Multimodality Evaluation in Cardiovascular Imaging in the Diagnosis of Atypical Cases of Chest Pain: Myasthenia Gravis

Roberta de Alvarenga Batista, Alexandre Henrique Cobucci Santana, Roberto Luiz Marino, Bárbara Campos Abreu Marino
Hospital Madre Teresa, Belo Horizonte, Minas Gerais – Brazil

Introduction

Myasthenia Gravis (MG) is an autoimmune disease characterized by the presence of antibodies against acetylcholine (Ach) receptors in skeletal muscle. It is a neuromuscular disease that develops with fluctuating weakness and muscular fatigability.[1] Besides, some patients have antibodies against myocardial antigens, which makes the heart a possible autoimmune target in MG.[2,3]

Regarding cardiac involvement, the clinical presentation is variable: from asymptomatic conditions, electrocardiogram (ECG) with non-specific abnormalities, presence of arrhythmias, myocarditis and Takotsubo syndrome.[4-7] Another form of cardiac involvement is related to anticholinesterase.[8] In MG, the number of available Ach receptors is decreased, and the use of anticholinesterase decreases Ach degradation and promotes a greater supply of Ach to the receptors. Frequent adverse effects of this medication are diarrhea, abdominal cramps and nausea. A severe yet less common effect is chest pain. This may mimic an acute coronary syndrome (ACS) caused by the vasoconstriction that Ach is capable of causing in coronary arteries with endothelial dysfunction.

In addition to chest pain, tiredness, dyspnea during exercise and orthopnea are typical symptoms of cardiac involvement that may also characterize MG.[4,5,8] Patients with MG with chest pain or other symptoms of cardiac dysfunction should be investigated extensively.

A multimodality evaluation with cardiovascular imaging tests may contribute significantly to the definition of the diagnosis in atypical cases of chest pain. These imaging tests report data that complement each other and are important in the search for the definitive diagnosis.

Case Report

A 31-year-old female patient with MG using pyridostigmine, under a therapeutic setting with recent increase in the dose of this medication. There were no risk factors for coronary artery disease (CAD), history of cardiovascular disease, systemic embolic events or previous infectious symptoms. The patient has been complaining, for three months, of chest discomfort. She sought emergency care after 2 days of precordial chest pain, with sudden onset, with worsening of intensity, burning sensation, irradiating to the left upper limb associated with recent influenza. Patient admitted with clinical stability presented septal ST segment depression on ECG. Myocardial Necrosis Markers (MNM) with high values, namely: troponin I 2.91/3.36 (Reference Value – VR < 0.05) and Creatine Kinase (CK) mass 22.9/22.90 (RV: 4,3). Upon admission, the initial diagnostic hypotheses formulated were myocarditis and ACS.

In the workup for chest pain, transthoracic echocardiography (TTE) was performed, which demonstrated preserved left ventricular systolic and diastolic function, and absence of segmental abnormalities of contractility. In the pursuit of diagnosis, cardiac magnetic resonance imaging (CMRI) was performed to obtain findings that confirmed the initial hypothesis of myocarditis: detection of edema, presence of inflammatory activity by searching for early global enhancement and fibrosis through late myocardial enhancement (LME).[9]

In this case, the pattern of ischemic LME distribution was observed, with subendocardial impairment suggestive of myocardial infarction – as in atherosclerotic and thrombotic coronary occlusion and vasospasm (Figure 1). In myocarditis, the most frequent pattern is multifocal (meso and/or subepicardial). The presence of LME, with ischemic pattern and absence of Lake Louise criteria,[9] considerably reduced the diagnostic possibility of myocarditis.

Once the CMRI information was evaluated, the diagnostic hypotheses of thrombotic obstructive coronary disease or vasospasm were formulated. The patient was referred to coronary angiography, which revealed coronary arteries free of significant obstructions (Figure 2). New troponin dosage presented normal levels, forming a typical ACS curve, characterizing ST-segment elevation myocardial infarction (STEMI) with coronary arteries without obstructive lesions, secondary to vasospasm due to the use of pyridostigmine. The patient was discharged on acetylsalicylic acid (ASA) and nitrate.

Discussion

Cardiac involvement may be associated with MG either by autoimmune myocardial involvement or due to the effect of the drugs used in the treatment.[2,3] In addition, the cardiac disease may be unrelated to MG, as in acute myocardial infarction due to atherosclerotic coronary obstruction.[4-7] In some cases of chest pain, medical history, physical examination, ECG and MNM may not be sufficient to accurately define the diagnosis of these patients.

Keywords

Diagnostic Imaging; Echocardiography; Electrocardiography; Magnetic Resonance Imaging; Chest Pain; Myasthenia Gravis/diagnosis.

Mailing Address: Roberta de Alvarenga Batista •
Rua Santa Maria Itabira, 200/501.Postal Code 30310-600, Belo Horizonte, Minas Gerais – Brazil
E-mail: robertabatista@cardiol.br
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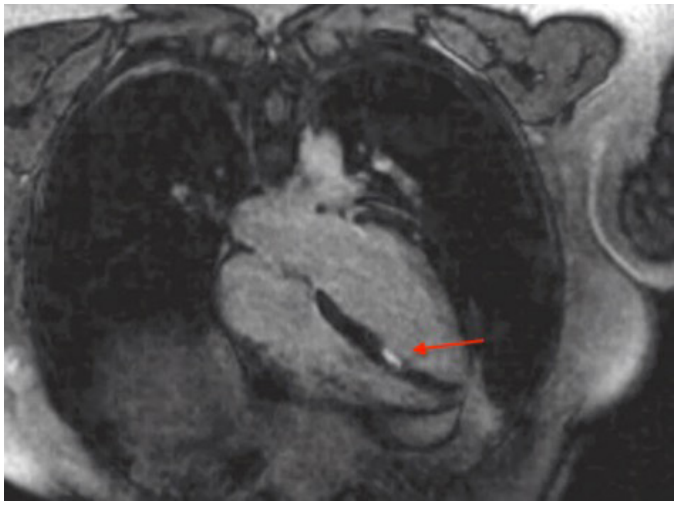

Figure 1 – *Cardiac magnetic resonance imaging: 4-chamber CMRI with late enhancement with pattern of subendocardial involvement. Ischemic pattern that can be observed in cases of atherosclerotic or thrombotic coronary obstruction and vasospasm (red arrow).*

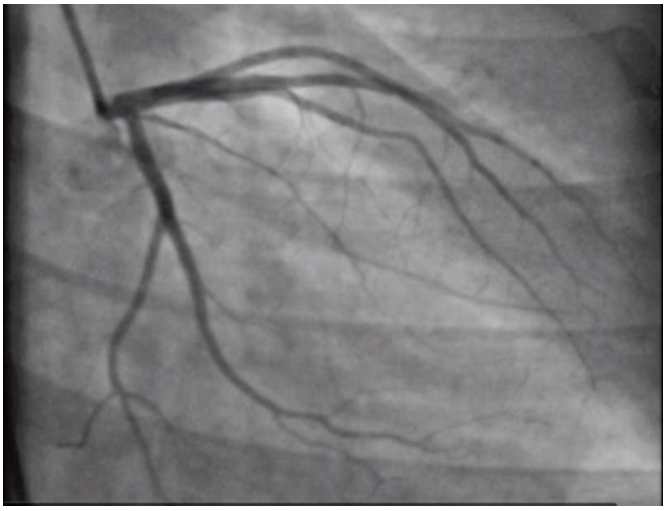

Figure 2 – *Cineangiocoronariography with coronary arteries free of obstructions.*

In the case presented, the first test was TTE, a non-invasive method that can be carried out in emergency care with no exposure to radiation. In patients with chest pain, the data provided by this test (heart anatomy, systolic and diastolic function, evaluation of valvulopathies, presence of segmental abnormalities in myocardial contractility, pericardial effusion) are the first tests required to formulate the main diagnostic hypotheses and propose the following approaches. In this report, TTE revealed normal systolic and diastolic function, and no segmental disorders, but the following diagnostic hypotheses were not confirmed: ACS and myocarditis.

CMRI, a second non-invasive test conducted with no exposure to radiation, available at the facility, is an excellent method to investigate diseases that present inflammation/tissue edema, given its unique capacity for tissue characterization. The findings corroborating the diagnosis of myocarditis by the CMRI were defined in a consensus known as the Lake Louise criteria.[9] These are based on regional or global edema in T2-weighted images; increased signal intensity ratio of myocardium and skeletal muscle in early enhancement images; and the presence of at least one focal lesion, with non-ischemic distribution pattern in LME images. In this technique, the images are acquired in the first minutes after administration of Gadolinium (Gd). The inflamed tissues with hyperemia and capillary extravasation increase Gd supply and slow down myocardial output. Therefore, in the early global enhancement images, the enhanced areas (greater signal intensity) represent the areas most affected by the inflammatory lesion. This evaluation is quantitative and is based on the pre and post-contrast signal intensity measurement and on the comparison with the signal intensity variation of the skeletal muscle. Myocardium-to-skeletal muscle ratios greater than

four times indicate hyperemia and capillary extravasation caused by inflammation. The patient in this case showed no signs of regional edema or global early enhancement. It is worth noting that both the noise signal of T2-weighted images and early enhancement are strongly dependent on the technical parameters of the images. Patients with arrhythmias or other movement artifacts may present insufficient image quality to allow adequate evaluation of edema areas. LME images revealed enhancement with ischemic distribution pattern, which compromises the subendocardium and seems to respect a coronary territory. In myocarditis, the LME pattern is the noninvasive involvement of the subendocardium, which is more commonly a multifocal pattern that affects the mesocardium and/or subepicardium. In the case reported here, the LME pattern was found to be ischemic, which reduced the chances of myocarditis being diagnosed, as well as the fact that there was no early enhancement or signs of regional edema, not fulfilling the Lake Louise criteria.[9] CMRI occurred because it was a young patient (whose exposure to radiation requires diligence), who did not have any risk factors for CAD, history of cardiovascular disease or prior systemic embolic events, and the method had great ability to differentiate between the diagnoses of myocarditis and ACS. The use of CMRI allows the evaluation of reversible injury markers, such as edema and inflammation, and irreversible injuries, such as necrosis and fibrosis, in addition to defining the regional distribution of the abnormalities.

Finally, cineangiocoronariography, an invasive test that uses contrast and entails exposure to radiation, was performed as an early invasive strategy. This test is necessary as it rules out obstructive atherosclerotic disease, especially when the patient is classified as high risk (*Thrombolysis in Myocardial Infarction* – TIMI for Unstable Angina/STEMI of the patient concerned equals to 3, classified as high risk).[10] Coronary angiography of this patient revealed absence of atherosclerotic disease with severe obstruction and corroborated the hypothesis of STEMI due to vasospasm. In this case, it was a pyridostigmine-induced coronary spasm.

Although coronary computed tomography angiography can be performed instead of coronary angiography in young individuals with low probability for obstructive CAD, this patient presented typical chest pain, ST-segment depression on ECG and positive troponin with curve evolution, characterizing STEMI. Coronary computed tomography angiography is certainly not indicated in this clinical context (Class IIa indication in case of low/intermediate probability of CAD and when troponin and/or ECG are inconclusive).[10] However, it is argued that coronary computed tomography angiography could rule out obstructive CAD, as well as provide further information of potential non-obstructive and non-calcified plaques (related to the endothelial lesion process and the vasospasm mechanism concerned). However, at the option of the assisting team and the high-risk criteria, coronary angiography was performed.

AMI with coronary arteries without obstructive lesions is frequent in patients admitted with ACS.[7,8] Myocardial infarction with non-obstructive coronary arteries occurs due to several causes: vasospasm, myocarditis and Takotsubo.[11,12] Establishing the cause of acute myocardial infarction with coronary arteries without obstruction is important to stratify the prognosis, which varies from very favorable, as in most cases of Takotsubo, to reserved, as in giant cell myocarditis. In addition, diagnosis is necessary to determine the most appropriate therapy for each case.[11,12]

Other complementary tests may also be used in the evaluation of chest pain. For example, myocardial scintigraphy is a test that provides information on perfusion and left ventricular function. It helps in the differential diagnosis of chest pain of ischemic, coronary or non-coronary origin.

MG is a multisystemic disease with potential cardiac involvement. In view of an atypical case of chest pain, a multimodality approach with association of cardiovascular imaging tests is important in defining the definitive diagnosis, in stratification of prognosis and in specific treatment.

Authors' contributions

Data acquisition: Batista RA, Santana AHC, Marino RL, Marino BCA; Data analysis and interpretation: Batista RA, Santana AHC, Marino RL, Marino BCA; Manuscript writing: Batista RA, Santana AHC, Marino RL, Marino BCA; Critical revision of the manuscript as for important intellectual content: Batista RA, Santana AHC, Marino RL, Marino BCA.

Potential Conflicts of Interest

There are no relevant potential conflicts of interest.

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Academic Association

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