CMC Ambroise Paré
25-27 Boulevard Victor Hugo
92200 Neuilly-sur-Seine

Centres Médico Chirurgicaux
Ambroise Paré, Pierre Cherest, Hartmann

Dear Editor and Reviewers,

It has been a great honor to attract your attention with our case report "**Sickle-cell and alpha-thalassemia traits resulting in non-atherosclerotic myocardial infarction: beyond coincidence?**"

As requested by peer reviewers, we have accordingly edited, corrected and completed the manuscript in order to improve the impact of its content.
Please also find herewith some specific replies to reviewers' comments.

Again, thank you for your time and benevolence.

Best regards,

Lee S. Nguyen, MD, MSc.

Reviewer #1:
"This manuscript focuses on the coexistence of Combination of sickle cell and alpha-thalassemia traits and incidence of non-atherosclerotic myocardial infarction in a young woman. It is interesting. There are some grammar errors should be corrected before accept. In addition, the discussion should be more detailed."

Further details were added onto discussion as requested by the author. Grammar errors were also addressed as suggested.

Added to manuscript in Discussion:
"*Mechanisms of infarction which have been suggested in the context of sickle cell trait include: a) rheological factors of altered viscosity and membrane flexibility contributing to microcirculatory stasis; b) lower platelet survival during sickle cell crisis and c) vasospasm*"
Added to manuscript in Differential diagnosis:
"*Coronary artery disease was ruled out by computed tomography coronary angiography, reference imagery in such case of a young woman not presenting with any other cardiovascular risk factor*."

Reviewer #2:
"This study features the rare finding of myocardial infarction in a case of sickle cell and alpha-thalassemia traits. The presented evidence of infarction is very weak. Revision should include more than just a figure showing a white spot in the myocardial wall in 2 cMRI views. What can be said about early enhancement? Was the quality of the exam such that LV mass, EDV, ESV and ejection fraction could not be documented? Also, a brief description of the cMRI acquisition parameters is necessary. Were any MRI sequences included to allow for measurement of heart iron and fat contents?"

Cardiac MRI was performed on a 1.5T Siemens magnet (Pitié-Salpêtrière) used in clinical routine. The acquisitions were ECG-gated and performed with an 8-channel cardiac-phased array surface coil, requiring several apneas. Presence of myocardial silent infarction was measured using cMRI by evaluating presence and quantification of late gadolinium enhancement (LGE). This contrast agent reduces the T1 relaxation time of the tissue. Indeed, local concentration of gadolinium in tissues induces differences in intensity in T1-weighted images. Such spatial and temporal differences are due to the heterogeneity of the tissue properties in terms of local perfusion, extracellular volume distribution, water exchange rate between vascular, interstitial and cellular spaces, as well as clearance kinetics of contrast media. These properties are strongly modified in the fibrotic tissue in which there is an increase in the volume of distribution of the contrast agent and a delayed myocardial clearance caused by capillary rarefaction. Such increase in concentration within the fibrotic tissue induces a T1 shortening which shows as a hyperintense area on MR images based on gradient echo sequences inversion recovery. This sequence (LGE) combined with an appropriate adjustment of the inversion time, is widely used in cMRI to characterize replacement fibrosis in the

setting of myocardial infarction. It was performed 10 minutes after Gadolinium bolus injection on 10 to 12 slice levels covering the LV from apex to base and myocardial scar volume will be quantified. LGE was considered present only if myocardial enhancement was confirmed on both short-axis and matching long-axis locations. In addition to LGE, cine SSFP acquisitions were acquired in the left ventricle to characterize its function and morphology. Left ventricle mass, volumes, mass/volumes indices were measured using Qmass Software (Medis, Netherlands ®). Epicardial and endocardial borders of short-axis cine planes at end systole and end diastole were semi-automatically traced using QMass (Medis ®) to determine the LV ejection fraction (LVEF), LV end-diastolic volume (EDV) index, LV end-systolic volume (EDS) index, and LV myocardial mass at end-diastole.

In our reported patient, infarction was diagnosed on basis of focal subendocardial late gadolinium enhancement in one apical-lateral segment (75% transmurality). LV mass was 106.2 g (60g/m²), EDV and ESV were respectively 168 ml (95.5 ml/m^2) and 84 ml (47.7 ml/m^2). LVEF was 50%. Specific MRI sequences to determine iron content were not anticipated by the protocol.

Added to manuscript in Case Report:

"*Presence of Myocardial silent infarction were measured using cMRI by evaluating presence and quantification of late gadolinium enhancement (LGE). In addition to LGE, cine SSFP acquisitions were acquired in the left ventricle (LV) to characterize its function and morphology*."

"LV mass was 106.2 g (60g/m²), LV end diastolic and systolic volumes were respectively 168 ml (95.5 ml/m^2) and 84 ml (47.7 ml/m^2). LV ejection fraction was 50%."

Reviewer #3:

"Please add recent references. Please discuss more about cause-effect or cause - association in your case. How other causes were ruled out"

Discussion and differential diagnosis were addressed as to methods to eliminate regular atherosclerotic infarction by computed coronary angiography.

Added to manuscript in Discussion:

"*Mechanisms of infarction which have been suggested in the context of sickle cell trait include: a) rheological factors of altered viscosity and membrane flexibility contributing to microcirculatory stasis; b) lower platelet survival during sickle cell crisis and c) vasospasm*"

Added to manuscript in Differential diagnosis:

"*Coronary artery disease was ruled out by computed tomography coronary angiography, reference imagery in such case of a young woman not presenting with any other cardiovascular risk factor*.

Added to manuscript as reference:

Wambua, S., et al., *Co-inheritance of alpha+-thalassaemia and sickle trait results in specific effects on haematological parameters.* Br J Haematol, 2006. **133**(2): p. 206-9. doi: 10.1111/j.1365-2141.2006.06006.x PMCID: 4394356

and
Jacobs, J.E., L. M. Boxt, B. Desjardins, E. K. Fishman, P. A. Larson and J. Schoepf; *ACR practice guideline for the performance and interpretation of cardiac computed tomography (CT).* J Am Coll Radiol, 2006. **3**(9): p. 677-85. doi:10.1016/j.jacr.2006.06.006. PMID:17412148

Reviewer #4:

« Very elegant presentation regarding the detection of asymptomatic ischemic heart disease in a patient without significant risk factors, except a combination of both alpha-thalassemia and sickle cell trait. Although no clear associations can be documented the presentation and the photos are of educational value. »

We thank you for your positive comment.