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Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine



Letter to the Editor

Post RNA-based COVID vaccines myocarditis: Proposed mechanisms



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ARTICLE INFO

Article history: Received 12 July 2021 Received in revised form 6 August 2021 Accepted 30 November 2021 Available online 9 December 2021

Keywords: COVID-19 Vaccine Myocarditis

There have been several reports of myo-(peri-)carditis after vaccination with the SARS-CoV-2 RNA-based vaccines (BNT162b2-mRNA and mRNA-1273) especially after the second dose [1–3]. Despite the tremendous success achieved by these vaccines, however, there remains a rare but significant risk of morbidity which may further augment vaccine hesitancy. Therefore, unravelling the underlying mechanism(s) leading to myo-(peri-)carditis may help with improving the current vaccines and/or raising awareness among clinicians and public health authorities.

The role of pericytes in susceptibility to COVID-19 through the expression of SARS-CoV-2 receptor, *i.e.*, angiotensin-converting enzyme 2 (ACE2) has been demonstrated [4]. Pericytes also play a significant role in repairing cardiac tissue injuries including those of cardiac endothelial cells. This is especially true in young male adults who may happen to more frequently experience subtle cardiac injuries compared with the general population [5]. It has also been shown that after infection with SARS-CoV-2, anamnestic humoral immune responses to previously-encountered common coronaviruses (CoVs) is augmented significantly [6]. Given the commonality among the spike glycoproteins of the latter with that of SARS-CoV-2, after COVID-19 vaccination two types of antibodies appear: one against SARS-CoV-2 spike and a group cross-reactive

one against common CoVs' spikes. This phenomenon is even much more pronounced in those who had been previously infected with SARS-CoV-2, even though asymptomatically, as well as in those after the second dose of COVID-19 vaccine. Myo-(peri-)carditis has been reported more frequently after the second dose of the RNA-based COVID-19 vaccines [2]. This brings us to the first hypothesis.

Anti-spike antibodies elicited as a result of past exposure to common CoVs and/or to SARS-CoV-2 spike (be it through prior infection or vaccination), may elicit anti-idiotype antibodies, that is, antibodies directed against the paratope region of anti-spike antibodies. Since the latter is the mirror image of the anti-spike antibodies, it may mimic the spike protein itself and bind ACE2 expressed on cardiac pericytes that express ACE2. This forms an immobilized immune complex on the surface of pericytes. This localized immune complex, in turn, may lead to activation of the complement system through its classical pathway and damage to the target cell.

A more likey mechanism is where the vaccine lipid nanoparticles leak from the injection site and enter circulation where injection practices are not very well observed [7]. Then they reach the heart and can be endocytosed by cardiac tissue including cardiac muscle, pericytes, endothelial cells, and macrophages. Local production of spike protein on the surface of cardiac cells and/or its shedding along with detached cell membranes may recruit neutrophils that also express ACE2 on their surface. Spike-activated

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neutrophils produce neutrophil extracellular traps [8] that subsequently activate alternative pathway of complement *in situ*, damaging cardiac endothelial cells. One may ask that these can simply happen anywhere else in the body, however, the simple answer is in the heart itself, because it is a vital organ, since there is not much wiggle room for immunopathology, clinical manifestations are noticed immediately, therefore, any subtle injuries are brought up faster to medical attention.

All in all, this is a rare phenomenon, and following best practices in vaccine administering may aid in mitigating this adverse effect and vaccine hesitancy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- [1] Kim HW et al. Patients With Acute Myocarditis Following mRNA COVID-19 Vaccination. JAMA Cardiol 2021.
- [2] Montgomery J, Ryan M, Engler R, Hoffman D, McClenathan B, Collins L, et al. Myocarditis Following Immunization With mRNA COVID-19 Vaccines in Members of the US Military. JAMA Cardiol 2021;6(10):1202. https://doi.org/10.1001/jamacardio.2021.2833.
- [3] Shay DK, Shimabukuro TT, DeStefano F. Myocarditis Occurring After Immunization With mRNA-Based COVID-19 Vaccines. JAMA Cardiol 2021;6 (10):1115. https://doi.org/10.1001/jamacardio.2021.2821.
- [4] Chen L et al. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. Cardiovasc Res 2020:116(6):1097-100.
- [5] Kytö V, Sipilä J, Rautava P. The effects of gender and age on occurrence of clinically suspected myocarditis in adulthood. Heart 2013;99(22):1681–4.
- [6] Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Nature 2020:581(7809):465–9.
- [7] Zuckerman JN. The importance of injecting vaccines into muscle. Different patients need different needle sizes. BMJ 2000;321(7271):1237–8.
- [8] Ackermann M et al. Patients with COVID-19: in the dark-NETs of neutrophils. Cell Death Differ 2021:1–15.