Author’s response to reviews

Title: Development of anthracycline-induced dilated cardiomyopathy due to mutation on LMNA gene in a breast cancer patient: a case report

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Author’s response to reviews:

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Dr. James Mockridge
Editor-In-Chief
BMC Cardiovascular Disorders

Dear Editor Mockridge,

I hereby submit a revised version of the manuscript BCAR-D-19-00138, Development of anthracycline-induced dilated cardiomyopathy due to mutation on LMNA gene in a breast cancer patient: a case report. Thank you for giving us the opportunity to revise and resubmit this manuscript. I
appreciate the time and valuable comments provided by the reviewers, and we have incorporated the suggested changes into the manuscript to the best of our ability. The manuscript has certainly benefited from these insightful revision and suggestions.

I have responded to the suggestions below. To make the changes easier to identify where necessary, I have numbered them.

Reviewer 1:

Chichaco-Kuruc et al. presented a short report on familial DCM related to very known mutation R190W LMNA. The disease in the proband manifested 2 years after anthracycline treatment of breast cancer. Authors were right to conclude that chemotherapy could accelerate the onset of symptoms in the proband.

1. From the scarce presented data, we can learn that the proband's brother presented with cardiomyopathy with significant left ventricular dilatation that is unusual in cardiolaminopathies.

1.1. Therefore it would be nice to learn what was the size of the left ventricle in the proband in the beginning and with the treatment. whether any sera' biomarkers were elevated, e.g. Nt-proBNP, hs TnT. R. Before the treatment the value of BNP was 6412 pg/mL. The echocardiogram reported a LVIDd of 5.9 cm with an EF of 25 %. After the treatment the EF increased to 40%.

1.2. Did the patients have Holter 24h ECG recording and any arrhythmia, advanced conduction system disease was detected (a hallmark of cardiolaminopathy). R. The proband’s Holter 24h ECG recording demonstrated the presence of an atrial fibrillation for a period of 18h. The mean heart rate was 63 bpm, with a maximum frequency of 120 bpm and a minimum of 43 bpm. Frequent monomorphic ventricular extrasystoles was registred. The pr, qrs and qtc interval were reported as normal.

In the case of the relative’s proband, the Holter 24h ECG report a mean heart rate of 59 bpm, with a maximum frequency of 108 bpm and a minimum of 36 bpm. Frequent episodes of nonsustained ventricular tachycardia were detected. The qrs interval was 143ms.

2. Authors are also encouraged to read other earlier papers (e.g. Sylvius et al. J Med Genet 2005;42:639-647) on the R190W LMNA and comment on the course of the disease in other families from the literature.

R. Following the recommendation of the reviewer the paper suggested was reviewed and the reference included in the manuscript (other references have been also included), in the Discussion and Conclusions section of the manuscript: “The LMNA variant identified in the proband, LMNA-p.Arg190Trp (NM_170707.3:c.568C>T), which alters the helical rod domain of the protein, has been described earlier and implicated in acute types of familial DCM with, and without, conduction-system disease [12-16]” (page 6, lines 126-129).

3. The names of genes LMNA, MYH7, TTN should be written in italic. R. Pursuant to the suggestion made by the reviewer we wrote the names of genes in italic.

Reviewer 2:

Authors reported an interesting case in a family suffering of DCM.
Only minor points to clarify:

1. Please, could you include data of global population (ExAC, gnomAD) concerning frequencies of variant in LMNA?
R. The max allele frequency reported in TOPMED is 0.00002.

2. Any other rare variant in any gene encoding heart proteins related to sarcomer? May be other rare variants (MAF<1%) could be of interest as genetic modifiers of DCM onset/evolution/outcome (with additonal role of anthracycline).
R. We did not find any other rare variant related to at the sarcomere in this study nor any other rare variants that could be of interest as genetic modifiers.

We hope that we have now fully addressed all the queries of the reviewers.

Thank you again for consideration of our revised manuscript.

Best regards,

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