admitted, classified as hemodynamic profile B[9], and he underwent treatment with intravenous diuretics (Figure 1).

On the third day of hospitalization, the patient progressed with worsened renal function, with creatinine clearance (Cockroft-Gault) of 19ml/min (creatinine 3.0 mg/dL) and hyperkalemia (6.1 mEq/l). On account of this complication, digoxin was suspended. After five days, the patient reached hemodynamic profile A, and the physician opted to change the furosemide route of administration from intravenous to oral. The same day, the patient presented macroscopic hematuria, and anticoagulation was suspended. On the seventh day of hospitalization, the patient complained of mild arthralgia in his knees and elbows, which he associated with his position in bed. Notwithstanding use of dipyrone, the following day, the symptoms worsened to bilateral arthralgia, which was highly intense in the knees, ankles, wrists, and elbows, thus restricting the patient's movement in bed. The patient did not present dyspnea or precordial pain, and he maintained hemodynamic profile A. Slight pain control was achieved with the regular use

Keywords

Heart Failure/physiopathology; Treatment Refusai; Pneumococcal Vaccine, Arbovirus Infections; Zika Virus Infection; ChiKungunia fever.

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Case Report

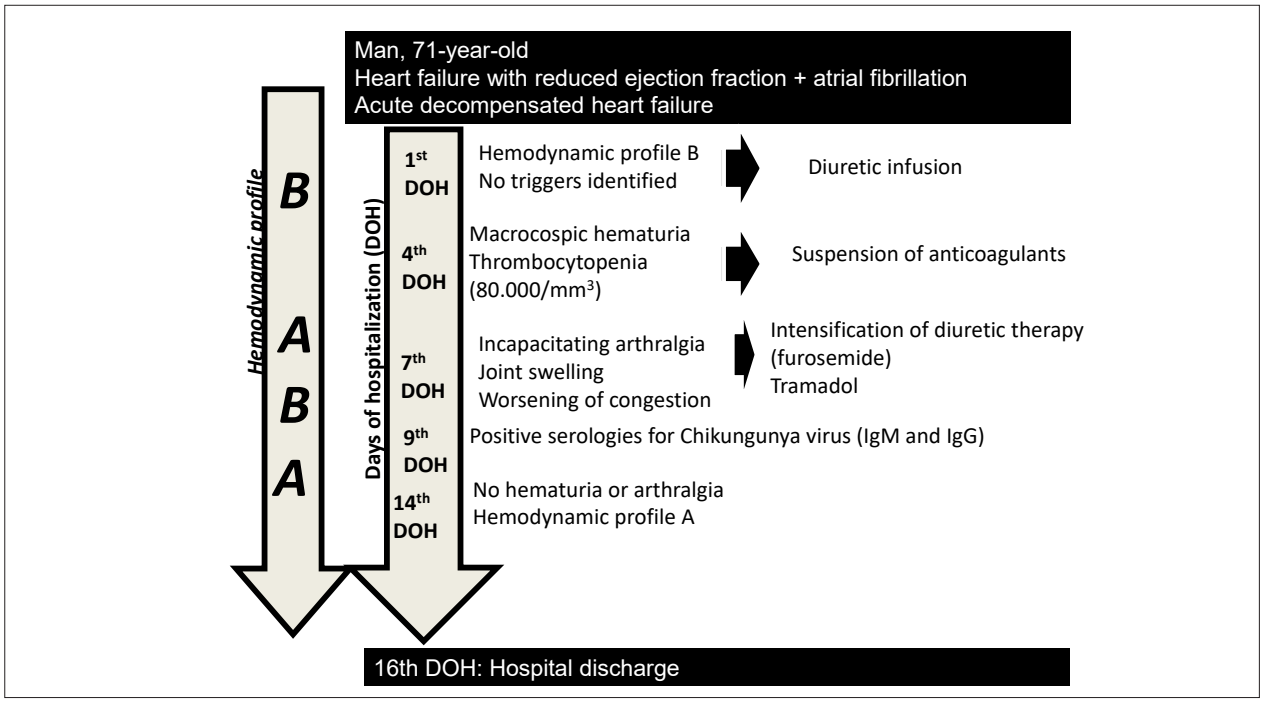

Figure 1 – *Case report timeline*

Table 1 – Laboratory results during hospitalization

Laboratory exams	Day of hospitalization				
	1	3	5	12	14
C-reactive protein (mg/dL)	3.00	2.90	2.56	10.60	10.30
Urea (mg/dL)	96	148	102	72	107
Potassium (mEq/L)	6.3	5.8	3.5	4.6	4.6
Creatinine (mg/dL)	2.0	3.6	2.2	1.6	1.9
Hemoglobin (g%)	14.9	16.3	14.0	14.1	13.0
Leukocytes (mil/mm^3)	6.9	7.9	5.7	8.7	5.7
Platelets (mil/mm^3)	106	135	87	80	111

of tramadol, and, the following day, laboratory exams revealed thrombocytopenia (drop from 135,000 to 87,000 per mm^3 in 5 days, Table 1). The arthralgia and thrombocytopenia led to clinical suspicion of arbovirus, and serology was thus requested for dengue and chikungunya. The patient progressed with worsened peripheral and central congestion, with lower limb edema (3+/4+), jugular venous distention, hepatojugular reflux, bibasilar crackles, and square-wave systolic blood pressure response to the Valsalva maneuver. There were no signs of hypoperfusion, and the patient was again classified as hemodynamic profile B, and intravenous diuretic therapy was reinitiated.

On the fourteenth day of hospitalization, the thrombocytopenia, arthralgia, and pattern of congestion (returning to hemodynamic profile A) improved. Laboratory exams did not reveal electrolytic disorders (Table 1) or alterations in liver function. The blood tests for chikungunya fever were positive (IgG and IgM). Thus, full anticoagulation with apixaban was reinitiated, and regular analgesia was changed to only if necessary. Throughout the entire hospitalization, the electrocardiographic pattern was maintained. The following day, the patient remained stable, maintaining a dry-warm hemodynamic profile, and he was discharged from the hospital with the following prescription: furosemide (40 mg, twice daily, carvedilol (25 mg, twice daily), atorvastatin (20 mg daily), formoterol + budesonide (12/400 mcg, twice daily), allopurinol (100 mg daily), apixaban (5 mg, twice daily). There were no new episodes of clinical decompensation during the three months following hospital discharge.

Discussion

According to the Brazilian Guidelines on Chronic and Acute HF,[3] systematizing care for discharging patients with decompensated HF from the hospital includes resolving precipitating factors. Infections, mainly pulmonary bacterial ones, represent important causes of decompensated HF.[1] Accordingly, vaccination against pneumococcus and influenza viruses has been recommended for patients with HF. This recommendation is aligned with United State´s and European guidelines, which have more temperate climates, where serious influenza virus infections are common.[3] Although these infections are also common in Brazil, it is necessary to emphasize the epidemic proportion that arboviruses have reached in diverse Brazilian states.[7]

Chikungunya fever is an arboviruses transmited by an alphavirus (CHIKV). Its vectors are mosquitoes of the *Aedes* genus, *Aedes aegypti* being the main one.[10] It was first documented in Tanzania in 1952, and the first case of autochthonous transmission in Brazil was reported in 2014.[10] The name chikungunya means "crooked walk," referring to the pronounced arthralgia caused by the disease, which is intense and at times disabling and can last for months or years.[10]

Notwithstanding the recent chikungunya fever epidemic in Brazil and the high prevalence of HF, we have not found any publications citing this virus as the cause of chronic HF becoming acute. A recently published meta-analysis[6] suggests that the cardiovascular system is involved in 54.2% of cases of chikungunya fever; it is, however, necessary to emphasize that this statistic is based on reports without any standardization of the definition of this involvement, including hypotension, shock, arrhythmias, increased troponin, and even acute myocarditis.[6-8] Based on these findings, the authors suggest myocardial tropism due to CHIKV, which, like the dengue virus, parvovirus, herpes virus, and enterovirus, can cause direct damage to myocardial cells.[6]

Similarly, the hemodynamic changes that are characteristic of systemic infections (such as vasodilation and tachycardia) may be sufficient for clinical decompensation to occur in patients with HF, generating hypotension and fluid leakage into extra-vascular space. In fact, when these patients are infected by CHIKV, clinical decompensation may occur, even in the absence of myocarditis.

Symptoms of chikungunya generally appear after an incubation period of one to twelve days.[11] Positivity for IgM and IgG antibodies indicates recent or current infection, given that IgM antibodies may remain positive for up to three months after the bite. The patient described had an atypical clinical progression, considering that hemodynamic decompensation occurred before the arthralgia characteristic of the fever. Nonetheless, the absence of other precipitating factors, the positive blood tests, and the clinical picture's evolution over time (Figure 1) corroborate the hypothesis of clinical decompensation due to chikungunya fever in the present case. Unfortunately, it was not possible to perform cardiac nuclear magnetic resonance, because it was not available at our hospital. It is worth emphasizing that the exam, although useful for diagnosis myocarditis, would not have been able to confirm the hypothesis of clinical decompensation due to chikungunya fever.

In addition to being difficult to diagnose, the present case was characterized by challenges in clinical management. As with other arboviruses, treatment of patients with chikungunya fever is based on adequate pain control, which is normally achieved through the use of nonsteroidal anti-inflammatory drugs (NSAID) that do not have an antiplatelet aggregation effect (such as acetylsalicylic acid). However, myocardial dysfunction counterindicated the used of NSAIDF, and, for this reason, it was necessary to opt for analgesia with opioids like tramadol. Furthermore, thrombocytopenia and active bleeding (hematuria) impeded continuation of prophylactic anticoagulation in the patient, in spite of the indication for chronic atrial fibrillation, thus increasing the risk of thromboembolic events secondary to arrhythmia.

Conclusion

Viral infections, especially those that are most prevalent in Brazil, such as chikungunya fever, should be considered as factors of decompensated HF in patients who were previously stable without any other clearly identified precipitating factors.

Author contributions

Conception and design of the research and analysis and interpretation of the data: Athayde C, Castro RRT; Acquisition of data and Writing of the manuscript: Athayde C, Nishijuka FA, Queiroz MC, Luna M, Figueiredo J, Albuquerque N, Castilho SC, Castro RRT; Critical revision of the manuscript for intellectual content: Castro RRT.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital Naval Marcilio Dias under the protocol number 02181318.1.0000.5256. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Glycogen Storage Disease Type I (Von Gierke disease): Report of Two Cases with Severe Dyslipidemia

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Introduction

Glycogen storage diseases are a group of disorders caused by inherited errors of metabolism, resulting in abnormal glycogen concentration and/or structure in various body tissues. Nowadays, there are 14 types of glycogen storage disease, which are classified according to enzyme or transporter deficiency and to the different organ distribution of these defects.[1]

In 1929, Edgar von Gierke described an increased deposition of glycogen in body tissues in the autopsy reports of young individuals with hemorrhagic manifestations. In 1952, Gerty and Cori analyzed liver biopsies of patients with similar symptoms, and observed a partial or total absence of glucose-6-phosphatase (G6Pase) enzyme activity – this entity became known as Von Gierke disease. Nordlie et al., in studies carried out in the 70's, also using liver biopsies, observed normal levels of G6Pase enzyme, but with decreased activity.[2] Thus, Glycogen Storage Disease Type I is characterized by G6Pase deficiency, a key enzyme in glycogen metabolism, which leads to the reduction in glycogenolysis and gluconeogenesis and, consequently, to hepatic accumulation of glucose-6-phosphate (G6P).[2]

G6Pase is composed of a catalytic subunit and three translocases. GSDI is further divided into subtypes, depending on which enzyme is affected: subtype Ia (GSDIa), which corresponds to a deficiency in the catalytic unit; subtypes Ib, Ic and Id, which refer to deficiency of translocases 1, 2 and 3, respectively. Deficiency in the SP catalytic subunit has also been demonstrated, characterizing, thus, the subtype 1aSP. The diagnosis of the subtypes is confirmed by liver biopsy, with G6Pase activity being determined in tissue samples.[2]

GSDIa is inherited as an autosomal recessive trait, representing about 80% of GSDI patients, with an incidence of 1/100,000 births worldwide.[3] It commonly manifests between the ages of 3 to 4 months, as a result of abnormal accumulation of glycogen in the liver, kidneys and intestine, by symptoms of hypoglycemia, hyperuricemia, lactic acidemia and severe dyslipidemia. Hypoglycemia usually manifests first as tremors, seizures, cyanosis and apnea and, in the long term, evolves to growth retardation. Physical examination shows non-painful hepatomegaly, with a smooth, palpable liver edge below the right costal margin, globe-like abdomen due to deposition of abdominal fat, often associated with short stature and a doll-like face.[3] As late complications, these patients may present an increase in kidney size (with or without worsening renal function), hepatic adenomas (with rare transformation into HCC) and neutropenia (a tendency to recurrent infections).[3-5]

Hypertriglyceridemia, most prominent in GSDIa, is associated with long-term outcome morbidity, due to its relation with pancreatitis and hepatic adenomas.[6]

Until the early 2000's, liver biopsies were routinely perfomed to obtain tissue for enzyme analysis. Nowadays, the diagnosis is made based on mutation analysis of the G6Pase (glucose-6-phosphatase) and G6PT (glucose-6-phosphate translocase) genes by PCR-RFLP (Restriction Fragment Length Polymorphism), or by direct gene sequencing, associated with clinical and laboratory manifestations. Enzymatic studies are carried out if results remain inconclusive.[7]

Patients with G6PD mutations may have the criteria for metabolic syndrome, especially hypertriglyceridemia,[8] reduced levels of high-density lipoproteins (HDL) and increased waist circumference. In this context, the monitoring of cardiovascular diseases in adult patients with GSDI would be justified. To a lesser extent, these patients may present with SAH (systemic arterial hypertension) as well, usually related to renal alterations, which may emerge from the second decade of life on. Focal segmental glomerulosclerosis, gout nephropathy and nephrocalcinosis are the likely etiologies of renal injury. Proteinuria is a frequent finding. However, renal alterations respond positively to dietary treatment, which explains why they are not common.[2]

We report the cases of two patients with GSDIa, associated with severe and difficult to manage dyslipidemia, sisters and daughters of consanguineous parents (first cousins), with deceased father and mother with Hashimoto's thyroiditis, without reports of other comorbidities.

Case 1: Patient MCS, 24 years of age. During her first year of life, in 1994, she was hospitalized with a picture of fever, vomiting, glycosuria, tachypnea, metabolic acidosis and hypoglycemia. At that moment, an investigation of the case was initiated, which revealed high levels of total cholesterol and triglycerides, in addition to hyperuricemia and metabolic acidosis. The possibility of Glycogen Storage Disease type I was considered, being subsequently confirmed by liver biopsy and the clinical picture. Other pathologies related to inborn errors of metabolism were ruled out. At that time, laboratory tests showed: hemoglobin A1c of 4.2% and blood glucose 65mg/dL. Dietary treatment, with

Keywords

Glycogen Strage Disease Type 1/complications; Gluconeogenesis; Dyslipidemias; Hepatomegaly; Hypoglycemia; Glucose-6-Phosphate.

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carbohydrate replacement (cornstarch), was initiated in childhood, leading to improvements of hypoglycemia. An increase in transaminases was noted and, around 3 years of age, she presented with hyperuricemia, which evolved with progressive reduction throughout the years, until normalization in adulthood. Throughout her life, she had recurrent episodes of hypoglicemia and infections, with admission to intensive care unit, at the age of 4 years, due to laryngitis and bronchopneumonia. She suffered a femur fracture at the age of 9 years, probably due to low bone density, when a new liver biopsy revealed signs of septal fibrosis. At the age of 14 years, she was diagnosed with Hashimoto's thyroiditis (positive anti-thyroperoxidase antibody), with thyroid scintigraphy showing a diffuse goiter. Later, at the age of 18 years, hepatic adenomas were diagnosed in check-up investigations and, at the age of 22, left lateral liver resection of segments II was required, due to an adenoma measuring 4.5cm. Regarding pondero-statural development, the patient was eutrophic, but having short stature even as an adult. Nowadays, her Body Mass Index (BMI) is within the normal ranges. During childhood and adolescence, she exhibited high concentrations of cholesterol and triglycerides, with little improvement after starting dietary treatment (Table 1). Pharmacological therapy for dyslipidemia was introduced at the age of 20. Despite regular adherence to treatment, total cholesterol and, especially, triglyceride levels, remained consistently increased. Thus, high-potency statin and ciprofibrate therapy was chosen, which was well tolerated, without any side effects, providing a partial improvement in the results found before. Throughout the clinical course, no renal alterations were observed.

Case 2: Patient GCS, 20 years old, with a sister diagnosed with Glycogen Storage Disease Type Ia, in the first year of life. She was found to have a hepatomegaly 3 cm below the right costal margin at birth, in 1998. In face of her clinical manifestations and family history, research for Glycogen Storage Disease was conducted. Since her birth, in addition to hepatomegaly, she presented alterations in the levels of total cholesterol and triglycerides, glycosylated hemoglobin, uric acid, lactate and transaminases, which supported the suspicion of GSD. She underwent her first biopsy at the age of 6 months, still with inconclusive results, but with signs of hepatic steatosis and mild fibrosis. The diagnosis was virtually confirmed by a new biopsy at the age of 3 years, revealing chronic hepatic disease with cirrhosis, probably caused by GSD. At the age of 4 years, the enzyme test was compatible with the diagnosis of Glycogen Storage Disease Type I. Additional tests were performed whose results were negative. The patient remained with altered levels of cholesterol and triglycerides throughout her childhood and adolescence when, in May 2015, at the age of 17 years, she started ciprofibrate (100mg/day) and high-potency statin combination therapy. In spite of the medications, she had severe hyperlipidemia, with elevated levels of total serum cholesterol and triglycerides (Table 1). As with the patient in Case 1, the medications were well tolerated and there were no side effects. There were no manifestations of renal lesion either. The patient remained eutrophic with short stature during her development, and presents normal BMI values nowadays.

In order to research for subclinical atherosclerotic disease, a carotid Doppler ultrasonography study was performed, which showed no alterations in both patients. Lipoprotein electrophoresis, used to define the phenotype of dyslipidemia, showed accumulation of pre-beta-lipoproteins, corresponding to the very-low-density lipoprotein (VLDL) fraction, Fredrickson classification Type IV (Table 2).

Discussion

GSDIa is associated to severe hypertriglyceridemia and hypercholesterolemia, with serum levels of triglycerides reaching 4.000 to 6.000mg/dL, and serum cholesterol values ranging from 400 to 600 mg/dL.[6] Hyperlipidemia is related to the increased products of glycolytic pathways, which are essential for cholesterol synthesis, such as NADP, NADH, phosphate, glycerol-3-phosphate and coenzyme A.[2] Usually, the concentrations of very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) are increased, whereas the concentrations of high-density lipoproteins (HDL) and

Table 1 – Data comparison between the two cases – lab results throughout the years

	TGP		LDL-c		HDL-c		TG		AU		Gli		TGO		TGP	
Patient	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**
1996	246	*	-	*	48	*	711	*	-	x	65	x	168	x	136	x
1999	269	117	-	-	-	-	778	362	9.0	-	-	-	77	100	62	70
2002	260	293	-	-	31	59	581	1059	8.5	8.3	-	-	92	121	101	133
2005	260	264	-	86	39	43	766	713	3.5	6.8	79	95	166	205	130	240
2008	314	326	-	220	53	39	497	335	-	4.6	-	-	43	251	39	252
2011	274	423	-	-	53	53	537	1132	4.9	7.4	60	78	48	96	23	109
2014 **	321	304	195	-	55	52	397	701	-	-	92	96	-	61	122	76
2017 **	282	282	165	164	56	48	303	352	-	-	91	-	49	-	29	-

** Case 2 patient was not born. ** Initiation of treatment with rosuvastatin (40 mg) and ciprofibrate (100 mg/day). TC: total cholesterol; TG: triglycerides; LDL-c: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol; UA: uric acid; Glu: blood glucose; HbA1c: glycohemoglobin; TGO: glutamic-oxaloacetic transaminase; TGP: glutamic pyruvic transaminase.*

Table 2 – Lipoprotein electrophoresis of patients

Dosage	Results (%)		Reference (%)
	Patient 2	Paciente 2	
Alpha lipoprotein	28.6	17.8	23-46
Pre-beta lipoprotein	36	36.8	3-18
Beta-lipoprotein	35.4	45.4	42-63
Lipoprotein (a) (Lp(a))	0	0	

of apolipoproteins AI, AII are reduced; in addition, the concentrations of apolipoproteins CIII, B and E are elevated. An increase is observed not only in the number of VLDL and LDL particles, as becomes evident from the elevated apoB levels, but also in their size, due to the triglycerides accumulation in these fractions.[6-8]

Bernier et al.9 demonstrated that the overall prevalence of hypercholesterolemia (31%) and hypertriglyceridemia (67%) are higher in GSDIa than in GSD-III patients. In adult populations, the biochemical abnormalities tend to attenuate, unlike hyperlipidemia, which persists in GSDIa, although with no higher related risk of atherosclerosis.[9]

In the cases reported, the concentrations of triglycerides were considerably elevated since childhood, with high cholesterolemia as well, but in lower proportions, thus evolving until adolescence.

It is possible to question whether, over time, hypoglycemia would tend to improve due to decreased metabolic rates in the body and to the influence of female sexual hormones, in addition to nutritional readaptation. Lipoprotein electrophoresis, performed in our patients, showed an increase in the pre-beta fraction in both of them. However, in the youngest patient, who had a more altered lipid profile, due to more severe hypertriglyceridemia, the electrophoresis test also exhibited a decrease in the alpha fraction.

The European Study on Glycogen Storage Disease Type I (ESGSD I) recommends follow-up and routine laboratory tests (including lipid profiles), according with the patient's age: age 0–3 years every 2 months; 3–20 years every 3 months; adults every 6 months, as well as monitoring of cardiovascular diseases.[7] In this context, triglyceride concentration is considered the most useful parameter for chronic metabolic control with advanced age, in the presence of hypoglycemia, due to considerable improvements in serum levels of lactate and uric acid.[10]

Regarding the research for subclinical atherosclerosis, since none of the patients had manifested atherosclerosis, a carotid Doppler ultrasound was performed, which revealed no alterations. However, healthy patients and of the same age, showed lower intimal thickness when compared to GSDI patients.[11] In a cohort of 28 patients with GSD I and 23 control subjects, Bernie et al.[9] compared carotid intima media thickness (cIMT) and mean augmentation index measured by radial artery tonometry. A greater cIMT value was found in the GSD cohort than in the control group, $p < 0.02$, adjusted for age, sex, and BMI (body mass index), in addition to mean augmentation index measured by radial artery tonometry, which was also higher in the GSD cohort (6.4% ± 14.0%) than in the control group (2.4% ± 8.7%) ($p < 0.001$).[8] These data suggest that GSDIa may be associated with major arterial dysfunction and increased risk for cardiovascular disease.

On the other hand, there would be a possible cardiovascular protection, with decreased platelet adherence and, therefore, prolonged bleeding time, leading to lower risk of atherothrombosis. Detoxification of free radicals seems to be the leading protection factor for cellular membrane integrity, because it enhances NADPH2 production and activates the system of free radical detoxification.[1]

Since their childhood, our patients had high triglycerides, which would correspond to a polygenic defect, with greater VLDL synthesis, followed or not by failure to metabolize it by lipoprotein lipase.[8] Later, in the 10 to 14 age range, both presented a proportional increase in cholesterol and triglycerides levels, usually greater than 300 mg/dL. This lipid profile, similar to Fredrickson phenotype III, would be the result of changes in apo E and/or due to a failure to metabolize IDL (intermediate density lipoproteins).[4]

The GSPIa lipid profile usually suffers expressive changes, especially in relation to hypertriglyceridemia, with pancreatitis and hepatic adenomas being two of the major complications.[7] Regarding the treatment, in addition to specific dietary measures, the use of statins and fibrates would be indicated, for a better control of dyslipidemia, reduction of cardiovascular risk and prevention of pancreatitis.[7]

Dietary management is traditionally based on the provision of exogenous carbohydrate to compensate for defective gluconeogenesis and achieve normoglicemia. Thus, frequent meals, continuous overnight enteral feeding and the administration of uncooked cornstarch are indicated.[12] The treatment also includes the use of fibrates as a way to prevent pancreatitis, sodium bicarbonate and xanthine oxidase inhibitors to treat metabolic acidosis and hyperuricemia, respectively.[7] Both patients have not presented renal alterations so far, which may be attributed to early dietetic treatment.[2]

If hypoglycemia can be prevented, as mentioned before, the clinical and biochemical abnormalities, in most patients, tend to improve.[2] Nevertheless, hyperlipidemia tends to persist, although no greater risk of atherosclerosis has been observed so far. Since its introduction, the phenotype of G6PD deficient individuals has changed from mortality to morbidity, and the focus of attention has moved to the prevention of long-term complications, such as the possible consequences of severe dyslipidemia, among others.[12-14]

The clinical management of GSPIa still requires a better understanding of the pathology and, for this reason, further studies should be performed in this respect.

Conclusion

GSPIa is a rare and underdiagnosed disease, which evolves with severe dyslipidemia, among other complications. Early diagnosis and the establishment of efficient therapy contribute to increase the life expectancy of these patients.

Author contributions

Conception and design of the research, analysis and interpretation of the data, writing of the manuscript and critical revision of the manuscript for intellectual content: Ballavenuto JMA, Oliveira JDD, Alves RJ; Acquisition of data: Ballavenuto JMA, Oliveira JDD.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Santa Casa de Misericórdia de São Paulo under the protocol number 12293019.0.0000.5479. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Acute Myocardial Infarction as First Onset of Polycythemia Vera

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Introduction

Polycythemia vera (PV) is a chronic clonal progressive myeloproliferative neoplasm characterized by an absolute increase in erythrocytes and, usually, leukocytosis, thrombocytosis, and splenomegaly. Its incidence rates around 2.8/100,000 people per year.[1] Diagnosis is confirmed using the criteria defined by the 2016 revised World Health Organization (WHO) guidelines.[2] Major criteria include hemoglobin levels over 16.5 and 16.0 g/dL or hematocrit over 49 and 48% in men and women, respectively, or increased red cell mass of more than 25% above the mean normal predicted value; bone marrow biopsy showing hypercellularity for age with trilineage growth; presence of JAK2V617F or JAK2 exon 12 mutation. A minor criterion is reduced serum erythropoietin level. Diagnosis requires meeting either all 3 major criteria or 2 major criteria and the minor criterion. The patient is also considered as at thrombosis risk; those aged over 60 or with thrombosis history are considered at considered high risk; if both risk factors are absent, low risk is considered.

Treatment includes cytoreductive drugs, such as hydroxyurea, antiplatelet agents and therapeutic sangrias.

Thrombosis is a major cause of morbidity and mortality in PV patients. These thrombotic events are most frequently microcirculatory and arterial.[2]

Acute myocardial infarction (AMI) in myeloproliferative diseases is mostly attributed to coronary thrombosis due to hyperviscosity and thrombocytosis. The risk is increased in the presence of cardiovascular risk factors.[3] Coronary events are common during the follow-up of PV, with a rate of 11.4% in 10-year follow-up in the literature.[4,5] Also, in recent studies, arterial thrombotic events were more common than venous thrombotic events when diagnosed shortly before the PV diagnosis. However, the first presentation of PV as AMI is considered rare, with fewer than 10 cases in the literature.[3, 6-15]

Case Report

Patient was a 68 years-old white male, regularly treating hypertension, without any previous history of thrombotic events. He presented at the emergency room with an unspecific malaise, without chest pain or dyspnea, numbness in the proximal portion of both arms. He was admitted hemodynamically stable with good oxygen saturation. At physical examination, he had a plethoric face and dullness to percussion over Traube's space. Due to the likelihood of atypical presentation of acute coronary syndrome, he was initially investigated with an electrocardiogram (ECG) and myocardial necrosis markers (MNM), blood cell count and kidney function. The rest ECG (Figure 1a) showed pathologic Q wave and inversion of T wave in DII, DIII and aVF, later evolving (Figure 1b) with elevation of the ST segment in DII, DIII and aVF, while the other characteristics were maintained. MNM came positive (CK-MB from 34 to 36 ng/mL; reference <16 ng/dL and troponin from 0.12 to 0.81 and then to 1.07 ng/mL; reference <0.01 ng/mL). Pulmonary embolism was ruled out due to negative D-dimer. Other laboratorial analysis showed normal renal function and hemoglobin 21.3 g/dL, hematocrit 65.4%, platelets 805,000/mm^3 (reference: 140,000–440,000/mm^3), thus characterizing hyperviscosity, macroplatelets and leucocytes 15,400/mm^3 (reference: 4,000–11,000/mm^3), mainly neutrophils. It also showed no lipids or glucose alterations. The patient was diagnosed with AMI caused by PV and, against what is mostly found in the literature, the AMI diagnosis came prior to the discovery of PV. He was classified as at high thrombosis risk due to his age and double anti-platelet therapy was initiated with AAS (loading dose of 300 mg plus 100 mg/day) and clopidogrel (loading dose of 300 mg plus 75 mg/day), as well as enoxaparin 1 mg/kg twice a day. As observed in Figure 1, ST elevation was less than 1 mm. Also, the symptoms did not get worse as the ECG changed, so the team opted for weighing the benefit-risk ratio regarding submitting a possible non ST segment elevation AMI or even a non-reperfused ST segment elevation AMI to angiography under a high hematocrit situation. He was then submitted to 3 therapeutic sangrias before the coronary angiography (Figure 2A and 2B) could be performed safely, showing absence of angiographic evidence of intra-coronary thrombus and aneurysmatic dilatation in the median portion of the right coronary artery and no abnormalities or obstructions in the left anterior descending coronary artery or circumflex artery. The patient had TIMI 3 flow grade in the right coronary, circumflex and left anterior descending arteries (Figure 2B). There is no information on TIMI frame count. Physiology assessment of the arteries was not available in the service. Even though no thrombus was found, as this may have been caused by treatment prior to angiography, and due to the lack of another hypothesis, we sustained the diagnosis of type 2 AMI. Echocardiogram showed preserved systolic function with an ejection fraction of 64% (Teichholz), mild diastolic dysfunction (E/A ratio of 1.0, E/e' ratio of 8.67) and no alteration of left ventricular contractility. The AMI area was viewed on cardiac magnetic

Keywords

Myocardial Infarction; Polycythemia Vera, Thrombocytosis; Myeloproliferative Disorders.

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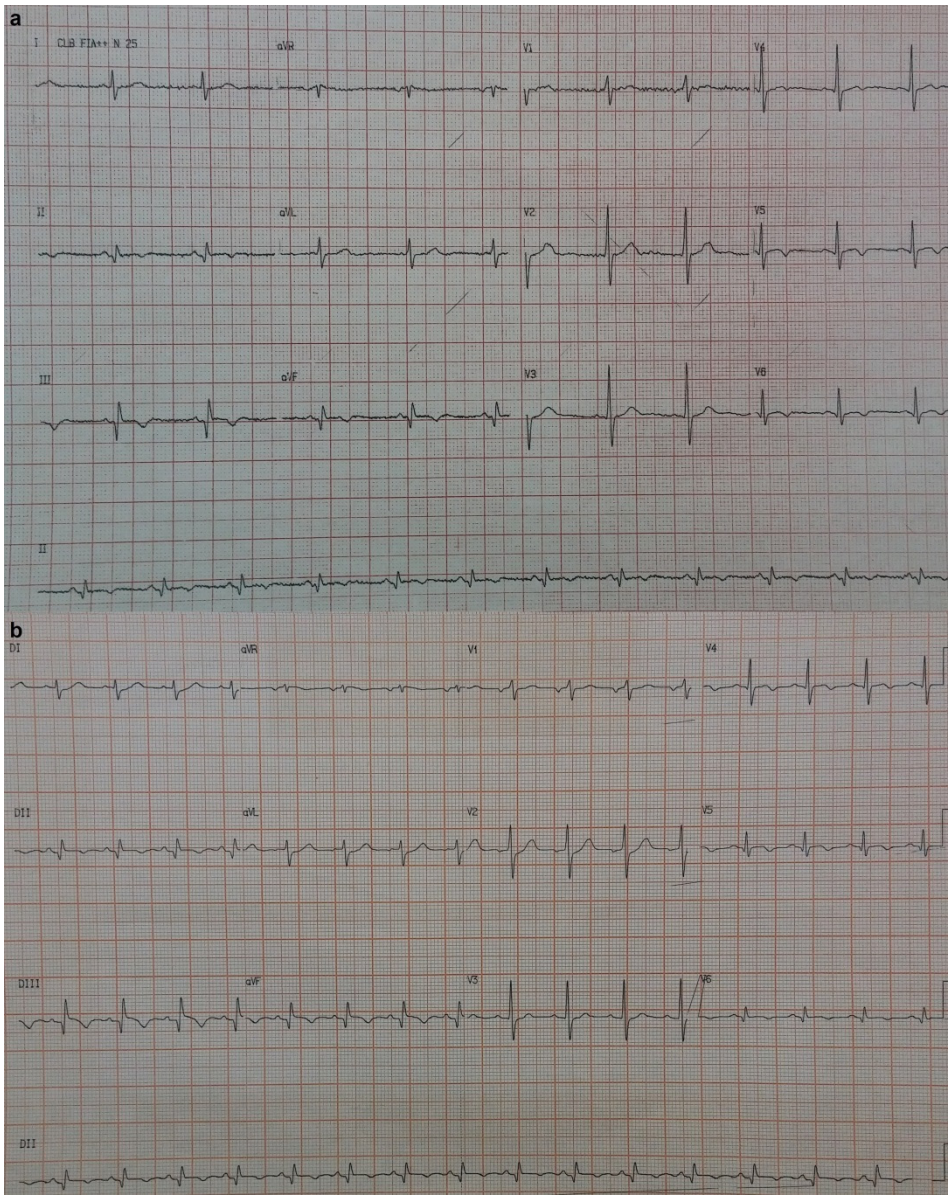

Figure 1 – *Electrocardiograms: at admission (a) with pathologic Q wave, inversion of T wave in DII, DIII and aVF, and asymmetric inversion of T wave in the precordial leads (V4–V6); and 1 hour after (b) with ST segment elevation in DII, DIII and aVF, keeping the other characteristics.*

resonance imaging (Figure 2C), which showed late enhancement of ischemic pattern, compatible with fibrotic area defining infarction of the medium and apex portion of the inferior wall, with preserved ejection fraction. Abdomen ultrasound confirmed homogeneous splenomegaly and low erythropoietin (1,5 mUI/mL; reference 5.4–31.9 mUI/mL), and JAK-2 mutation confirmed our hypothesis. He was then started on hydroxyurea, clopidogrel was suspended and anticoagulation was kept until discharge (8 days). The patient evolved without complications during his in-hospital stay or during early follow-up.

Discussion

We report here a very rare case of first presentation of PV as AMI. To our knowledge, fewer than 10 cases similar to this have been reported so far.[3] Usually, the patients are diagnosed with PV and, later, present some form of coronary acute syndrome, in about 11.4% of cases.[4]

Our patient had only hypertension and age as risk factors, and had no significant alterations in lipid profile, fasting glucose level, renal function or family history that could have increased the risk of developing AMI. In this patient's case, there were two conditions that could have contributed to myocardial

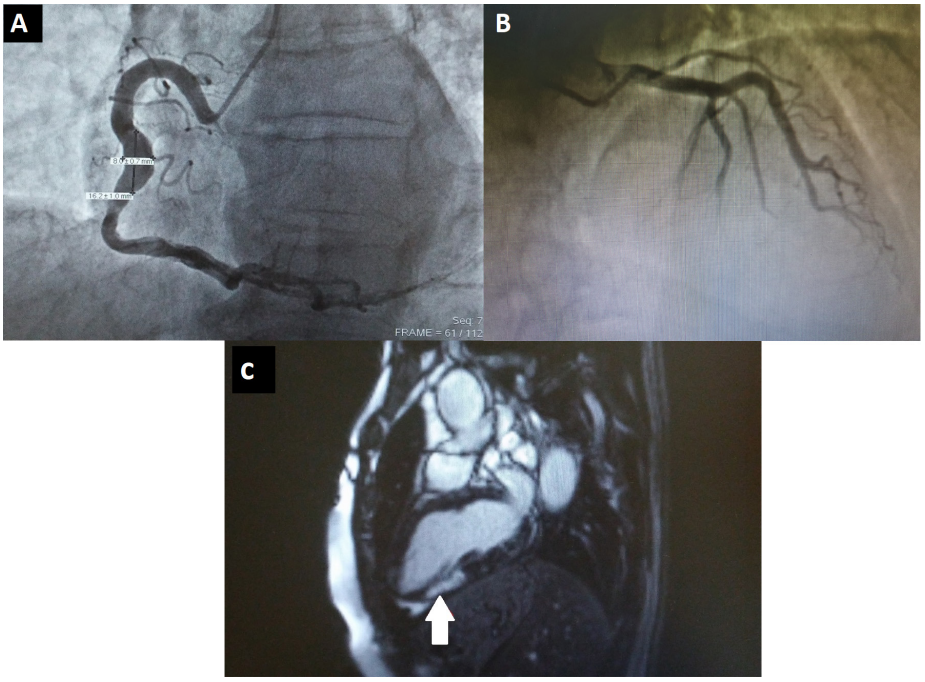

Figure 2 – *A. Coronary angiography. Frame showing the right coronary with aneurysm, 8.0-mm wide and 16.2-mm long; B. Coronary angiography. Frame showing the left anterior descending coronary artery TIMI 3 flow; C. Cardiac magnetic resonance imaging. Frame showing late gadolinium enhancement in the apical inferior segment, ischemic pattern.*

infarction: the coronary aneurysm and the PV itself, both of which can contribute to the formation of thrombus and AMI.

The mechanisms through which PV would lead to vascular events are not yet well established. However, some hypotheses have been displayed in literature, such as overproduction of thromboxane A2, endothelial dysfunction and platelet and leukocyte activation.[16] Elevation of leukocyte count occurs in 50 to 60% of PV patients, which may also have a detrimental effect on microcirculation in PV. Activated leukocytes may release proteases and oxygen radicals that alter endothelial cells and platelets in order to favor the development of a prothrombotic state. Platelet-leukocyte aggregates are increased in number in PV and are associated with increased propensity of thrombosis. In addition, the prothrombotic state in PV has been attributed to an acquired resistance to the naturally occurring anticoagulant — protein C — which is associated with reduced levels of protein S[2]. In agreement with that statement, our patient had an increase not only in platelet but also in leukocyte count, mainly neutrophils, without any signs of infection, although that could also correspond to the AMI inflammation process.

Another interesting finding in the literature is that thrombotic events might happen even when hematocrit and platelet levels are acceptable[17] indicating that the physician should be alert to that differential diagnosis even in controlled diseases.

In conclusion, this is a rare case of first onset of PV as AMI, interestingly with lack of obstruction in the angiography, indicating a possible resolution of the thrombus after antiplatelet therapy. The challenge in those cases remains the therapy in patients with sustained obstruction, once stent placing might mean a higher risk of subsequent occlusion due to the patient's susceptibility to form platelet thrombi.

Author contributions

Conception and design of the research: Silveira CFSMP; Acquisition of data: Silveira CFSMP, Vitali LBSL, Faustino FG, Maurício ADCV; Analysis and interpretation of the data: Silveira CFSMP, Vitali LBSL, Faustino FG, Maurício ADCV, Teixeira R, Bazan SGZ; Writing of the manuscript: Silveira CFSMP, Vitali LBSL, Faustino FG, Maurício ADCV, Teixeira R; Critical revision of the manuscript for intellectual content: Bazan SGZ.

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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Recurrent Atrial Myxoma in a Patient with Carney Complex. A Case Report and Literature Review

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Introduction

Primary cardiac tumors are uncommon. They have an incidence between 0.0017% and 0.28% corresponding to 17 and 2,800 of primary heart tumors per 1 million autopsies.[1] Cardiac Myxoma (CM) is a benign neoplasm and represents the most common one among primary cardiac tumors in adults.[2]

CMs have an annual incidence of 0.5–0.7 of surgically resected cases per one million; with the majority of cases showing sporadic appearance and less than 10%, a family inheritance pattern.[3]

The left atrium (LA) is the most common site of origin (75–80%), followed by the right atrium. Multiple CMs represents 5% of all CMs and only 50% of them have a bilateral origin.[4]

CMs have a wide range of manifestations, mostly obstructive symptoms, but they can also produce embolisms being the worst of their scenarios.[1]

There are 2 types of CM: 1. Simple, the most common one, representing 95% of all CMs. Its highest prevalence is at 56 years of age, with a risk of developing a second myxoma between 1 and 3%. 2. Autosomal dominant family forms, such as Carney Complex (CNC).[2]

These types of CM present an atypical anatomic distribution that is different from the LA.[5] They appear at an average age of 25 years and tend to be multiple in 45% of cases, with a relapse rate between 15% and 22%.[1,4,6]

Case Report

We report the case of a 22-year-old male patient with a previous history of right atrial CM resection at 12 years of age and resection of a cutaneous abdominal myxoma at 20 years of age; he was brought to the ER for generalized sudden onset paresthesia associated with right fascio-corporal hemiparesis and motor aphasia. On physical examination, acromegalic-like appearance, short neck, lentiginosis with grayish nevi on his lower lip and multiple café-au-lait spots on his face (Figure 1-A).

Brain axial CT scan showed intra-axial hypodense image in the left parietal-temporal region of 40 x 24 mm in diameter (Figure 1-B). Then, echocardiography was performed, showing normal LVEF (64%) and mild LA dilatation. LA mobile mass (5.4 cm x 2.8 cm in diameter) of homogeneous appearance and regular contours adhered to the interatrial septum with prolapse to the left ventricle without no gradient of stenosis or signs of regurgitation. (Figure 1-C)

CNC was suspected, due to an abnormal hormonal profile [secondary hyperthyroidism and hypercortisolism]. (Table 1)

Additional tests were performed: brain MRI, which showed in axial sequence T1 a hypointense area of 7 mm in diameter, corresponding to a pituitary microadenoma and testicular ultrasound, which revealed bilateral microlithiasis (Figure 1-F).

As recommended in international guidelines, he was taken to cardiac surgery for tumor resection and concomitant resection of the atrial septum, because this is absolutely mandatory during the resection of CM in CNC to avoid atrial myxoma recurrence. LA mass of soft and friable consistency, compatible with CM of 5.5 cm x 3 cm was found (Figure 1-D and E). Histological analysis, again, confirmed atrial myxoma.

The patient had a favorable postoperative outcome, without any complication, and progressive improvement of neurological symptoms. CNC diagnosis was established mainly due to the multiple cutaneous disorders, "recurrent" and "bilateral" CM, prior history of extra-cardiac myxoma, as well as endocrine disorders and testicular calcifications.

Discussion

CMs are the most common primary cardiac tumors.[2] However, cases of recurrence are very rare.[7,8] CNC is an uncommon genetic disorder inherited in an autosomal dominant manner; characterized by multiple benign tumors most often affecting the heart, skin and the endocrine system; and abnormalities in skin coloring (pigment) resulting in a spotty appearance to the skin of affected areas. Its mean age of presentation is 20 years, and its prevalence remains unknown.[5]

Diagnosis is made with at least two of the 12 criteria proposed by Stratakis (Table 2) or one of these abnormalities plus the affection of a first-degree relative or mutation in the gene of regulatory subunit type I protein kinase A [gene PRKAR1A].[5]

It is important to approach and monitor both individual and family cases of recurrent myxomas as, to date, more than 125 mutations of gene-PRKAR1A have been described. It is the main gene associated with CNC.[9] The inactivating mutations of gene PRKAR1A are responsible for the phenotypic manifestations of CNC in more than 70% of cases.[6,9]

Keywords

Carney Complex/complications; Atrial Myxoma; Genetic Loci; PRKAR1A.

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Table 1 – Endocrine profile

IGF-1	922 ng/ml (z. Score: +4.8)
ACTH	22.6 pmol/l
PRL	3.42 ng/dl
Cortisol	33.01 mcg/dl
TSH	7.26 mcU/ml
T4l	2.34

The gene PRKAR1A is a key component of the cellular signaling pathway of cyclic adenosine monophosphate (cAMP) involved in tumorigenesis. Therefore, this pathology could be considered a form of multiple endocrine neoplasia with involvement of the adrenal, pituitary, thyroid glands and gonads.[3,6,9]

Cerebrovascular disease can be the presentation of CM.[10] Besides, neurological manifestations have a typical presentation in young patients with predominance in males, being the main clinical presentation of our case.

Conclusion

CNC is a rare entity that is associated with multiple cutaneous and endocrinological manifestations, and is related to the appearance and recurrence of myxomas. CNC must be suspected in any patient with recurrent CM. In patients diagnosed with CNC, a complete and multidisciplinary approach should be followed both on the patient and on close relatives meeting some diagnostic criteria, since they could be carriers of mutations of gene PRKAR1A. Diagnosis of Carney complex should be considered when it fulfills the diagnostic criteria even if the genetic test is not available or confirmed.

Author contributions

Conception and design of the research: Cervantes-Molina LA, Masini-Aguilera ID, Pineda-De Paz DO; Acquisition of data: Cervantes-Molina LA, Masini-Aguilera ID, Pineda-De Paz DO; Writing of the manuscript: Cervantes-Molina LA, Machuca-Hernández M, Pineda-De Paz DO; Critical revision of the manuscript for intellectual content: Cervantes-Molina LA, Cedillo-Ramírez D, Masini-Aguilera ID, López Taylor JG, Machuca-Hernández M, Pineda-De Paz DO.

Potential Conflict of Interest

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Sources of Funding

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Table 2 – Major diagnostic criteria according to Stratakis

1 - Cutaneous lentiginosis with typical distribution (lips, conjunctiva, mucous membranes)
2 - Myxoma (cutaneous and mucosal) or cardiac myxoma
3 - Mammary myxomatosis or MRI findings suggestive of the diagnosis
4 - Pigmented primary nodular disease or paradoxical increase in the excretion of urinary glucocorticoids after dexamethasone administration
5 - Acromegaly associated with pituitary adenoma producing GH
6 - Testicular tumor of large calcified sertoli cells or presence of calcifications in testicular ultrasound
7 - Thyroid carcinoma or presence of multiple hypoechoic nodules in prepubertal thyroid ultrasound
8 - Psammomatous melanocytic schwannomas
9 - Blue nevus, multiple epithelioid blue nevus
10 - Multiple ductal mammary adenomas
11 - Osteochondromyoma
Supplementary Criteria
1 - Affected family member
2 - Presence of inactivating mutations of the PRKAR1A gene
3 - Activating variants of the PRKACA gene or PRKACB gene

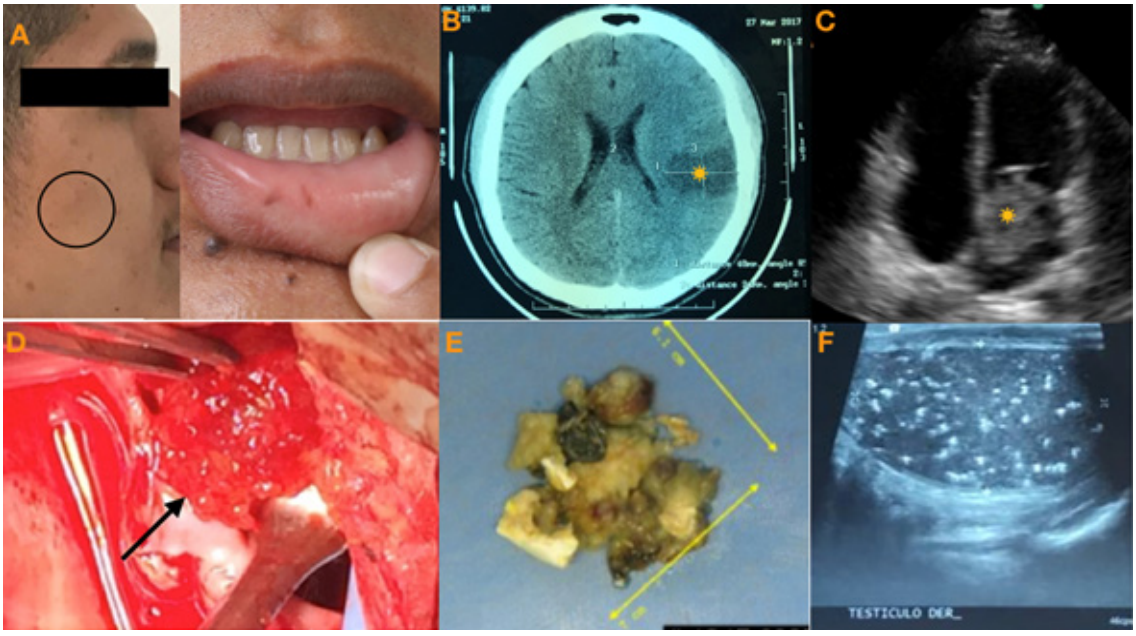

Figure 1 – *Panel A. Patient's image showing grayish nevi (arrow) and café-au-lait spots (circle). Panel B. Axial computed tomography (CT scan) of the brain showing intra-axial hypodense image in the left parieto-temporal region of 40 * 24 mm (asterisk) with mild/moderate surrounding edema. Panel C. Apical four-chamber transthoracic view showing a large left atrial mass (asterisk) and panel D showing its correlation with surgical view (arrow). Panel E. Macroscopic view of left atrial myxoma. Panel F. Right testicular ultrasound shows multiple calcifications.*

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Painful Left Bundle Branch Block Syndrome in a Patient Referred to Electrophysiologic Study: A Case Report

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Introduction

The development of chest pain associated with intermittent left bundle branch block (LBBB) in the absence of coronary artery disease has been described in the literature as painful left bundle branch block syndrome. The mechanism responsible for the chest pain is unknown, but the main current hypothesis is related to acute cardiac dyssynchrony.

In this syndrome, the LBBB occurs when the cycle length is equal to or less than the refractory period of the left bundle, mainly during physical effort. The chest pain in the case of the painful LBBB syndrome may range from a mild discomfort to a disabling condition.

This report describes the case of a patient with typical rate-dependent LBBB associated with chest pain who was referred to electrophysiologic study (EPS) without evidence of arrhythmias.

Case Report

A 41-year-old woman with a history of controlled hypertension and a 2-year history of palpitations associated with chest pain triggered by minimal efforts during daily activity, which lasted up to 2 hours. The chest pain was described as a pressure sensation that radiated to the left arm associated with nausea and dyspnea. The episodes were characterized by sudden onset, without any prodromes, with spontaneous improvement. She was initially treated with atenolol 25 mg bid, with partial relief of symptoms. There was no family history of unexplained syncope or sudden cardiac death. Her physical examination was unremarkable. The 12-lead electrocardiogram (ECG) during crisis revealed a wide complex tachycardia with complete left bundle branch block (LBBB), with inferior axis and a P wave compatible with sinus rhythm. Even so, the patient was referred to EPS, which did not evidence arrhythmogenic substrates.

Keywords

Heart Block; Chest Pain; Coronary Artery Diseases/physiopathology; Cardiac Electrophysiology; Electrocardiography; Ecocardiography.

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However, at the start of a 600 miliseconds continuous atrial pacing, a rate-dependent LBBB was noted. Immediately succeeding the blockade of the LBBB, the patient, who was not maintained under sedation, started to complain about the same symptoms already described. The LBBB persisted during some minutes and relieved itself, concomitant to the relief of pain. The ECG is shown in Figure 1. It is a typical third degree LBBB with a 138 ms QRS complex duration, superior axis and a sinus P wave.

The basal 12-lead ECG was normal (Figure 2). The 24-hour ECG Holter monitoring revealed that basal HR was between 56 and 116 bpm during daily activities, with no evidence of LBBB. Transthoracic echocardiography and cardiac magnetic resonance both showed normal systolic function with no myocardial or valve pathologies. All cardiac chambers were normal in size. A stress test evidenced the development of left bundle branch block associated with thoracic pain. The CT angiography discarded coronary artery disease and myocardial perfusion defects on dypiridamole. Currently, the patient is receiving atenolol 50 mg bid and no recurrence of palpitations or chest pain was evidenced at the 6-month follow-up.

Discussion

In 1946, the first report on intermittent left bundle branch block induced by effort was published. The patient presented with palpitations and aching feeling in precordium during crises. However, the coronary angiography was not performed due to the technology available at the time.[1] In 1976, Vieweg et al.[2] reported the first case of left bundle branch block associated with angina of effort, with angiographic evidence of normal coronary arteries. Although the patient was considered to have angina, atypical characteristics were present: sudden onset and offset, concomitantly with LBBB and after its disappearance, respectively.[2] In 1982, Virtanen et al. carried out a study with 7 patients with new left bundle branch block and chest pain during exercise test, all of them with normal coronary angiography. In this study, the patient's pain pattern was evaluated and considered as atypical pain, because of sudden onset and offset.[3] Subsequently, new cases were reported, and this condition was called painful left bundle branch block syndrome.

The mechanisms of painful LBBB syndrome are unclear. The possibility of demand ischemia due to coronary lesions or spasms was initially considered as a possible cause for this syndrome. However, this assumption was soon proved wrong. Immediate onset/offset of pain is incompatible with ischemia.[4] Nitroglycerin was proved to be ineffective[2] and sometimes induced LBBB due to tachycardia. Nuclear imaging is frequently negative in these patients and vasospasm has also been discarded.[5,6]

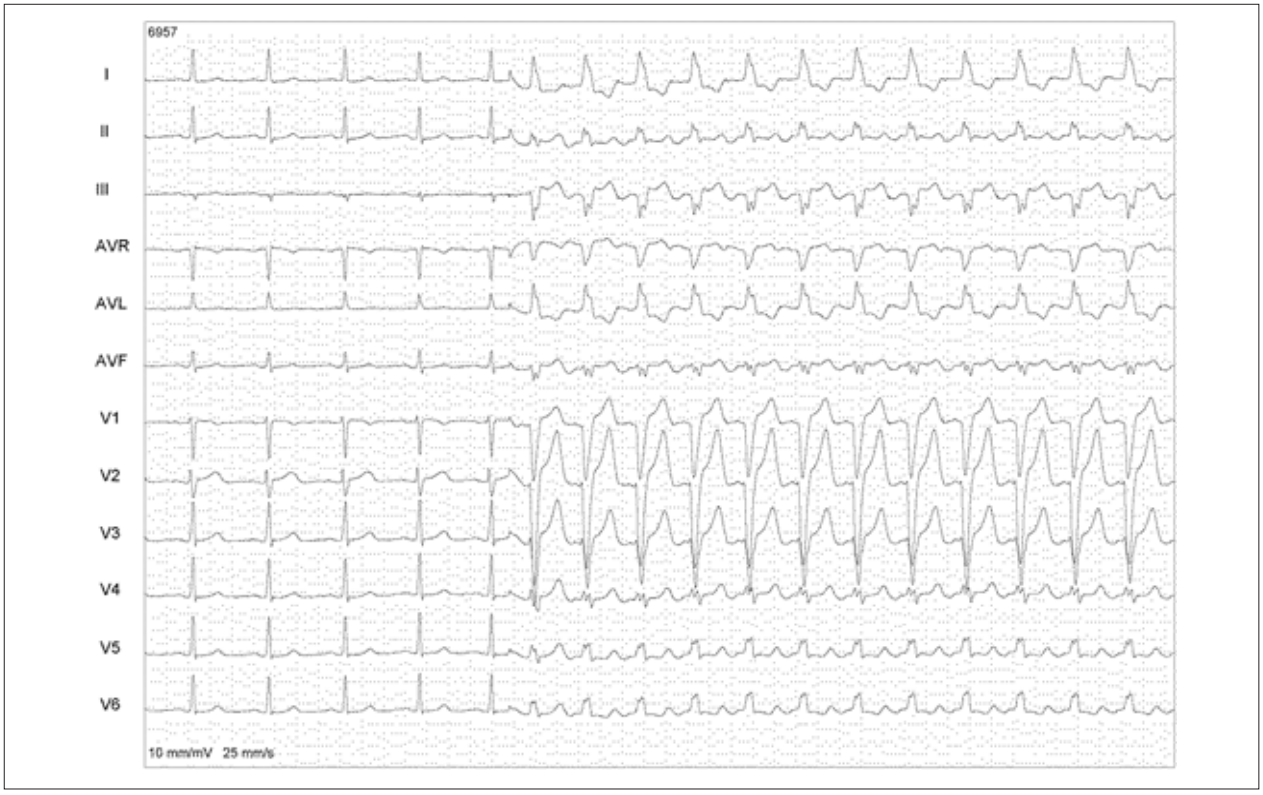

Figure 1 – *12-lead ECG of the onset of pain immediately after left bundle branch block*

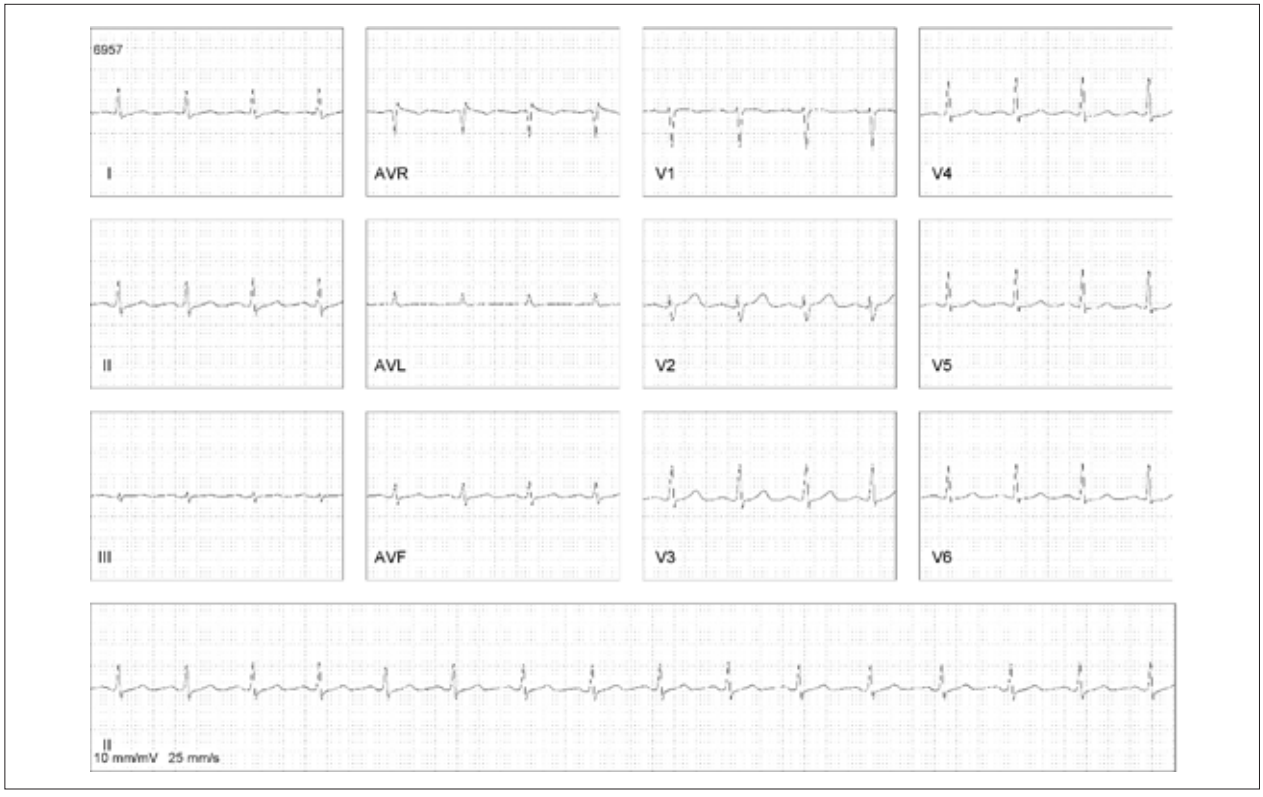

Figure 2 – *Normal basal 12-lead ECG.*

The best theory so far was proposed by Virtanen et al.,[3] who speculated that the pain could be induced by abnormal systolic motion of the septum in ventriculography. An inferior axis which presented uniformly in a series of cases made the authors hypothesize that this could reflect a specific contractility pattern. Shvlikin et al.[7] proposed criteria to the diagnosis of painful LBBB syndrome (Table 1).[7]

Similar to the memory T waves of paced patients, chronic LBBB has lower amplitude T waves than acute LBBB. In a prospective study, a S/T ratio < 2.5 in precordial leads proved to be useful (100% sensitivity and 89% specificity) to help distinguish between new-onset or chronic LBBB,[8] which refers to one of the items of the criteria proposed in Table 1.

The patient described in this paper was referred to EPS because of the mistaken hypothesis of supraventricular tachycardia with aberrancy. During the study, with continuous atrial pacing, we had the opportunity to register the exact moment of left bundle branch blockade and the immediate complain about the same pain she referred to as chronic.

Regarding the criteria proposed by Schvilkin et al.,[8] our case matches all but one criterion: the "inferior axis criterion". However, other publications evidenced superior QRS complex axis as well.[9,10] The S/T wave ratio was 1,33 in V2 (Figure 3), which is compatible with acute onset LBBB. The patient had abrupt onset of pain, as registered by the members of our team in our electrophysiology lab; the resolution of the symptoms occurred immediately after the resolution of the LBBB; The basal 12-lead ECG was normal. A stress test discarded myocardial ischemia and the CT angiography evidenced normal coronary arteries. Echocardiography and cardiac resonance were both normal, excluding secondary causes of angina.

Conclusion

We reported the case of a patient with painful LBBB who was referred to electrophysiology study. The abrupt onset of pain immediate after left bundle blockade is incompatible with ischemia and the patient underwent exams that discarded coronary and myocardial involvement. The best hypothesis for the pathophysiology of this syndrome is painful desynchrony of the heart due to acute onset LBBB. To our knowledge, this is the first case report of this syndrome in a Brazilian medical journal.

Author contributions

Conception and design of the research: Alencar Neto JN, Cirenza C, Paola AAV; Acquisition of data: Alencar Neto JN, Sakai MH, Moraes SRR; Writing of the manuscript: Alencar Neto JN, Sakai MH, Moraes SRR, Paola AAV; Critical revision of the manuscript for intellectual content: Cirenza C, Paola AAV.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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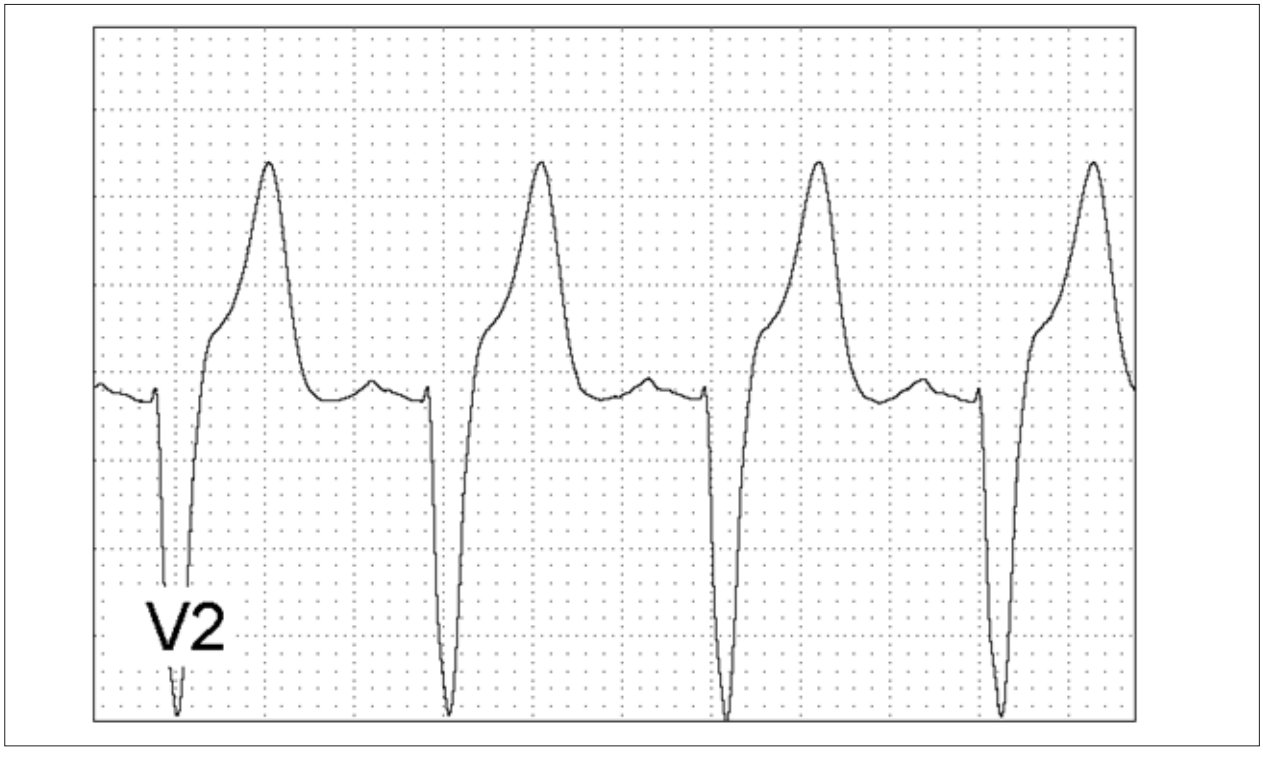

Figure 3 – *S/T ratio < 1.8 in V2.*

Table 1 – Painful LBBB syndrome criteria

Abrupt onset of chest pain with development of LBBB
Simultaneous resolution of symptoms with resolution of LBBB (occasionally absent)
Normal 12-lead ECG before and after LBBB
Absence of myocardial ischemia during functional stress test
Normal left ventricular function and absence of other conditions that may explain the symptoms
Low precordial S/T wave ratio (< 1.8) and inferior axis

Criteria proposed for the diagnosis of the painful LBBB syndrome. Adapted from Shvilkin.[7]

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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Case 1/2020 – Very Accentuated Isthmic Coarctation of the Aorta in a Young Individual with Arterial Hypertension Relieved by Interventional Catheterization

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Clinical data

Arterial hypertension had been detected 6 months before, after study-related stress in a 16-year-old individual. At the time, diagnostic images (echocardiography and angiotomography) confirmed the presence of accentuated isthmic coarctation of the aorta, with many collaterals that filled the descending aorta. Blood pressure was 170/80 mmHg, which decreased to 130 to 150/80 mmHg with propranolol-80 mg/day. He had been previously submitted to surgery for atrial septal defect closure at 4 years of age. He reported fatigue at exertion since a few months before.

Physical examination: Good overall status, eupneic, acyanotic, wide pulses in the upper limbs and absent in the lower limbs. Weight: 45.5 Kg, Height: 163 cm, right upper limb BP and left upper limb BP = 155/80 mmHg, HR: 55 bpm. Aorta easily palpated at the suprasternal notch.

Precordium: non-palpable apex beat and no systolic impulses along the left sternal border. Normal heart sounds, rough systolic murmur, ++/4 in the suprasternal notch and lateral neck surfaces, and mild and aspirating diastolic murmur, +++/4, in the left sternal border. There were no audible murmurs on the back of the thorax. The liver was not palpated, and the lungs were clear.

Complementary examinations

Electrocardiogram: Sinus rhythm, signs of left ventricular overload with Sokoloff index of 46 mm and normal ventricular repolarization. AP = +40º, AQRS = +60º, AT = +30º.

Chest x-ray: Normal cardiac area (cardiothoracic index = 0.50). High vascular pedicle shows a three (3)-shaped image with greater dilation in the lower part, leading to the diagnosis of coarctation of the aorta (CoAo) in this region. There were signs of costal corrosion on the right (Figure 1).

Echocardiography: It showed normal heart chambers without myocardial hypertrophy. Maximum gradient 14.7 and mean 6.8 mmHg in the aortic valve. The dimensions were: Ao = 27, LA = 28, LV = 47, septum = 9, LVEF = 68%, RVSP = 28 mmHg.

Angiotomography: Coarctation of the aorta after emergence of the left subclavian artery with pronounced and marked collateral circulation. Ascending aorta = 28 mm, descending aorta after CoAo = 21 mm and thoracoabdominal aorta = 14 mm.

Ambulatory Blood Pressure Monitoring (ABPM): Maximum blood pressure = 170/100 mmHg and most of the time = 130-140/60-70 mmHg.

Holter: Ventricular extrasystoles: 2,315 (3%) of 77,166 beats.

Clinical diagnosis: Accentuated coarctation of the aorta in the isthmus with exuberant collateral circulation and bivalvular aortic valve undergoing natural evolution in young individual with arterial hypertension.

Clinical reasoning: The diagnostic elements of coarctation of the aorta were evident, represented by the absence of arterial pulses in the lower limbs, arterial hypertension in the upper limbs, accompanied by systolic murmur in the suprasternal notch, and left ventricular overload on the electrocardiogram, in addition to the three (3)-shaped image on chest X-ray. Diagnostic confirmation was easily established by the echocardiogram and angiotomography images.

Differential diagnosis: Congenital coarctation of the aorta should be differentiated from acquired anomalies that also cause obstruction at several levels of the aorta, such as Takayasu disease.

Conduct: Of the two approaches for correction of aortic coarctation, the surgical[1] and the percutaneous,[2] the latter was chosen. Previously, cardiac catheterization was performed, which disclosed pressure in the ascending aorta of 150/80 with a mean of 96 mmHg and in the descending aorta of 50/30 and mean of 40 mmHg. The angiography showed progressively greater narrowing from the left subclavian artery, of which diameter of 12 mm was the same as that of the aortic arch, up to about 40 mm below, when it then became punctiform with a maximum orifice of 2 mm and post-stenotic dilation with 18 mm in diameter. There was large collateral circulation.

Considering this picture, a pre-dilation with Mustang balloon (Boston-5/20 mm) was performed of the isthmus region with coarctation. A new angiography showed increased diameter of the aorta with coarctation without signs of dissection or aneurysm. Using a 14 fr Mullins sheath, a covered 14/40 mm CP stent (BIB balloon) was positioned and

Keywords

Heart Defects Congenital/surgery; Aortic, Coarctation/surgery; Stress Psychological; Hypertension: Angioplasty, Balloon/methods; Stent.

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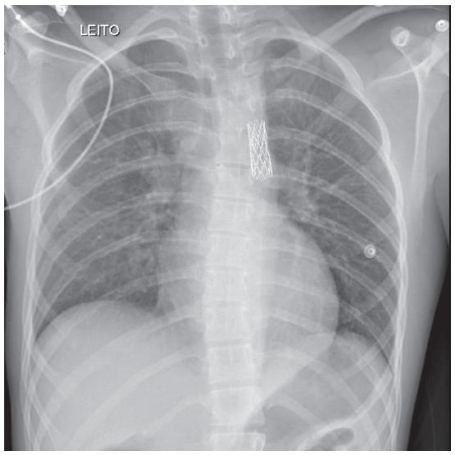

Figure 1 – *PA Chest X-ray highlights normal cardiac area with a cardiothoracic index of 0.50 and normal pulmonary vascular network. Stent placement at the beginning of the descending aorta highlights post-stenotic dilation of the aorta.*

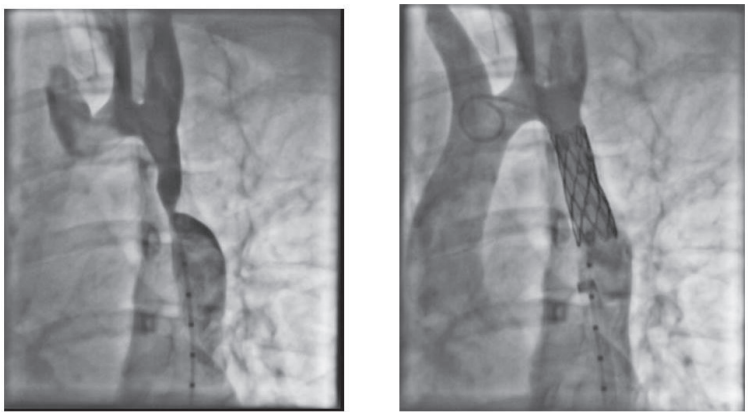

Figure 2 – *Cardiac angiography shows the accentuated coarctation of the aorta, approximately 40 mm after the emergence of the left subclavian artery in the image on the left and the wide dilation of this region after stent placement in the image on the right.*

implanted. New angiographies showed a clear improvement in aortic coarctation (Figure 2). Posterior pressures were equivalent in the ascending and descending aorta at 127/67 and mean of 87 mmHg.

Comments: Coarctation of the aorta, even when accentuated, can have a long-term evolution without significant changes, as long as collateral circulation develops to minimize aortic obstruction. This thought is in opposition with the evolution observed in this case, which did not develop even myocardial hypertrophy or some degree of myocardial dysfunction. Another aspect that draws attention in this clinical case was the late diagnosis of the anomaly, when a high blood pressure in the upper limbs was incidentally observed. This fact shows that the previous clinical examination of this patient had certainly not been performed with the refinements of a more adequate semiology. The percutaneous procedure has become the most indicated in the coarctation of the aorta, especially in young individuals and adults, due to fewer complications and similar effectiveness to that of the surgical procedure.[1,2] Angiographic images demonstrate this assertion.

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Case 2/2020 – Anomalous Origin of the Left Coronary Artery from the Pulmonary Trunk, Under Natural Evolution in a 75-Year-old Asymptomatic Woman

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Clinical data

Patient evolves without symptoms in her daily routine as a domestic worker. She denies any symptoms of palpitations, precordial pain or fatigue. When she was aged 62, a cardiac catheterization revealed the diagnosis of anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA, or Bland-White-Garland syndrome), after an altered routine exercise stress test. Since then, the patient reports her well-being, although she is aware of the existence of this anomaly. She is being treated with rosuvastatin, levothyroxine and vitamin D.

Physical examination: good overall status, eupneic, acyanotic, normal pulses in the four limbs. Weight: 49.8 Kg, Height: 143 cm, BP:120 x 80 mmHg, HR: 74 bpm.

Precordium: Patient presented ictus cordis impulsive and displaced to the left of the midclavicular line, without systolic impulses at left sternal border. Hyperphonetic heart sound, with a split S2. Mild continuous murmur, +/++/4, more intense in the suprasternal notch and in the 1st and 2nd left intercostal spaces. Non-palpable liver and clean lungs.

Complementary examinations

Electrocardiography (ECG): Junctional rhythm, with a flat P wave in the frontal plane and left precordial leads. Negative T waves in leads I, L, and of low amplitude in leads V4-V6, suggestive of anterolateral ischemia. Signs of overload of left cavities with a biphasic P wave in lead V1 and a Sokolof index equal to 37mm. QRS 102 ms (AQRS= 0º, AT= +110º) (Figure 1).

Chest radiography: Slightly enlarged cardiac area, with elongated left ventricular arch (CTI=0.68). Clearly increased pulmonary vascular network (Figure 1).

Echocardiography: Normal atrioventricular and ventriculoarterial connections. Significantly increased left atrium size (52 mm; LAVI = 125 ml/m^2). The other cavities (RV= 20, LV= 56, RA= 31), as well as the cardiac valves, were normal. There was no myocardial hypertrophy, with septum and posterior wall = 8 mm. The pulmonary artery systolic pressure was 82 mmHg as estimated by Doppler echocardiography. Biventricular function was normal and left ventricular ejection fraction was 60% (Figure 1).

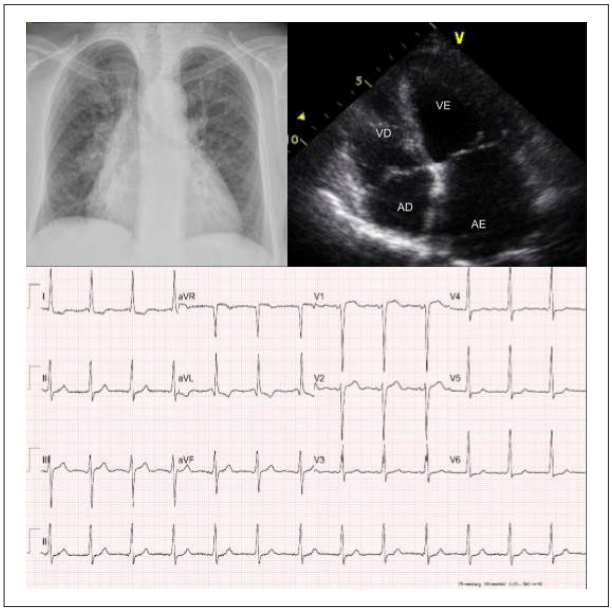

Figure 1 – *Chest x-ray highlights increased cardiac area and pulmonary vascular network. ECG shows overload of left cavities with inferolateral wall ischemia of the left ventricle. A 4-chamber view echocardiogram study highlights increased left cavities. RA: right atrium; LA: left atrium; RV: right ventricle; LV: left ventricle.*

Cinecoronariography and cardiac catheterization: Large and extremely tortuous right coronary (RC) artery without obstruction. There was retrograde filling of the left coronary artery, which was also quite tortuous, by exuberant collateral circulation from the RC. The LC artery trunk flowed at the beginning of the dilated pulmonary trunk, with the flow originating from the RC. Left ventriculography showed preserved myocardial contractility (Figure 2).

Clinical Diagnosis: Anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA), under prolonged natural evolution in asymptomatic patient until 75 years of age, but with signs of myocardial ischemia, left cavities overload and preserved myocardial function.

Clinical Reasoning: There were clinical elements of diagnostic orientation of congenital heart disease, despite the absence of clear symptoms. A clear continuous murmur located at the suprasternal notch and at the uppermost spaces of the left sternal border, with an increase in pulmonary

Keywords

Congenital Heart Disease; Bland White-Garland Syndrome; Coronary Vessel Anomalies/diagnostic imaging; Ischemia.

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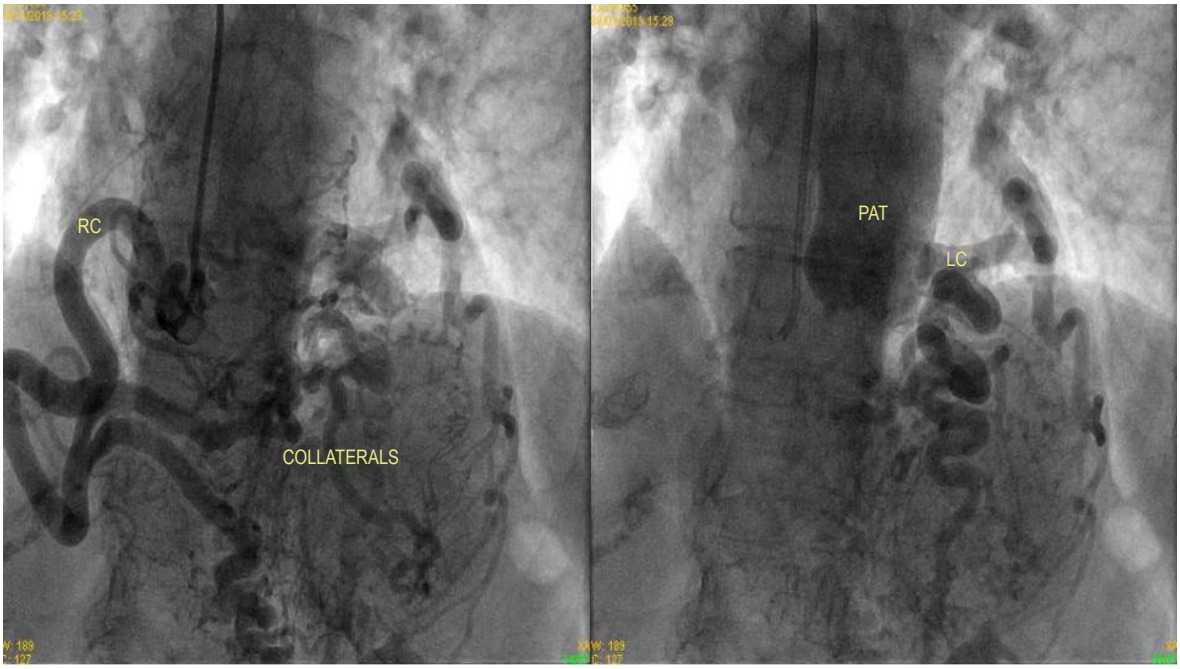

Figure 2 – *Cinecoronariography demonstrates filling of left coronary (LC) artery and pulmonary artery trunk (PAT) from the right coronary (RC) artery, a characterization of coronary artery anomalies. The arteries are dilated and extremely tortuous, with several collateral pathways and no obstruction.*

vascular network leading to an increase in left atrium, in combination with ischemic events, as detected by the ECG, would orient towards the diagnosis of anomalous origin of the LCA from the PA trunk. This elaborated clinical diagnosis could not be made earlier due to the lack of symptoms, but also to the lack of a duly performed and evaluated symptomatic/clinical examination, with adequate accuracy. The diagnosis in this case was established by the cardiac catheterization.

Differential diagnosis: Other heart diseases that combine with continuous murmur refer to persistent arterial channel, aortopulmonary window and arteriovenous fistulas in general. However, the signs of myocardial ischemia described and evident at the ECG, in combination with altered stress testing, do not occur in the other anomalies just mentioned, unless there is a blockage of the coronary arteries caused by atherosclerosis.

Approach: In face of the impact of hyperflow on the pulmonary circulation, and also on left heart cavities, in addition to myocardial ischemia, we considered the possibility of removing the junction point of the left coronary artery and the pulmonary trunk by means of a simple terminal ligature of the coronary artery. With this in view, we would mainly preserve the ventricular function, as well as eliminate left ventricular volume overload. As a consequence, we would prevent long-term adverse events. Nevertheless, since the patient presents asymptomatic and – according to herself – her clinical picture has changed very little since her diagnosis, around 13 years ago, we decided to adopt an expectant strategy. Refusal to surgery has also occurred in similar cases reported in the literature.[1-3]

Comments: This patient's natural evolution until advanced age, with no symptoms and a few adverse manifestations, is undoubtedly a very rare phenomenon. This favorable evolution, under good clinical and hemodynamic conditions, was primarily due to the exuberant collateral circulation from the RC, which managed to ensure adequate coronary circulation as a whole. The anterolateral ischemia revealed by the ECG was not combined with other elements that could be harmful to the patient. From now on, there may be the new onset of arrhythmias, myocardial dysfunction and even thrombosis and embolism events. These acquired traits, which have an effect on the evolution, should have manifested earlier. About 90% of these patients die within the first years of life, if they are not surgically treated, and very few reach higher age.[1-3] It is important to highlight that these patients can benefit from surgical treatment even in adulthood, leading to the decrease of volume overload and of ischemic events, as in a study reported elsewhere with a sample of 50 patients, with an average age of 31.6 ± 15.6 years.[4]

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Case 3/2020 – Pulmonary Atresia, Interventricular Communication and Anomalous Origin of the Right Pulmonary Artery from the Ascending Aorta developing after Prior Left Central Shunt, in a Symptomatic 40-year-old Adult.

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Clinical Data: The patient had no symptoms from birth to young adulthood, when he developed more progressive mild hypoxia, which required an anastomosis with 8 mm PTFE graft between the brachiocephalic trunk and the pulmonary trunk, at the age of 32. Since then, the patient remains stable with oxygen saturation levels above 80%, fatigue on moderate exertion and precordial palpitations. He used warfarin and enalapril.

Physical examination: Good overall health status, eupneic, mild cyanosis in the extremities, moderate digital clubbing, normal pulses in the 4 limbs. Weight: 67 Kg; height: 170 cm; right upper limb blood pressure: 140x90 mmHg; HR: 105 bpm; O2 Saturation = 83%, Hg= 22.1 g/l; Hct= 66%.

Precordium: Left chest bulge, apex beat palpable outside the left hemiclavicular line, with clear systolic impulses at the left sternal border (LSB). Hyperphonetic heart sounds, protosystolic click, constant split 2nd heart sound, discrete and mild systolic murmur along the LSB and moderate continuous murmur in the mitral region. The liver was not palpable, and the lungs were clear.

Complementary examinations

Electrocardiogram: Sinus rhythm, signs of right cavity overload, with apiculate P wave + 70º, QRS complex showing predominance of S waves from V4 to V6 and axis deviated to the right (AQRS= +110°). The T wave was negative in the precordial leads with diffuse ventricular repolarization changes in all other leads (Figure 1).

Chest X-ray: Marked enlargement of the cardiac area on account of the elongated left ventricular arch, and bulging middle arch (CTI=0.53). The increased pulmonary vascular network in the right hila tapers off towards the lower lobes, in pulmonary artery hypertension expression, and is clearly reduced on the left side with thin blood vessels coursing through several lobes (Figure 1).

Keywords

Heart Defects, Congenital; Pulmonary Atresia, Heart Septal Defects, Ventricular; Pulmonary Artery; Aorta/abnormalities; Hypertension, Pulmonary; Hypoxia; Diagnostic, Imaging, origin of right pulmonary artery from ascending aorta.

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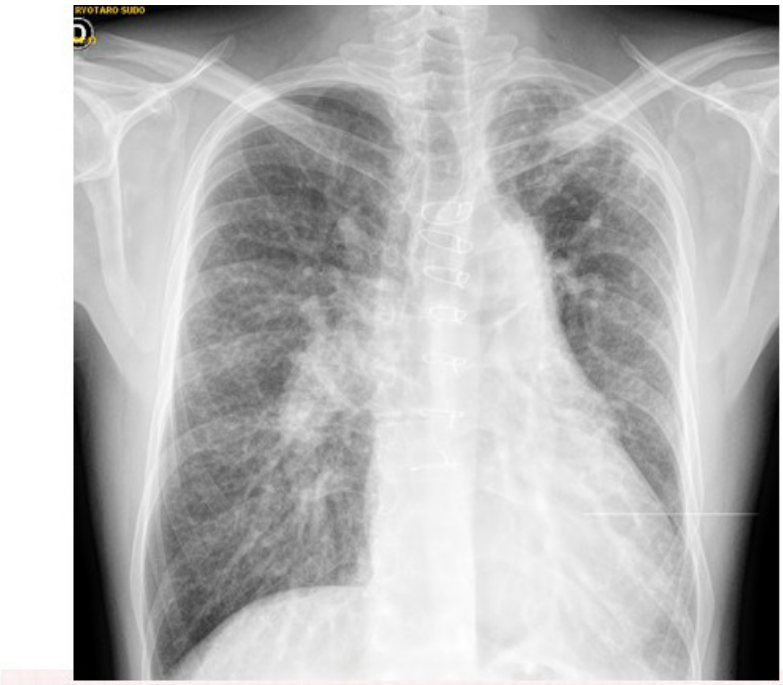
Echocardiogram: Normal atrioventricular connection, pulmonary atresia, wide perimembranous interventricular communication (27 mm) and single outflow tract with aorta (50 mm), overriding the interventricular septum for more than 50%. The right atrium is very dilated (RAV=67.2 ml/m^2), as well as the left atrium (62.1 ml/m^2). The right ventricle (39 mm) is dilated and hypertrophic, with moderate dysfunction and apical hypokinesia. The left ventricle (60 mm) shows dysfunction with ejection fraction of 47%, but without hypertrophy (septum=posterior wall= 10 mm). Right-sided aortic arch with left-sided abdominal aorta. Shunt anastomosis between the brachiocephalic trunk and the pulmonary trunk is visualized. The right pulmonary artery originates from the ascending aorta, and the left one is hypoplastic.

Cardiac catheterization: It revealed the anatomy of a double outlet of the great arteries from the right ventricle with minimal antegrade pulmonary blood flow (considered as pulmonary atresia), hypoplastic left pulmonary artery in continuity, associated with hypoplasia of the pulmonary trunk, dilated right pulmonary artery and systemic hypertension originating from the ascending aorta (Figure 2).

Clinical diagnosis: Pulmonary atresia, interventricular communication, anomalous origin of the right pulmonary artery from the ascending aorta, right-sided pulmonary artery hypertension and anastomosis between the brachiocephalic trunk and the pulmonary trunk, with left pulmonary hypoplasia, biventricular dysfunction and signs of chronic progressive hypoxia in later adulthood.

Clinical reasoning: There were clinical elements leading to a diagnosis of cyanogenic congenital heart disease with decreased pulmonary flow, with arterial malposition considering the hyperphonetic heart sounds and pulmonary atresia in association with interventricular communication. The right ventricular overload on the electrocardiogram demonstrates the predominance of this ventricle, given the marked pulmonary obstruction. The diagnosis of anomalous origin of the right pulmonary artery from the ascending aorta, leading to ipsilateral pulmonary artery hypertension, could be considered by means of the appreciation and adequate analysis of the markedly dilated pulmonary vascular network. The discrete degree of hypoxia with oxygen saturation of approximately 80% is associated with this increased pulmonary vascular network on the chest X-ray, despite the pulmonary vascular disease. Still, even in adults, it provides a considerable increase in red blood cells and their levels in relation to that of serum. The diagnosis of the anomaly was well established by the echocardiography and mainly by the angiography.



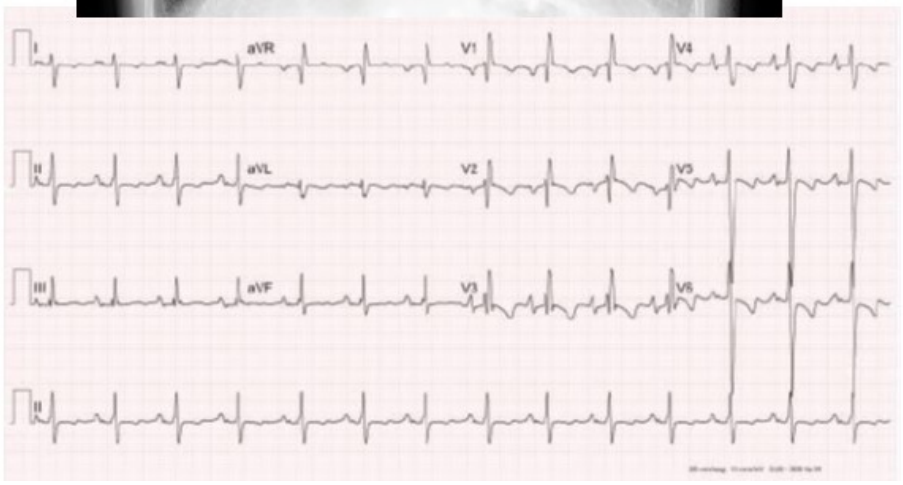


Figure 1 – *Chest X-ray showing enlarged cardiac area with left ventricular dominance and increased pulmonary vascular network in the right hila, with a reduction towards the lower lobe. It is reduced to the left with thinner blood vessels. Electrocardiogram shows right cavity overload and diffuse ventricular repolarization changes.*

Differential diagnosis: Other heart diseases that accompany interventricular communication and pulmonary atresia show other features that differentiate them in the usual complementary exams, such as the double inlet left or right ventricle, in atrioventricular valve atresia, corrected transposition of the great arteries and in rarer diseases. The contrasts in the two pulmonary circulations, more marked on the right and reduced on the left, could orient towards the presence of stenosis on this side and hyperflow due to collateral circulation on the other side. However, in this condition there would be a clear continuous murmur, mainly at the right back. Thus, origin of the right pulmonary artery from the ascending aorta could be clinically considered, even before the anatomical diagnosis.

Conduct: Despite the balance of the pulmonary and systemic flows over time, with signs of hypoxemia and myocardial dysfunction, the need to increase pulmonary flow to improve quality of life with better physical tolerance is presumed. In face of the anatomical complexity, right-sided pulmonary artery hypertension and biventricular dysfunction, the consideration of the expectant conduct was not ruled out, despite the development risks involved.

Comments: The natural evolution of this patient until the adult age highlights unfavorable elements, related to right-sided pulmonary vascular disease, given the anomalous origin of the right pulmonary artery from the ascending aorta, with clear transmission of systemic blood pressure. Furthermore,

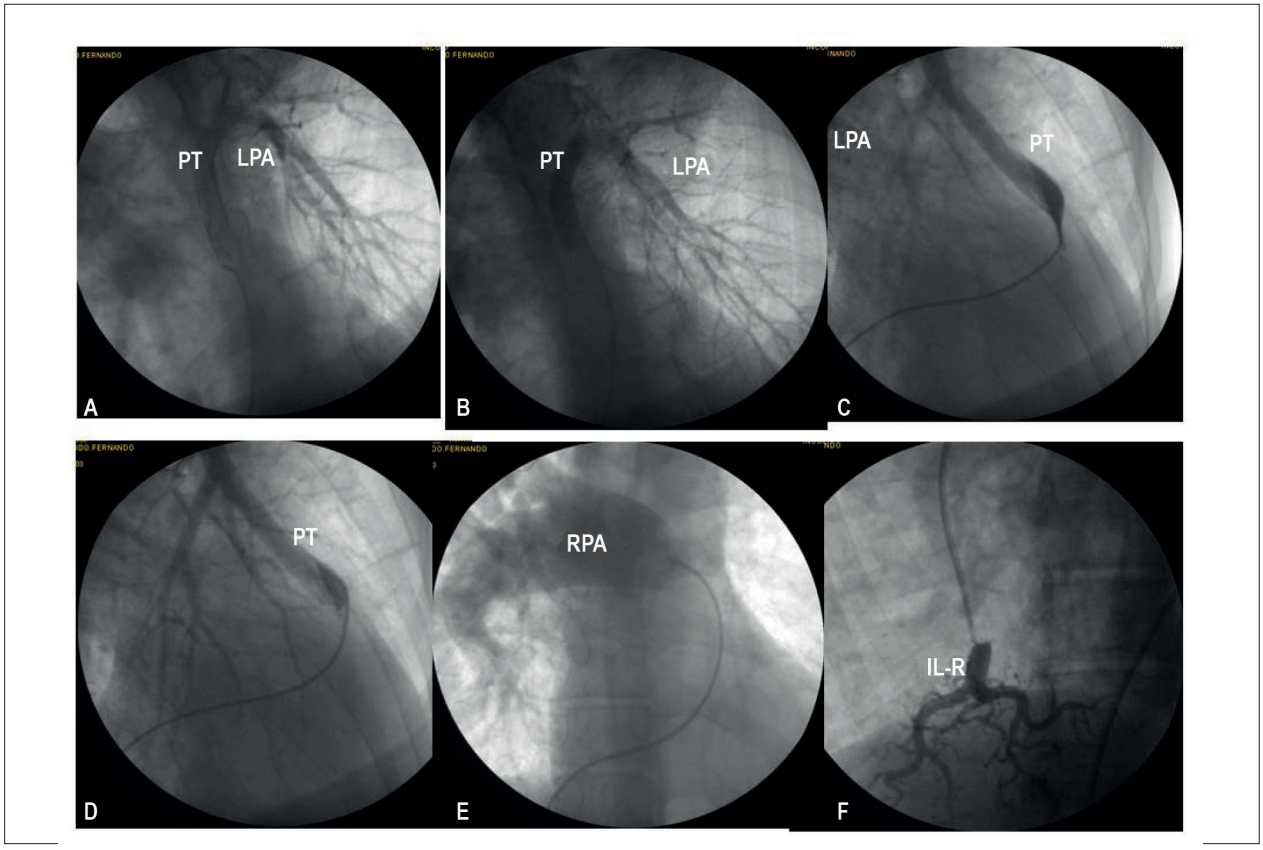


Figure 2 – *Angiotomography showing hypoplasia of the left pulmonary artery, with hypoplastic pulmonary artery continuity emerging from the right ventricle with minimum annular opening (A-D), and origin from dilated and hypertensive right pulmonary artery directly from the ascending aorta (E,F), Thinner inferior right lobe artery (F). RPA: right pulmonary artery; LPA: left pulmonary artery; IL-R: inferior right lobe.*

chronic hypoxia induced biventricular dysfunction, in addition to other injuries responsible for the greatest ventricular hypertrophy, such as pulmonary atresia and even aortic dextroposition. There was clinical improvement after the performance of systemic-pulmonary anastomosis, which was a useful strategy for hypoxia mitigation. However, in face of the other parameters, a quicker deterioration is expected, with the emergence of thrombosis, embolism, arrhythmias, heart failure complications and even sudden events. On the other hand, the expectant conduct considered was the most plausible in view of the high and considerable surgical risk in this age group, in addition to right-sided pulmonary arterial hypertension, and no adequate functional solution.[1]

The question is, in similar cases in childhood, whether it would be more convenient to attempt an earlier correction. Undoubtedly, it should always be considered at different conditions to create an anatomic shape that is adequate and favorable to blood dynamics.[2]

The combination of these defects is extremely rare since in the literature three similar cases are described, all of them involving the anomalous origin of the left pulmonary artery from the ascending aorta.[1-3]

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Case 1/2020 - A 56 Year-Old Woman Developed Heart Failure after a Presumed Diagnosis of Acute Myocardial Infarction and Mitral Valve Regurgitation with Rupture of Chordae Tendineae

Desiderio Favarato e *Luiz Alberto Benvenuti*

Instituto do Coração (InCor), HC-FMUSP, São Paulo, SP – Brazil

A 55-year-old female patient, from the municipality of Carapicuiba, state of São Paulo, had arterial hypertension and started having dyspnea on major exertion a year and a half before hospitalization. In September 2016, she started having severe chest pain that felt like tightness, which was relieved a little with rest, associated with nausea. She sought medical care in her city, was medicated and discharged to go home. In the next morning, she had a recurrence of pain and was hospitalized. During hospitalization, she had a cardiac arrest, which was reversed with electric shocks. The patient remained hospitalized for 10 days and was discharged with a diagnosis of acute myocardial infarction and mitral valve disease.

After hospital discharge, she developed functional class IV (New York Heart Association) dyspnea, sporadic episodes of paroxysmal nocturnal dyspnea and orthopnea, being referred to InCor-HCFMUSP. She was using ASA 100 mg / day; Furosemide 40mg 3xday; Captopril 50mg 3xday; Clopidogrel 75mg once a day; Simvastatin 40mg 1xd.

The physical examination disclosed a heart rate of 102 bpm, blood pressure of 118x86 mmHg, pulmonary auscultation disclosed crackling rales in lung bases, cardiac auscultation showed rhythmic heart sounds with +++ / 6+ mitral systolic murmur; abdominal examination was normal and there was no lower -limb edema.

The echocardiogram (09/28/16) showed aortic diameter measuring 28 mm, left atrium 47 mm, diastolic left ventricle 48 mm and systolic 26 mm, left ventricular ejection fraction of 77%, septal thickness 11 mm and posterior wall thickness, 9 mm. The mitral valve showed partially ruptured chordae tendineae, posterior cusp eversion into the left atrium, with coaptation failure between the cusps and marked eccentric reflux. The tricuspid valve also showed marked reflux. The pulmonary artery systolic pressure was estimated at 62 mm Hg.

Laboratory tests (Nov. 08, 2016) showed 4300000 red blood cells / mm^3, hemoglobin 12.3 g / dL, hematocrit 38%, 8110 leukocytes / mm^3, creatinine of 1.75mg / dL, sodium 140 mEq / L, and potassium 3.8 mEq / L.

The electrocardiogram (11/08/16) showed left atrial overload and final intraventricular conduction delay of the stimulus (Figure 1). Marked cardiomegaly and signs of pulmonary congestion were observed on the chest X-ray (Figure 2). Echocardiogram and cardiac catheterization with coronary angiography were requested.

The coronary angiography (02/08/17) showed a 40% left coronary artery trunk lesion, two lesions in the anterior interventricular branch, 50% in the ostium and 90% in mid-third; a 60% proximal lesion in the circumflex branch and 60% lesion in the mid-third of the right coronary artery. (Figure 3)

A surgical procedure to correct valve regurgitation and coronary artery bypass grafting (CABG) surgery were indicated.

Preoperative tests showed: red blood cells 4300000 / mm^3, hemoglobin 12.4 g / dL, hematocrit 37%, leukocytes 13990 / mm^3 (2% band cells, 80% segmented, 0% eosinophils, 8% lymphocytes and 10% monocytes), platelets 173000 / mm^3; total cholesterol 158 mg / dL, HDL-C 28 mg / dL, LDL-C 109 mg / dL, triglycerides 103 mg / dL, creatine-phosphokinase (CPK) 2938 U / L, glucose 120 mg / dL, urea 310 mg / dL, creatinine 4.79 mg / dL, sodium 136 mEq, potassium 4.9 mEq / L, Alanine aminotransferase (ALT) 988 U / L, aspartate aminotransferase (AST) 681 U / L; uric acid 27.1 md / dL, glycated hemoglobin 5.4%, Urinalysis with proteinuria of 0.38 g / L and sediment with 14000 epithelial cells / mL, 63000 leukocytes / mL and 4290 hyaline casts / mL. TSH was 6.25 μIU / mL, free T4 was 0.98 mg / dL. Thrombin time (INR) was 1.4; activated partial thromboplastin time (APTT) ratio was 0.96. Serology for hepatitis B and C and for HIV were negative.

Considering these laboratory alterations, the patient was called to the emergency department of InCor (Feb. 23, 2017).

The patient reported that after undergoing cardiac catheterization on February 8, 2017, she received a prescription for atorvastatin and since then she had been progressing with diffuse myalgia and functional class worsening with dyspnea at rest and orthopnea up to 3 days before hospitalization, associated with reduced urinary output and darkened urine. She also reported chest pain in the infra-mammary region, with irradiation to the epigastric region, with worsening at usual efforts, poorly characterized, lasting for hours without improvement factors. She denied fever and cough. She said she had been constipated for 3 days.

Keywords

Heart Failure/physiopathology; Mitral Valve Prolapse/surgery; Myocardial Infarction; Sepsis; Postoperative Care; Shock, Cardiogenic; Renal Insufficiency.

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Anatomopathological Correlation

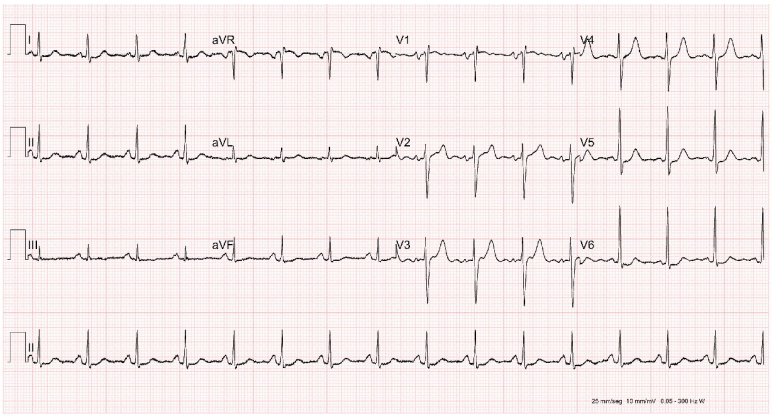

Figure 1 - *ECG (Nov. 08, 2016) showing sinus rhythm, bi-atrial overload and final intraventricular conduction delay.*

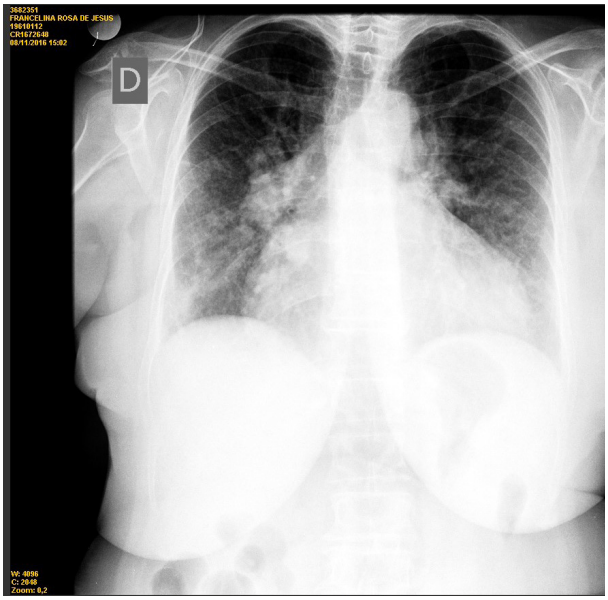

Figure 2 - *Chest radiography (Nov. 08, 2016) showing pulmonary congestion and marked cardiomegaly.*

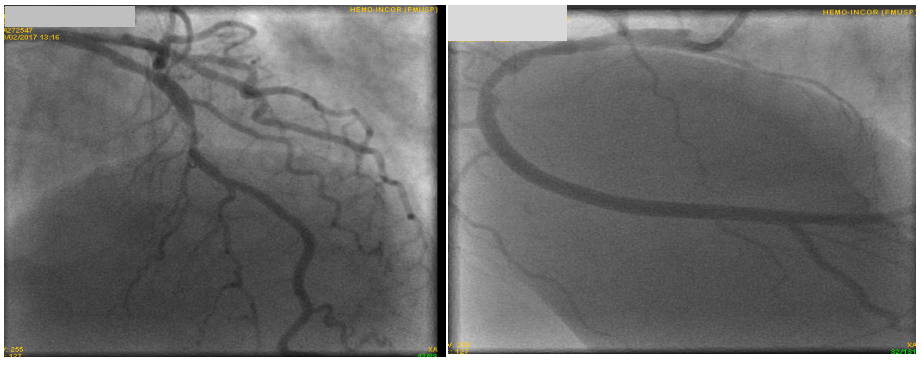

Figure 3 - *Coronary angiography. Left panel - left coronary artery in RAO view - 80% anterior interventricular injury and 50% proximal circumflex artery; Right panel - right coronary artery - 50% focal lesion.*

On physical examination, the patient was in regular general condition, 2+/4+ skin pallor, hydrated, +/4+ icteric skin, acyanotic and afebrile. Heart rate was 65 bpm, blood pressure was 70x50 mm Hg, oxygen saturation was 90%, with fine crackles in lung bases; auscultation disclosed rhythmic heart sounds, and 3+ / 6+ regurgitation holosystolic murmur in mitral focus; the abdomen was flat and intestinal sounds noises were present, with a palpable liver at 2 cm from the right costal margin; there was no edema or signs of deep vein thrombosis in the lower limbs.

The diagnoses of cardiogenic shock and rhabdomyolysis, acute renal failure, ischemic hepatitis and possible infective endocarditis were made. Norepinephrine, intravenous furosemide 40 mg every 8 hours, and ceftriaxone and oxacillin antibiotics were prescribed.

Laboratory tests (23 Feb 2017) showed hemoglobin 12 g/dL, hematocrit 35%, leukocytes 14230/mm^3 (82% neutrophils, 8% lymphocytes and 10% monocytes), 147000 platelets/m^3, CK-MB mass 54.5ng/dL, troponin I 0.349 ng/mL; urea 313 mg / dL, creatinine 4.94 mg/dL, AST 938 U / L, ALT 746 U/L, gamma glutamyl transferase (Gamma-GT) 473 U/L, alkaline phosphatase (AP) 279 U/L, total serum proteins 7 g/dL, total bilirubins 1.67 mg/dL, direct bilirubin 1.15 gm/dL, lipase 799 U /L, C-reactive protein (CRP) 98.69 mg/L. Prothrombin time (INR) was 1.4 and the activated partial thromboplastin time (APTT) ratio was 0.96. Urinary analysis showed free hemoglobin ++, leukocytes 32000/mL, erythrocytes 13000/mL, without casts. Gasometry showed a pH of 7.40, pCO_2 of 18.7 mm Hg, pO_2 of 99.9 mmHg, O_2 saturation of 99.9% and bicarbonate level of 11.2 mmol/L. The lactate level was 49 mg / dL.

Blood culture was positive for *Staphylococcus hominis*, sensitive to oxacillin and the urine culture was positive for multisensitive *E.coli*. The antibiotics were then switched to vancomycin, piperacillin and tazobactam on March 3, 2017. In addition to vasoactive drugs, hemodialysis was performed.

The transthoracic echocardiogram did not disclose vegetations, the left ventricular ejection fraction was estimated at 65%, with no change in segmental motility. The mitral valve showed posterior leaflet prolapse, with signs of associated rupture of chordae tendineae. The Doppler study and color flow mapping showed eccentric regurgitation jet of marked degree.

Laboratory tests (March 02, 2017) showed: hemoglobin 9.2 g/dL, hematocrit 28%, leukocytes 12220 / mm^3 (1% band cells, 88% segmented, 5% lymphocytes and 6% monocytes), platelets 123000 / mm^3, urea 54 mg/dL, creatinine 1.68 mg / dL, sodium 139 mEq / L, potassium 3.0 mEq / L, AST 44 U/L, ALT 160 U/L.

The patient underwent surgery (March 03, 2017) with mitral valve repair and reconstruction and commissurotomy without annuloplasty (quadrangular resection), atrial septal defect closure and left internal mammary artery bypass grafting to the anterior interventricular artery and saphenous vein grafting to the right posterior descending artery, in addition to atrial septal defect closure.

The echocardiogram in the immediate postoperative period (March 03, 2017) disclosed mild mitral regurgitation.

Chest x-ray (March 03, 2017) at the bedside in the immediate postoperative period showed cardiac monitoring electrodes, central venous catheter, pleural drain in the left hemithorax, sternal metal suture, clear lung fields and normal cardiac area.

Biopsy of the mitral valve posterior leaflet showed fibrosis and marked mucoid degeneration of the cusp stroma (B17-0412)

She had a seizure on March 4, 2017 and started treatment with lamotrigine. The cranial tomography showed no alterations.

The echocardiogram (03/20/17) disclosed mitral valve with reduced cusp coaptation, posterior cusp with mild calcification and reduced mobility, and mild regurgitation. There were no images of thrombi in the atria and their appendages or images suggestive of vegetation.

She was discharged on March 29, 2017 and three days later she came to the emergency department complaining of feeding problems, with vomiting episodes, despite the use of ondansetron and diarrhea. She also complained of hoarseness and tinnitus in both ears. She denied dizziness, vertigo, and fever, but reported dyspnea at rest for 1 day.

She was using Amiodarone 200mg 1x /day, AAS 100mg / day, Lamotrigine 25mg / day, Furosemide 40mg 1x / day, Ondansetron 8mg 3x / day, Omeprazole 20mg 1x / day, and Dipyrone 500mg 4x / day.

On physical examination, she showed 3+/ 4+ skin pallor. Blood pressure was 94x68 mmHg and heart rate was 64 bpm; pulmonary auscultation was normal, and the cardiac auscultation disclosed a 2 + / 6 + mitral systolic murmur; abdomen and lower limbs showed no alterations.

Chest x-ray (Apr. 01, 2017) showed para-hilar and right cardiac border condensation foci and blunting basal pleural effusions of the and global +++ cardiomegaly, with unfolding of the left middle arch and dislocated left main bronchus (Figure 4).

The ECG (Apr. 02, 2017) disclosed sinus rhythm, left atrial overload, right bundle branch block and changes in ventricular repolarization (Figure 5).

Laboratory tests disclosed hemoglobin of 12.3 g / dL, hematocrit 37%, leukocytes 4980 / mm^3, platelets 213000 / mm^3, C-reactive protein 23.87mg / L, creatinine 1.56 mg / dL, urea 107 mg / dL, sodium 134 meq / L and potassium 3.4 mEq / L.

The echocardiogram (Apr. 04, 2017) disclosed a left ventricle with preserved systolic dimensions and function, without segmental alterations. The mitral valve showed marked regurgitation with reduced posterior cusp mobility, albeit without stenosis. Filamentary structure was observed at the base of the posterior cusp. The tricuspid valve showed marked regurgitation, with alterations of the valve cusps. Pulmonary systolic blood pressure was estimated at 75 mm Hg.

Chest tomography showed a condensation focus in the anterior segment of the right upper lobe and areas of atelectasis and pleural effusion in both lung bases.

The transesophageal echocardiogram (Apr. 07, 2017) was similar to the transthoracic echocardiogram performed on April 04, 2017.

Anatomopathological Correlation

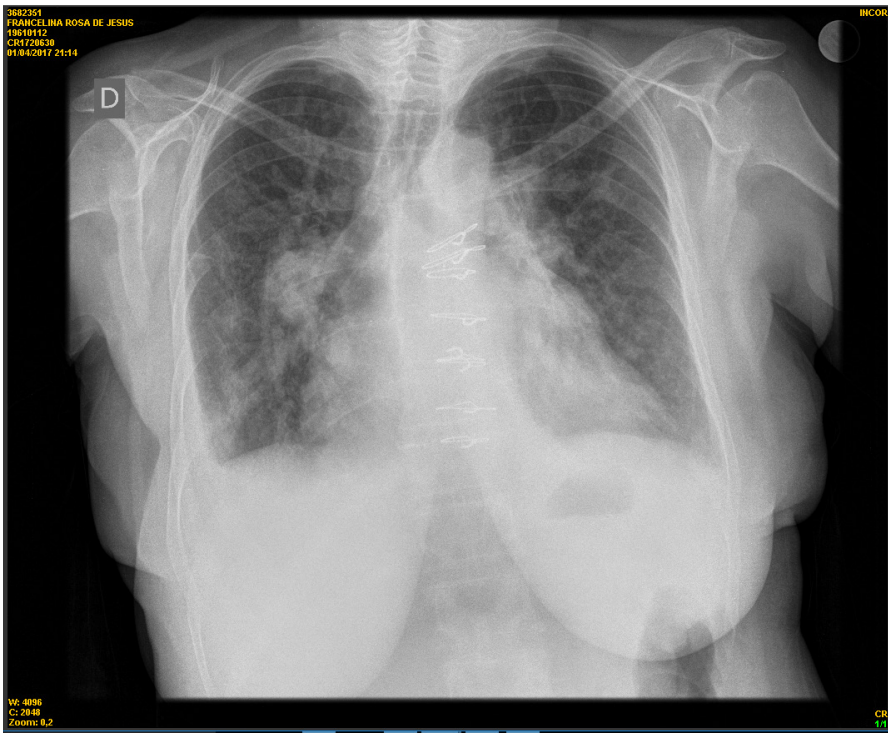

Figure 4 - *Chest radiography - right perihilar condensation and right cardiac border, signs of pulmonary congestion and cardiomegaly.*

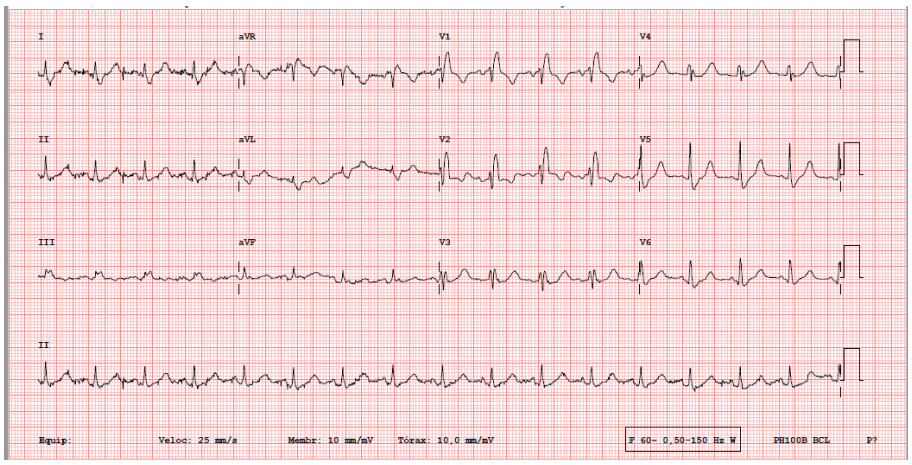

Figure 5 - *ECG showing left atrial overload, right bundle branch block.*

The patient received antibiotic therapy with vancomycin and meropenem and as there was clinical improvement, she was discharged on April 19, 2017.

On May 21, 2017, she returned to the InCor Emergency Department due to worsening dyspnea, now with orthopnea and lower-limb edema. Moreover, she had had anuria for one day. She also complained of daily vomiting and diarrhea since the second hospital discharge. Five days before this hospitalization, she had been treated at an outpatient clinic and, due to suspected pseudomembranous colitis, she received a prescription for ciprofloxacin and metronidazole.

Physical examination disclosed a respiratory rate of 22 breaths per minute, heart rate of 134 bpm, blood pressure was 105x80 mm Hg, oxygen saturation 98% under 2L / min of O_2. Pulmonary auscultation showed crackling rales up to the middle third; the heart rate rhythm was regular, without murmurs; the abdomen showed a slight distension, with

hydro-air noises were present; bilateral +++ / 4+ lower-limb edema, with no signs of deep venous thrombosis.

Chest radiography (May 21, 2017) showed clear lung fields and cardiomegaly (Figure 6).

Laboratory tests showed hemoglobin 8.2 g/dL, hematocrit 25%; leukocytes 22750 / mm^3 (94% neutrophils, 3% lymphocytes, 3% monocytes), platelets 217000 / mm^3; urea 147 mg / dL, creatinine 3.21 mg / dL, C-Reactive Protein 49.19 mg / L; sodium 133 mEq / L and potassium 3.7 mEq / L; lactate 34 mg / dL.

She had a seizure episode and received phenytoin. There was asystole which did not respond to resuscitation maneuvers and she died at 10:55 pm on May 21, 2017.

Clinical aspects

A 55-year-old patient with arterial hypertension and heart failure for one year and with chest pain, had a cardiorespiratory arrest five months before, developed heart failure and mitral regurgitation due to mitral valve prolapse and rupture of chordae tendineae.

The diagnostic impression is that heart failure due to mitral valve disease preceded the episode of precordial pain and severe dyspnea.

As for the episode of precordial pain, it is discussed whether it was really a myocardial infarction or an episode of rupture of chordae tendineae with a sudden worsening of mitral regurgitation and acute pulmonary edema.

The most recent classification of myocardial infarction (the fourth universal definition) introduced a new concept – "myocardial injury" (myocardial injury without infarction) in which there is an elevation of the lesion marker (troponin level), however without constituting an infarction due to the concomitant absence of suggestive clinical picture and electrocardiographic and wall motility alterations. This situation can be found in a large number of clinical conditions – anemia, ventricular tachycardia, heart failure, kidney disease, hypotension and shock, hypoxemia.

The new definition included two types of myocardial injury: the acute one with troponin curve, elevation and fall, and the chronic one, with sustained elevation of troponin.[1]

In the same publication it can be noted that there is a continuum between the "isolated myocardial injury" and type 2 infarction, as the conditions that originate them are the same, depending only on the intensity and occurrence of electrocardiographic and echocardiographic alterations and a clinical picture compatible with the diagnosis of infarction.

In this sense, there is a case report of a patient who sought the Emergency Services for abdominal discomfort and severe dyspnea. The condition was preceded by chest pain 24 hours before the event. The patient already had a previous diagnosis of mitral valve prolapse. There was an increase in troponin levels and nonspecific alterations in ventricular repolarization. The echocardiogram showed severe mitral regurgitation, rupture of chordae tendineae and severe prolapse of half of the posterior cusp. Unlike the

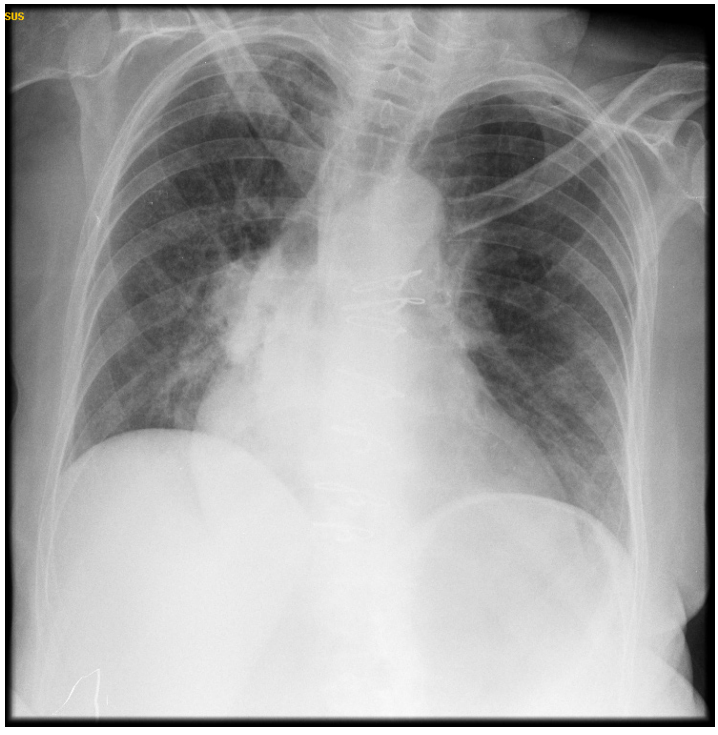

Figure 6 - *Chest radiography (May 21, 2017) showing clear lungs and cardiomegaly.*

current case, there were no coronary angiography alterations. Diagnoses of acute pulmonary edema and severe mitral regurgitation, probably acute, were made due to rupture of the chordae tendineae.[2]

Thus, in the current case, despite the presence of critical lesions in the coronary arteries, the event described as acute myocardial infarction could have been only an increase in cardiac injury markers in the absence of infarction.

Although mitral valve prolapse is generally associated with a low risk of cardiovascular complications, some publications have doubted this assumption. Avierinos et al.,[3] in a population study in Olmsted County, Minnesota, found moderate or severe mitral regurgitation and left ventricular dysfunction as primary risk factors for cardiovascular mortality, with the first being greater than the latter. Mild mitral regurgitation, left atrial enlargement, a prolapsed cusp, atrial fibrillation and age older than 50 years were considered secondary risk factors. In this study, cardiovascular morbidity was 30%, overall mortality was 19% and cardiovascular mortality 9% in 10 years of follow-up.[3] In the Framingham study, 25% of patients with mitral valve prolapse developed significant mitral regurgitation or required surgery in a period of 3 to 16 years.[4]

The rupture of the valvar chordae tendineae is the most common cause of acute mitral regurgitation and its most frequent causes are infective endocarditis, myxomatous degeneration and mitral valve prolapse; however, they can occur in rheumatic valve disease, chest trauma and atherosclerotic heart disease.[3,5,6]

In the current case, tissue changes in the prolapse itself may be the cause of the rupture; however, one should always rule out infectious endocarditis in this type of complication.

The diagnosis of infective endocarditis is based on clinical, laboratory and echocardiographic aspects. Duke's criteria are the recommended ones. The diagnosis is made in the presence of 2 major criteria or 1 major and 3 minor, or even 5 minor criteria.

The following are considered major criteria: positive blood culture for endocarditis (two cultures within a 12-hour interval or 3 cultures from two samples collected within a 1-hour interval between them for microorganisms commonly related to endocarditis - *Streptococcus viridans*, *S. bovis*, *Staphylococcus aureus*, or HACEK group, or *Coxiella burnetiid* culture. In addition to the blood culture, evidence of endocardial involvement on echocardiogram (preferably transesophageal) is considered as major criteria: oscillating intracardiac mass in the valve or its supporting structures; valve annular abscess, new or intensified regurgitation.

Among the minor criteria are: predisposition – previous valvar heart disease, use of injectable drugs or venous catheters; elevation of inflammation markers; splenomegaly, hematuria; purpura; fever > 38ºC; vascular phenomena (arterial embolism, septic pulmonary infarction, mycotic aneurysm, intracranial or conjunctival hemorrhage and Janeway lesions); immunological phenomena (glomerulonephritis, Osler nodes, Roth's spots and elevation of the Rheumatoid Factor); positive blood culture of microorganisms not usually associated with endocarditis.[7]

In the current case, no vegetations were detected on the echocardiogram, there was no fever and a staphylococcus strain was identified in the blood culture that is not usually associated with endocarditis. Moreover, there was no evidence of endocarditis in the histopathological analysis of the valve fragments removed during surgery. Thus, the diagnosis of infectious endocarditis can be ruled out.

This patient had rhabdomyolysis with the use of statins or due to severe ischemia, because in addition to the increase in creatine kinase (CK) levels, she also had an increase in liver enzymes suggestive of ischemic hepatitis.

The rhabdomyolysis presentation was the classic one, with the presence of muscle pain, weakness, darkened urine and marked increase in creatine kinase (CK) levels. Also, its most common complication, acute renal failure, was present.

Simvastatin and atorvastatin are metabolized by CYP3A4 (the most common cytochrome P450 isoenzyme), while rosuvastatin is metabolized by CYP2A9. Thus, the former are more susceptible to drug interactions that increase plasma concentrations and the probability of toxicity. Muscle symptoms are complaints that range from 1% to 10% of patients using statins; however, there is an increase in CK levels in less than 1%.[8]

Ischemic hepatitis is characterized by cardiopulmonary or circulatory failure associated or not with arterial hypotension, massive and reversible elevation of liver aminotransferase enzymes (AST and ALT) and exclusion of other causes of severe liver damage, such as acetaminophen poisoning, viral hepatitis or another type of toxic hepatitis. In the current case, liver damage caused by statins cannot be ruled out and there was no increase in prothrombin times with iNR > 1.5 and the APTT time ratio was normal, alterations present in ischemic hepatitis.[9]

The final stage of the disease of this patient was due to septicemia, which could be due to infection by toxin-producing *Clostridium difficile*. Only toxin-B producing *C. difficile* (TBcd) strains cause infection; however, some strains also produce toxin A (TAcd). They act by inactivating the Rho GTPases pathway through the glycosylation of the threonine residue, which leads to actin depolymerization and cell death and stimulates the inflammation cascade responsible for major tissue damage, diarrhea and pseudomembranous colitis.

The use of antibiotics can lead to an imbalance of the intestinal microbiome with a decrease in Bacteroides and Firmicutes, allowing the proliferation of *Clostridium difficile*. Remember that the patient received broad spectrum antibiotics for a prolonged period.[10] **(Dr. Desiderio Favarato)**.

Diagnostic hypothesis: mitral regurgitation due to ruptured chordae tendineae in mitral valve prolapse, septicemia and multiple organ failure. **(Dr. Desiderio Favarato)**.

Necropsy

On external examination of the corpse, partial dehiscence of the saphenectomy suture was noted, with little secretion from the surgical wound; the histological examination disclosed an extensive acute purulent inflammatory process in the dermis and hypodermis, with

areas of necrosis and the presence of microstructures compatible with degenerated bacteria (Figure 7). The heart weighed 396 g, with dilation in both atria, particularly the left one. Presence of a pericardium patch measuring 15 mm in diameter, adequately occluding the atrial septal defect in the oval fossa (Figure 8). The mitral valve showed posterior cusp repair, with the presence of recent extensive surgical sutures with a reinforcement area; however, there was a clear retraction of part of the cusp, with a consequent absence of adequate coaptation (Figure 8). The anterior cusp showed slight thickening and bulging, with thin and delicate chordae tendineae. There were no vegetations. The other cardiac valves showed no abnormalities. There was evidence of recent CABG surgery, with anastomosis of the mammary artery to the anterior interventricular artery and a saphenous vein graft to the distal segment of the right coronary artery, both patent. Cross- sections of the ventricles showed mild left myocardiosclerosis, with no areas of acute infarction. The pulmonary artery was dilated, with the presence of discrete atherosclerotic plaques in the main branches. The aorta and coronary arteries showed mild / moderate atherosclerosis, with focally calcified and ulcerated plaques in the first. Lung examination showed chronic passive congestion and extensive infarction areas at the base of the right lower lobe, with smaller ones in posterior regions of the upper and lower left lobes. The histological examination confirmed the diagnosis of pulmonary infarction, with areas of septic aspect showing intense purulent neutrophilic infiltrate, with the presence of microstructures compatible with degenerated bacteria (Figure 9).

Examination of the digestive tract showed multifocal brownish granular areas covering the mucosa of the large intestine, with histological examination compatible with acute pseudomembranous colitis (Figure 10). Other necropsy findings were diffuse liver steatosis, vascular kidney with renal scarring and areas of parenchymal atrophy, and mild lymphocytic pancreatitis with parenchymal cells showing viral inclusion with a cytomegalic pattern (Figure 11). The examination of the brain showed no abnormalities. **(Dr. Luiz Alberto Benvenuti)**

Anatomopathological diagnoses

Operated degenerative mitral valve prolapse, with residual mitral regurgitation; atherosclerosis of the aorta and coronary arteries, with CABG surgery; soft tissue bacterial infection in the saphenectomy region; acute pseudomembranous colitis; pancreatitis due to cytomegalovirus; hepatic steatosis; septicemia with multiple pulmonary infarctions (cause of death). **(Dr. Luiz Alberto Benvenuti)**

Comments

The present case refers to a 56-year-old woman submitted to mitral valve surgery and CABG surgery approximately 2 ½ months before death. The patient had congestive heart failure, mitral valve prolapse with severe regurgitation[11] and coronary obstruction detected by coronary angiography, with the largest lesion located in the posterior descending artery (90% obstruction). She underwent surgical correction of valvar heart disease (repair with quadrangular resection of the posterior cusp), on which occasion the presence of a large

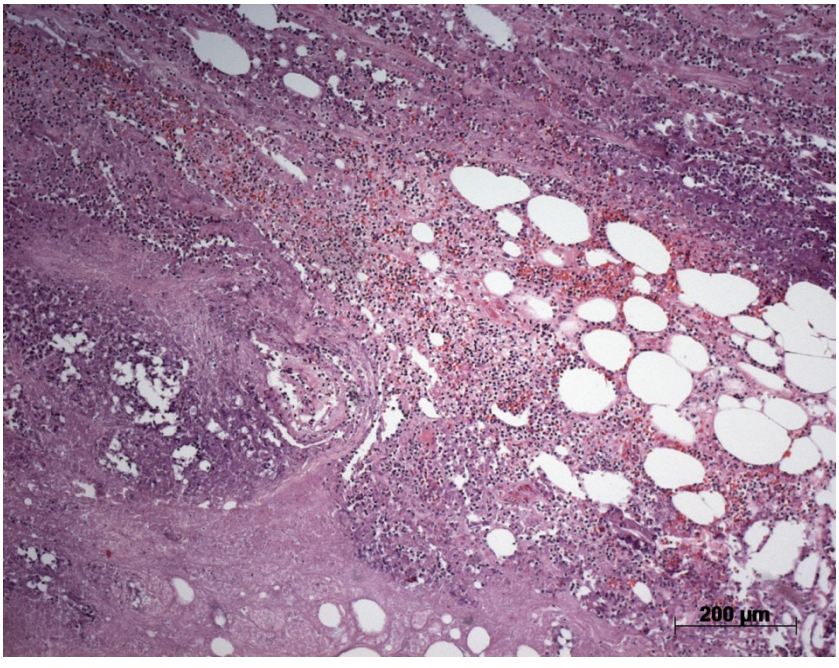

Figure 7 - *Histological section of the subcutaneous tissue in the saphenectomy suture region showing an intense purulent inflammatory process with areas of tissue necrosis. Hematoxylin-eosin staining.*

Anatomopathological Correlation

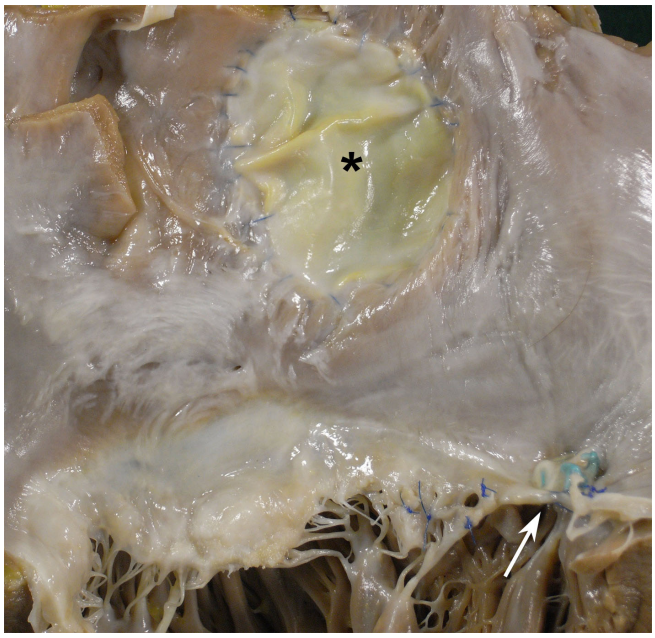

Figure 8 - *View of the left open atrium and mitral valve. Note the patch adequately closing the large atrial septal defect (asterisk), and surgical suture on the posterior cusp with an extensive retraction area (arrow) that prevents adequate cusp coaptation.*

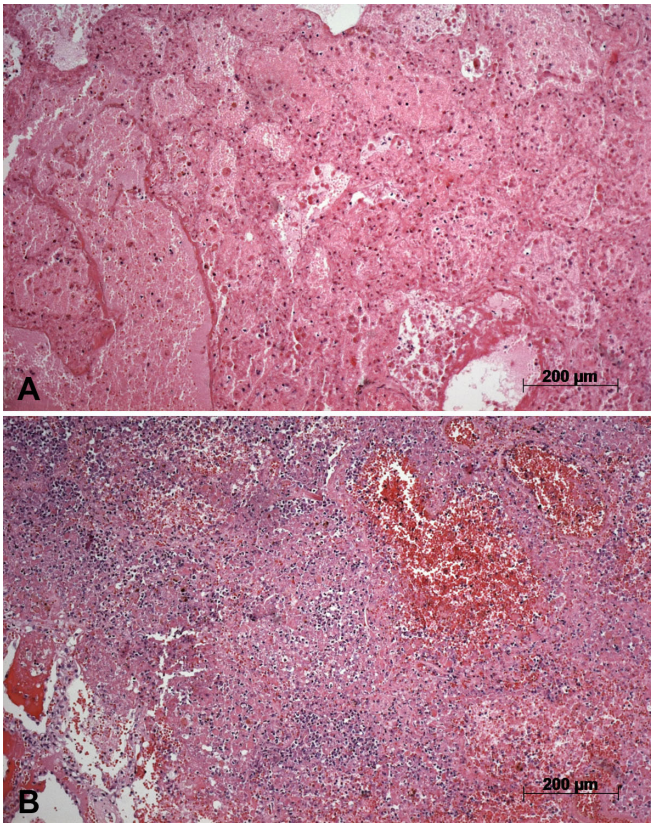

Figure 9 - *Histological sections of the lungs showing an area of pulmonary infarction (A), with obliteration of the tissue structure, leakage of fibrin and hemorrhage, and an area of septic infarction (B), with extensive purulent inflammatory infiltrate similar to that shown in Figure 7. Hematoxylin-eosin staining.*

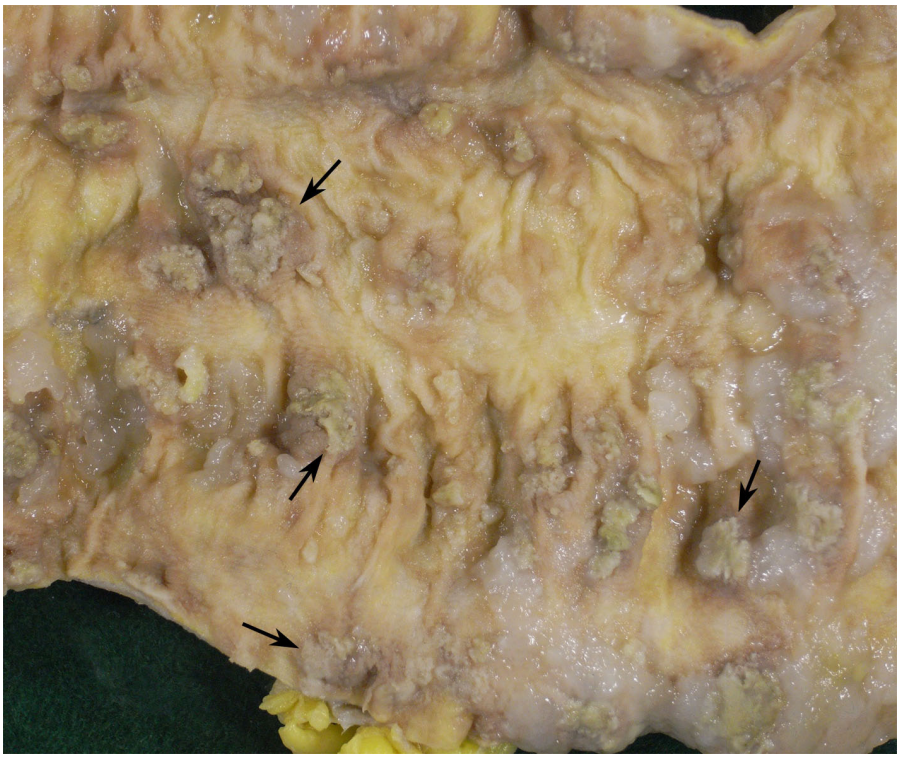

Figura 10 - *Macroscopic view of the colon with multiple brownish and granular pseudomembranes (arrows) covering the mucosa in a multifocal manner.*

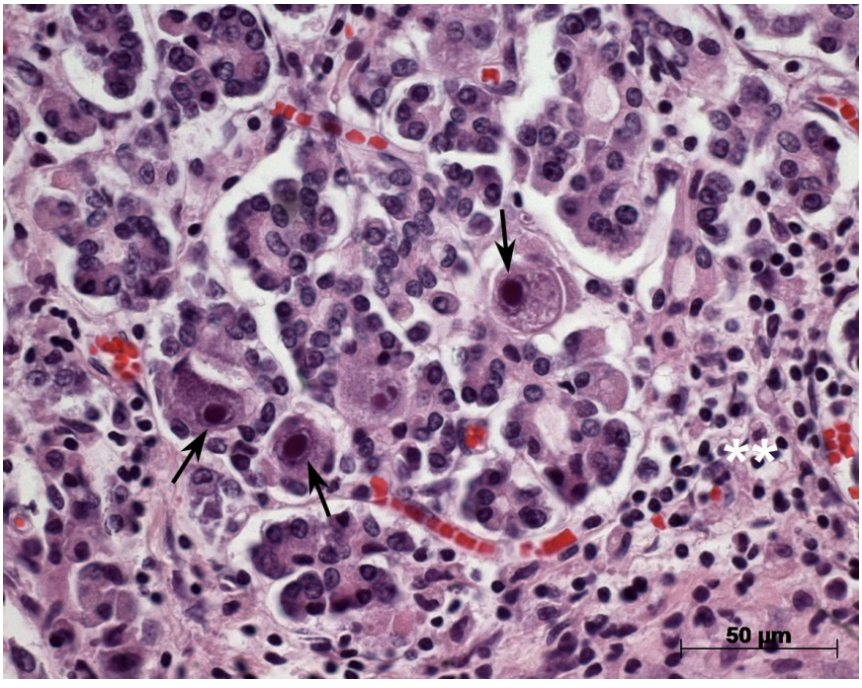

Figura 11 - *Histological section of the pancreatic parenchyma showing a mild lymphocytic inflammatory infiltrate (double asterisk) and glandular cells with clear nuclear viral inclusion with a cytomegalic pattern (arrows). Hematoxylin-eosin staining.*

atrial septal defect was observed in the oval fossa, measuring 15 mm. It is noteworthy that the association between mitral valve prolapse and atrial septal defect is not common, having been reported many years ago in a study published in this same journal.[12] After surgery, the patient developed residual mitral regurgitation, classified as moderate on imaging exams. At the autopsy, a marked retraction of the posterior cusp in the repair region was observed, which prevented the adequate coaptation of the cusps and justified the residual regurgitation. There was no infectious endocarditis, which was clinically considered and consists of one of the complications of valve prolapse.[13] The closure of the atrial septal defect and CABG did not have any complications. It should be noted that coronary artery disease was of atherosclerotic origin and did not have any major myocardial consequences, with only mild left ventricular myocardiosclerosis. The patient had soft tissue infection in the saphenectomy region and septicemia with positive blood culture for staphylococci, with progressive worsening of the clinical picture until death. At autopsy, we confirmed the acute purulent infection at the saphenectomy site, with areas of necrosis.It was not possible to safely identify the presence of bacteria, which is certainly due to prolonged antibiotic therapy, a probable cause of the acute pseudomembranous colitis. There was no detailed examination of the lower-limb venous system, which could have identified septic thrombophlebitis, probable origin of the emboli that caused pulmonary infarctions, considered the final cause of death.

In a recently published review, deep vein thrombosis and pulmonary thromboembolism were detected in 1.62% and 0.38% of 3 million patients undergoing cardiac surgery and were associated with higher mortality.[14] Pancreatitis caused by cytomegalovirus was found at the autopsy, which, however, did not have significant clinical consequences. It is important to note that this was not a generalized cytomegalovirus infection, which was identified only in the pancreatic parenchyma. Pancreatic infection by cytomegalovirus is rare, and very few cases have been reported so far, both in immunocompromised and immunocompetent patients.[14] **(Dr. Luiz Alberto Benvenuti)**

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