Author’s response to reviews

Title: Multi-modality imaging evaluation of recurrent Tako-tsubo syndrome in a patient with coronary artery fibromuscular dysplasia

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Version: 1 Date: 11 Nov 2017

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The response to the reviewer’s questions

Reviewer reports:

Reviewer #1: Cheng et al. reported the case of a 57 years old woman with transmural myocardial infarction due to coronary artery fibromuscular dysplasia (FMD) and concomitant, recurrent, Takotsubo syndrome (TTS). The authors focused on the importance of a multi-modality imaging approach to assess different features of acute myocardial infarction (AMI) and TTS. The manuscript is very interesting and tries to emphasise a possible correlation between different clinical conditions such as fibromuscular dysplasia, AMI and TTS whose underlying mechanisms are not yet well understood.

Comments to the authors:

1. TTS is prevalent in postmenopausal women and is often triggered by an emotional or physical stressful event. The presented case denotes these features and looks like an acute TTS occurred in a patient with underlying chronic artery disease.

Whether the authors might provide the value of acute phase myocardial biomarkers (at least Troponin) this hypotheses could be further corroborated.

Response: we added Troponin T result in revised manuscript and marked with track change.
2. TTS is characterized by transient abnormality of left ventricle wall motion beyond a single coronary artery perfusion territory in absence of obstructive coronary artery disease. Can the authors better clarify the meaning of the expression "takotsubo effect", recurrently used in the manuscript? If the TTS diagnostic criteria (Prasad et al. Am Heart J 2008) were completely fulfilled, might the authors prefer the expression "takotsubo syndrome"?

Response: we agreed to the reviewer’s opinion. We changed "Tako-tsubo effect" to "Tako-tsubo syndrome" in revised manuscript and marked with track change.

3. FMD is a disease associated with arterial wall abnormalities which can lead to multiple stenosis and less frequently to aneurysms or dissections. (Wuerzner et al. Rev Med Suisse 2017). The coronary artery involvement is a rare but possible condition which can present, among the possibilities, as acute coronary syndrome. In the presented case, the coronary angiogram revealed a tapering and long narrowing distal left anterior descending artery which is consistent with FMD, but doesn't allow a definitive diagnosis of such disease. (Michelis et al. J Am Coll Cardiol 2014)

Can the authors provide further elements proving the involvement of at least one other non-coronary artery to confirm the diagnosis?

Response: We agreed to reviewer’s comments. We ruled out coronary spasm by nitroglycerin injection during diagnostic angiography, but did not obtain definitive imaging evidences of FMD in other arteries (including renal arteries). The isolated coronary FMD has been described/defined recently (Saw J, et al JACC 2017;70:1148). In the present case, the characteristic angiographic feature and CMR results support this diagnosis.

4. AMI and TTS are thought to be not mutually exclusive. The coexistence of these clinical entities has been described mainly through case reports. It has been hypothesised that the psychological stress and/or the physical pain due to acute coronary syndrome may precipitate TTS. (Hurtado Rendón et al. Am J Med 2017)

The authors should rephrase the sentence: "The current case illustrates a unique scenario, in which "Tako-tsubo" effects occur recurrently in the heart with pre-existing localized myocardial infarction, suggesting that TTS and AMI might share some fundamentally common mechanic characters and underlying mechanisms" Since there are no data suggesting common pathophysiology mechanisms between TTS and AMI.

Response: We agreed to reviewer’s comments. We rephrased the sentence as: “In acute MI, psychological stress and/or physical pain can stimulate central/autonomic nervous systems, and
increase bioavailability of cortisol and circulating catecholamines, which may affect the myocardium supported by both culprit and non-culprit coronary arteries.”

5. Cardiac MRI provide important information regarding morphology and tissue characterization and can play a key role in differentiating TTS and AMI secondary to coronary artery disease. Late gadolinium enhancement (LGE) images allow the identification of areas affected by myocardial fibrosis, while T2-weighted images can prove the eventual presence of myocardial edema. The authors should provide further LGE (4- and 2- chamber) and T2-weighted images to confirm that the scar area is limited to the distribution territory of distal LAD and that the myocardial edema is extended to the entire area of TTS-related wall motion abnormalities.

Response: We added LGE 2-chamber and short-axis images to confirm that the scar area was limited to the distribution tertiary of distal LAD. There was no evidence of myocardial edema. We also changed figure legend accordingly.