Reviewer #1

1. Patients with SAH and concomitant MI are difficult to assess. Troponin elevation and EKG changes occur in SAH patients. In most cases, these patients develop Takotsubo Syndrome. In your case report you're describing apical ballooning which might also be a hint for Takotsubo Syndrome

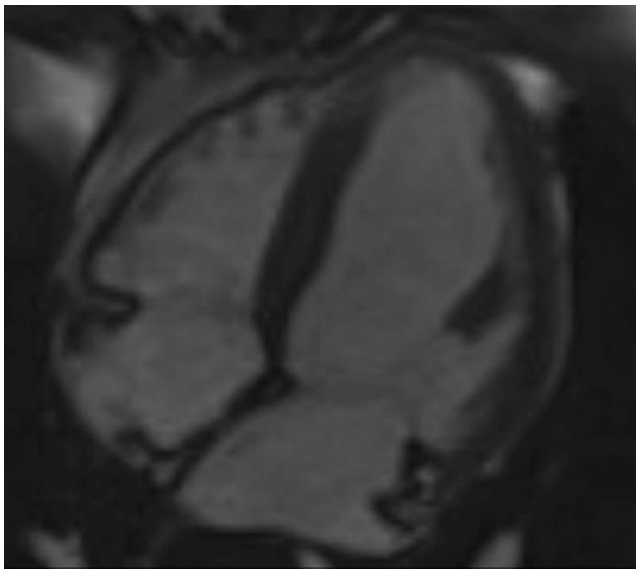
We thank the reviewer for making this point. We think that the patient suffered vasospasm of the coronary arteries. Literature suggest presence of diffuse cerebral vasospasm in patients with SAH.

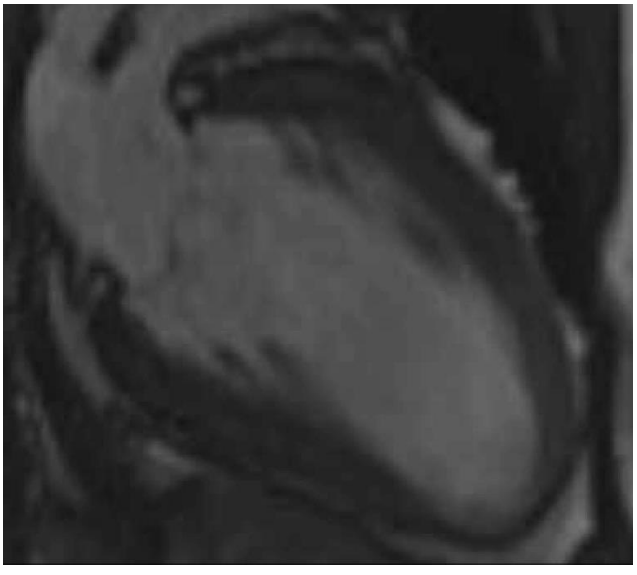
(Dorsch NW, King MT. A review of cerebral vasospasm in aneurysmal subarachnoid hemorrhage Part I: Incidence and effects. J Clin Neurosci. 1994)

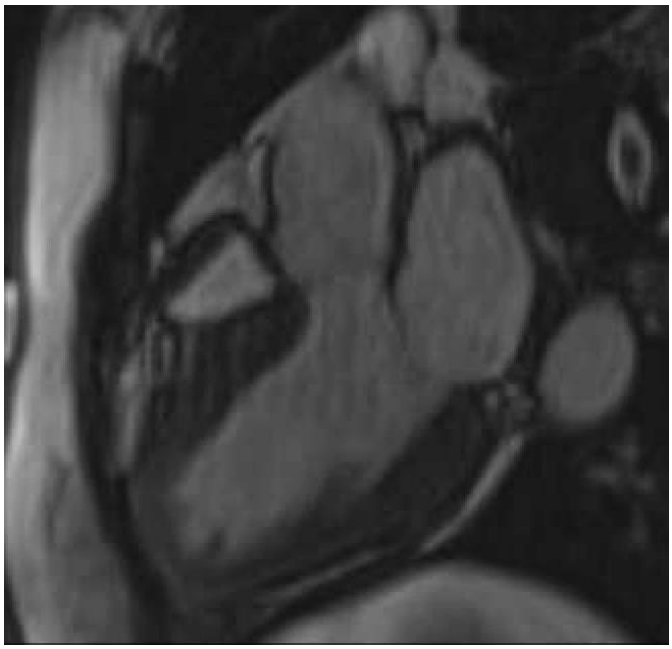
We think on hospital day 15 she developed ST elevations on EKG which we believe happened from diffuse cerebral vasospasm.

Initially apical ballooning from stress induced cardiomyopathy was in the differential however on CMR done 3 weeks after the initial presentation, she was found to have intense subendocardial apical scar consistent with myocardial infarction. There was also persistent wall motion in the apical territory at 3 weeks and even at follow up with low EF- these findings do not favor the diagnosis of stress induced cardiomyopathy.

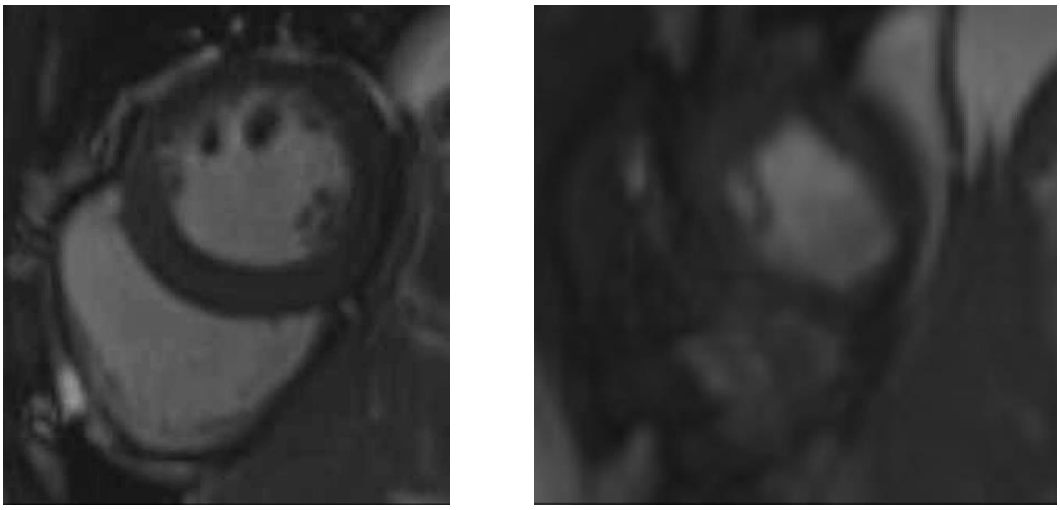
CMR Cine images are depicted below showing apical hypokinesis. Please see attached PowerPoint file for the video files.



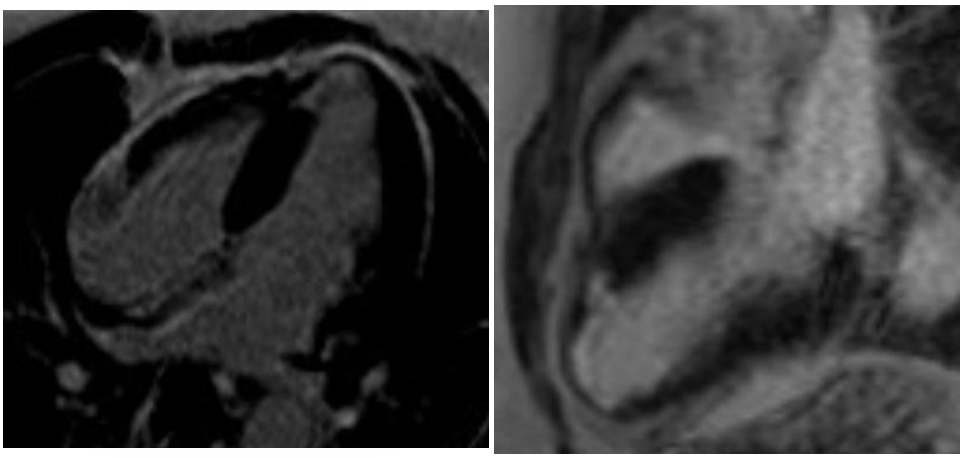




3C CMR Cine



CMR Cine of the SAX at the mid LV level on the left and more apical LV segments on the right.



LGE 4 chamber on the left showing no delayed enhancement of the anterolateral wall, however there is intense subendocardial enhancement in the apical inferoseptal wall.

LGE 3 chamber on the right also shows intense apical delayed enhancement with extension into the anteroseptal wall

To our best knowledge, CMR findings in stress induced cardiomyopathy is generally "little" or "slight" and generally midmyocardial, patchy fashion. In our case the delayed enhancement appears too well defined, too intense and in subendocardial fashion which is consistent with myocardial infarction.

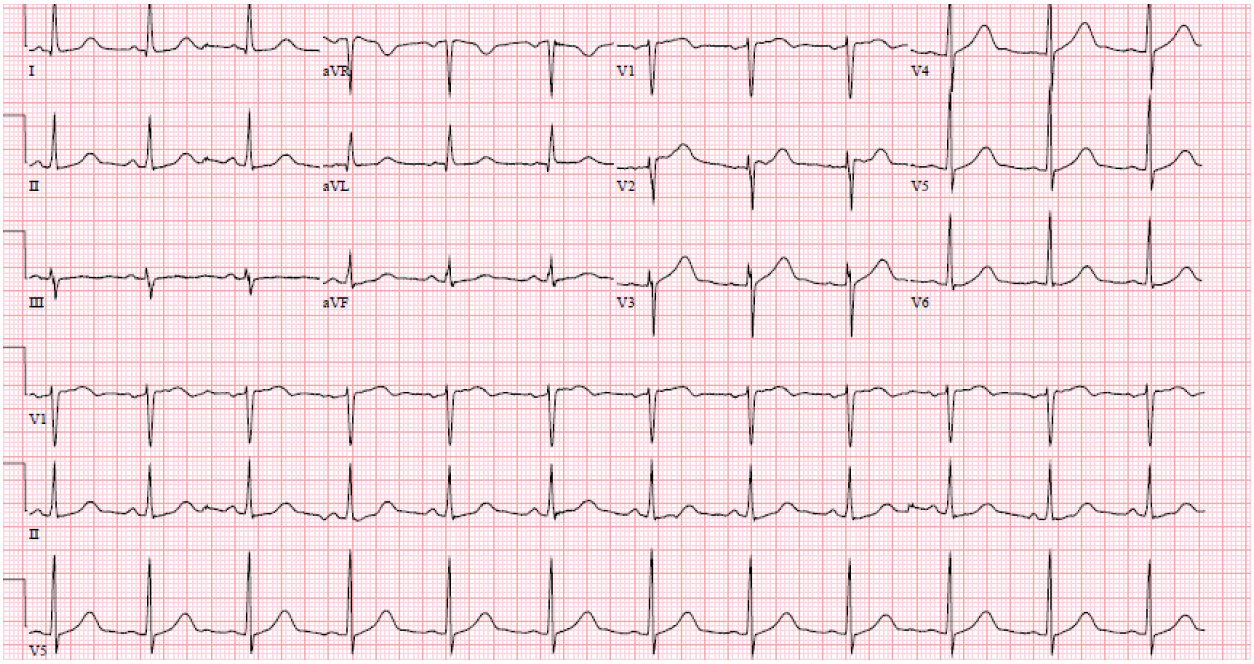
(Andreas Rolf et al. Immunohistological basis of the late gadolinium enhancement phenomenon in tako-tsubo cardiomyopathy, European Heart Journal July 2009)

2. The scar in the MRI might be a chronic scar. Please provide further MR evidence of an acute myocardial infarction (T2 weighted Images or T2 mapping Images demonstrating oedem in the infarcted zone and not demonstrating typical Takotsubo pattern oedema)

We thank the reviewer for their valid comment. Patient was not very cooperative or comfortable in the CMR scanner. We had to modify our sequences by skipping T2 weighted imaging and directly obtaining delayed enhancement imaging. As the literature suggests, both MI and stress induced cardiomyopathy can have edema on T2 weighted imaging. However, the LGE in subendocardial fashion with intensity as shown in this

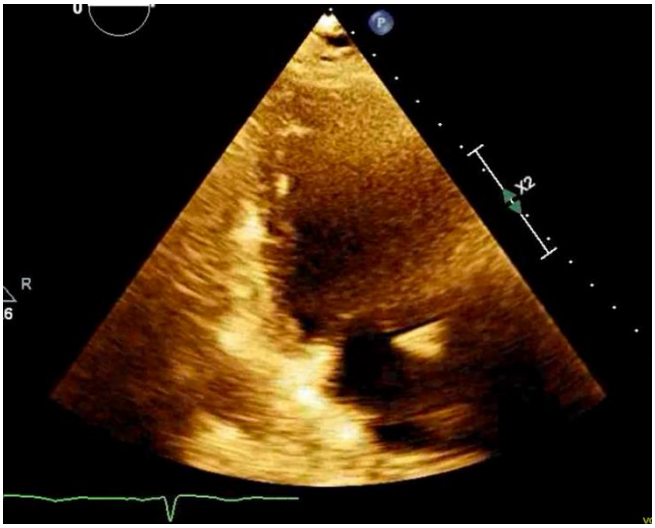
(Eitel I, Florian KB, Bernhardt P. Clinical Characteristics and Cardiovascular Magnetic Resonance Findings in Stress (Takotsubo) Cardiomyopathy. JAMA Cardiology 2011.)

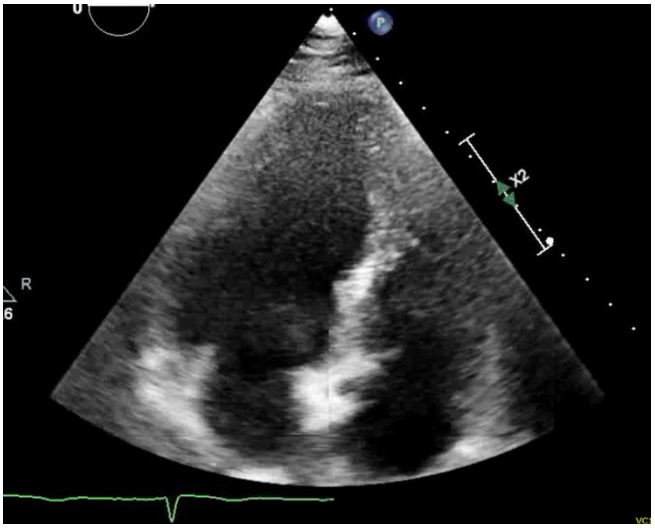
Our patient was a 44-year-old woman with only history of hypertension. She presented with SAH that resulted from an aneurysmal rupture. On further questioning, she didn't have any previous history of myocardial infarction or even distant episode of chest pain. Her baseline EKG is shown below:

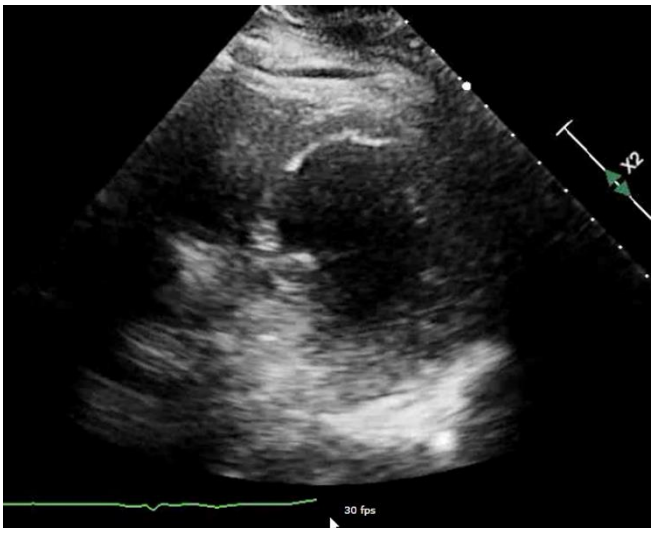


As the reviewers can see, her EKG is absolutely normal. Although we don't have any baseline MRI, patient's baseline TTE is shown below. She had normal EF with normal apical wall motion. No previous history of CAD, a normal baseline EKG and TTE followed by her NSTEMI which resulted in wall motion abnormalities and delayed enhancement in the same distribution as wall motion, rules out the possibility of previous myocardial infarction leading to intense subendocardial scar.

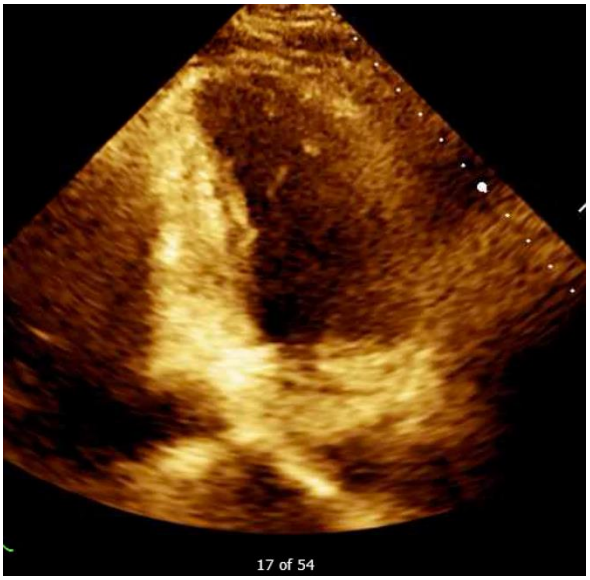
Baseline ECHO video attached here:

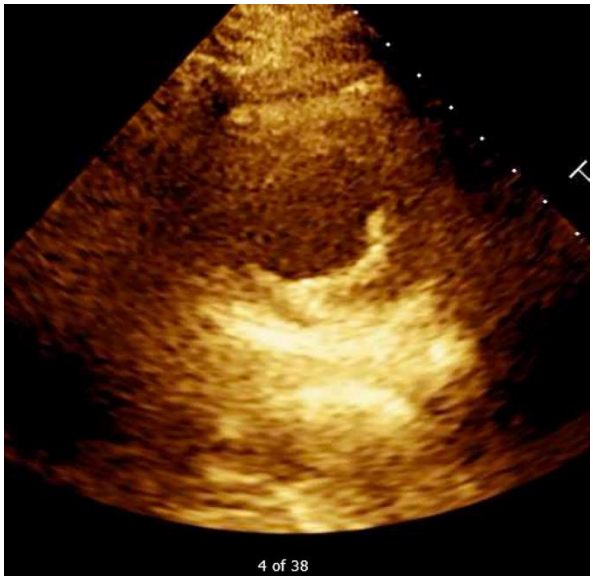






The following images were obtained around 8 hours after her MI:





2 chamber TTE showing apical ballooning and PSAX shows apical hypokinesis.

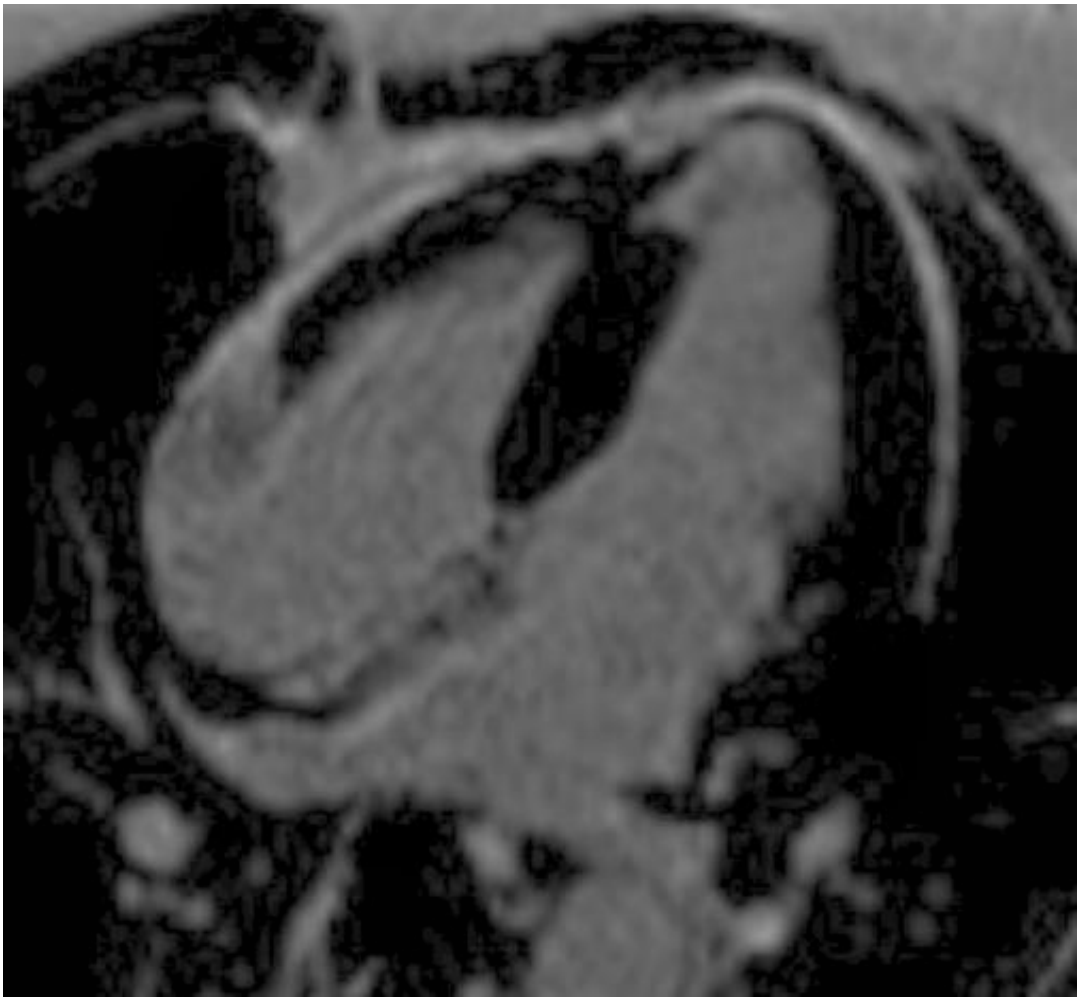
3. How do you explain that you only had an "acute" septoapical myocardial infarction (100% occlusion of the mid to distal LAD) but no infarction in the distal LCx territory (100% occlusion of distal LcX) territory. How can you be sure this was due to vasospasm? Was nitroglycerin applied during the invasive angiography with normalization of vessels?

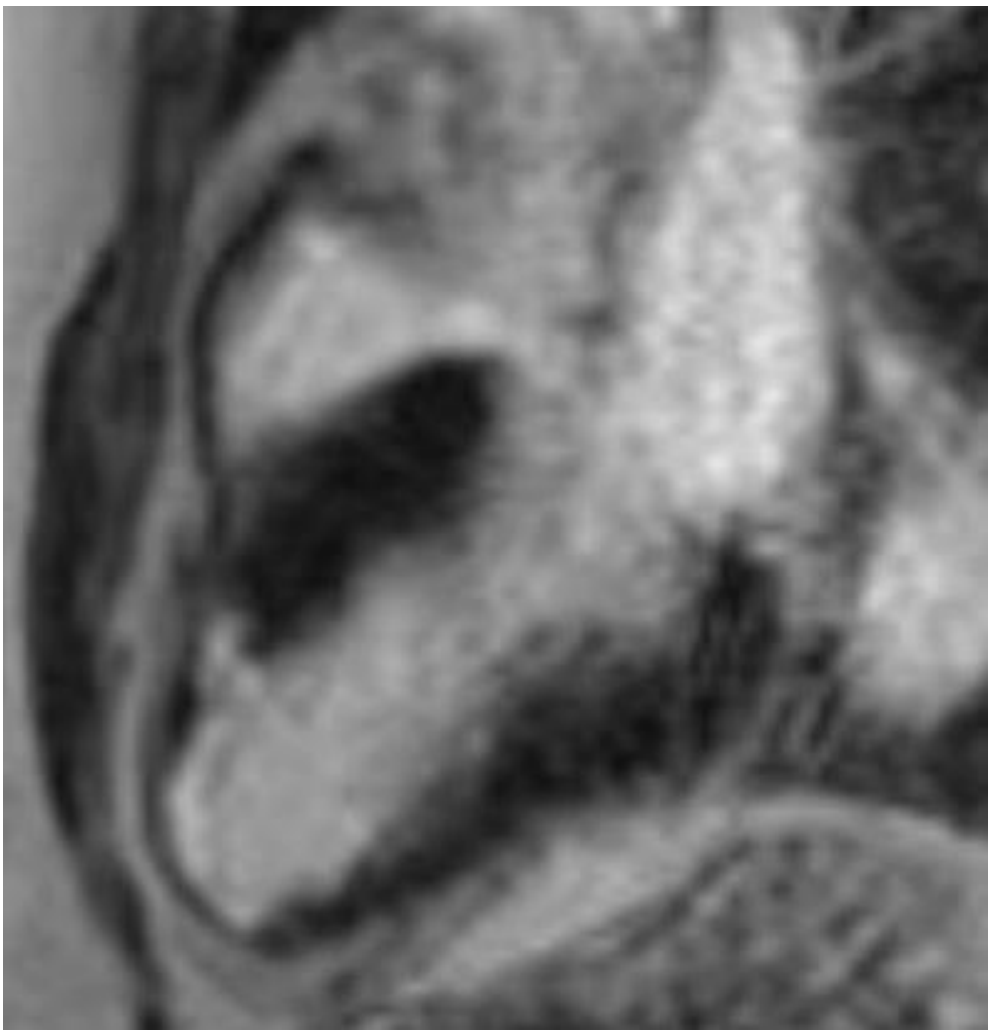
We thank the reviewer for making this point. As the EKG suggests there were extensive ST-T changes seen from V1-V5. This suggests involvement of multiple coronary vessels. After the initiation of medical therapy, her ST elevation/chest pain resolved 4 days after the initial

presentation. The histopathological changes with the 100% LCx vasospasm are difficult to predict.

We were unable to give nitroglycerin due to patient's persistent hypotension in cardiac catheterization laboratory and with concomitant subarachnoid hemorrhage, we were instructed to keep permissive hypertension for full recovery by our neurology colleagues.

5. The windowing of Figure 4 is not optimal. Please provide LGE Images of the whole ventricle (including Lcx territory).





Reviewer #2

1. Coronary angiography showed patent left main artery, but 100% occlusion of the mid to distal LAD and distal LCx. Did the authors try to administrate nitrates into the coronary artery to resolve the coronary spasm?

We thank the reviewer for this excellent comment. We were unable to give nitroglycerin due to patient's persistent hypotension in the cardiac catheterization laboratory and with concomitant subarachnoid hemorrhage, we were instructed to keep permissive hypertension for full recovery by our neurology colleagues.

2. Ergonovine provocation testing was performed in order to diagnose CAV. Did the authors try to perform ergonovine provocation testing?

We thank the reviewer for making this point. Ergonovine provocation test is suggested in the patients with MINOCA where coronary angiogram appears negative and if the patient doesn't meet criteria for coronary vasospasm.

(Stefan Agewall et al. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. European Heart Journal January 2017)

(Borja Ibanez et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology. European Heart Journal January 2018)

In the present case however, patient had 100% vasospasm of all the vessels in the mid-distal territory and met the criteria for vasospasm. Given provocative testing in a patient already vasospastic, can induce ventricular fibrillation, hence we avoided reestablishing the diagnosis.

(Takagi Y et al. Clinical implications of provocation tests for coronary artery spasm: safety, arrhythmic complications and prognostic impact: Multicentre Registry Study of the Japanese Coronary Spasm Association. European Heart Journal 2013.)

3. Beta-blockers were contraindication for CAV because of exacerbation of coronary spasm.

Authors bring up a great point. In literature for vasospastic angina, the nonselective beta blockers theoretically can worsen the vasospastic angina however the cardio-selective betablockers can be used.

Robertson RM et al. Exacerbation of vasotonic angina pectoris by proponalol. Circulation Feb 1982.)

While she was having her ACS, unfortunately due to her blood pressure, we were not able to titrate her medications very well. Once her EKG normalized after four days, her chest pain had resolved and she was started on Carvedilol for her cardiomyopathy.