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Post-COVID-19 Vaccination Myocarditis

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ABSTRACT

A cluster of young patients with myocarditis after SARS-CoV-2 RNA vaccination, started several days up to 2 weeks after the second shot, was reported in Israel, without a solid evidence for a cause and effect sequence of events, or any scientific, peer review publication. Most of the patients were young men who recovered with or without steroid therapy, but one 22 year-old woman died within 72 hours from start of the symptoms (chest pain and fatigue) with elevated troponin and CRP, ECG changes but normal echocardiogram.

After injection of RNA the body manufactures the S protein and starts synthesize antibodies against it. My speculation is that the connection between S protein and the receptor ACE2, which is abundant on the myocardium, builds a stabile complex with high antigenicity. Antibodies attached to this complex which is now under attack by both – antibodies and T-cells. The result is severe inflammation and cytokine storm. Another possible explanation is the presence of a mediator between the receptor (ACE2) and S protein such as Defensin 5, and a complex of higher molecular weight and antigenicity causing a severe immunological attack.

Keywords
SARS-CoV-2, COVID-19, Myocarditis, Vaccination, RNA.

Introduction
Corona virus disease 2019 (COVID-19), a pandemia emerged at the end of 2019, caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). On January 30, 2020 the World Health Organization (WHO) declared the outbreak as a Public Health Emergency of International Concern [1]. As of June 3, 2021 172 million laboratory-confirmed patients and 3.6 million deaths have been reported globally. In Israel there were 839518 PCR positive patients and 6413 deaths due to the pandemia.

At the end of 2020 vaccination against COVID-19 became available. Israel purchased the RNA vaccine BNT162b2 from Pfizer-BioNTech Inc., and immediately the Israeli health system started a vaccination project for all citizens 16 year of age and older. The vaccine showed protection of 95%, 7 days after the second dose [2]. Israel was the first country to reach a herd immunity of near 75% of the population, and the pandemia subsided quickly since the start of the vaccination project at the end of December 2020. On June 3, 2021 more than 5 million people were at least 7 days after the second dose of the vaccine, only 40/day new patients were reported, with zero daily mortality. Efficiency and safety of the vaccination process in Israel was clearly demonstrated [3]. The vaccine prevented infection, symptoms, hospitalization or severe disease in 92%, 94%, 87% and 92%, respectively.

Being the first country in the world with this achievement, side effects and adverse events were carefully looked for and reported. A significant number of acute myocarditis were observed in young men several days after the second injection. The signal of possible side effect was clearly found, yet a pathophysiological explanation was lacking. Most of the cases were mild and self-limited and only one case did not survive.

The receptor for adherence of SARS-CoV-2, similar to Influenza A, is ACE2 (angiotensin converting enzyme 2), which is abundant on the respiratory and gastrointestinal mucosal cells, especially on alveolar type 2 pneumocytes, but also in the myocardium [4]. The spike protein of coronavirus (S) is divided into the S1 and S2 domains, in which S1 is the ligand for the receptor binding, and

S2 is responsible for cell membrane fusion [5,6]. After injection of RNA based vaccine, S protein is produced by human cells in vivo, and circulates in the blood. Being target for humoral and cell mediated immunity, specific antibodies and activated T cells are present, and protect the body against COVID-19 infection [7]. SARS-CoV-2 S protein has characteristics of "super-antigen" which activates the immune system very strongly [8]. S protein produced after RNA injection may also attach to ACE2 receptors and cause a specific immunological attack against the complex S-ACE2 [9]. In addition S protein is toxic to live cells and attacks human cells directly [10]. Exposing healthy endothelial cells to the spike protein damaged the cells by binding ACE2. This binding disrupted ACE2's molecular signaling to mitochondria causing the mitochondria to become damaged and fragmented. Previous studies have shown a similar effect when cells were exposed to the whole SARS-CoV-2 virus, but this is the first study to show that the damage occurs when cells are exposed to the spike protein on its own [10]. This potential hazard may be time and concentration dependent, and also synchronized with the immunological response. Thus, rarely, S1 protein causes inflammation of the myocardium, and being attached to the ACE2 receptor, may activate the immune system as an antigenicity complex, in addition to activation the immune system as a single protein in the circulation.

Hypothesis

The immune system is divided into the innate and adaptive systems [11]. The cells responsible for the adaptive system are B cells, which produce antibodies, CD4+ T cells, which have helper and effector functions, and CD8+ T cells that kill infected cells. Adaptive immune response and cell memory are essential for the success of COVID-19 vaccines.

Vaccine associated myocarditis has been following small pox vaccination, streptococcal pneumonia vaccine and influenza vaccine [12-16]. Most of the patients with post-vaccination myocarditis were men. This may be explained by the effect of sex-hormones or X-chromosome linked molecules that are involved in inflammation and immune response [17,18]. In a cohort of 2354 patients with severe COVID-19, 90-day mortality was 23.4% in women and 28.2% in men, with HR 1.28, 95%CI 1.06-1.54 [19].

Virus infection has been widely described as a common cause of acute myocarditis [20]. The clinical spectrum of myocarditis includes chest pain after influenza-like syndrome, ECG changes, elevated troponin and typical MRI examination [21,22]. A systemic viral infection may trigger an exaggerated inflammatory response, which can cause myocardial injury. Binding to ACE2 on the myocyte favors internalization and replication of the SARS-CoV-2 virus. Cases of acute myocarditis were described following COVID-19 disease and are explained by direct attack of the virus with or without immune response to the viral S-protein or the complex S-ACE2 [23]. Myocarditis may be a part of the multisystem inflammatory syndrome or cytokine storm. SARS-CoV-2 S protein acts as a super-antigen, triggers escalation of the cytotoxic adaptive immune response by binding to T cell receptors or major histocompatibility complex class II molecules [24]. Super-antigens bind directly to a MHC molecule and one of the variable domains of the T cell receptor, and this cross- linking leads to an excessive release of inflammatory cytokines. In a cohort of German patients recently recovered from COVID-19 infection, cardiovascular magnetic resonance revealed cardiac involvement in 78%, and ongoing myocardial inflammation in 60%, independent of the severity and overall course of the acute illness [25]. In Israel a cluster of young patients with myocarditis after the RNA vaccination, started several days up to 2 weeks after the second shot, was supported by several sources, without a solid evidence for a cause and effect sequence of events, or any scientific, peer review publication. Most of the patients were young men who recovered with or without steroid therapy, but one 22 year-old woman died within 72 hours from start of the symptoms (chest pain and fatigue) with elevated troponin and CRP, ECG changes but a normal echocardiogram.

My speculation is that acute myocarditis can happen after SARS-CoV-2 RNA vaccination at the same pathophysiological process as in the course of COVID-19 disease. After injection of RNA the body manufactures the protein (S protein) and start to synthesize antibodies against it. The S protein attached to its receptor – ACE2 (abundant on the myocardium), thus the antibodies attached to the complex S-ACE2 on the myocardium, which now is under attack by both – antibodies and T-cells. This attack may result with severe inflammation and cytokine storm.

Another possible explanation is that a mediator between the receptor (ACE2) and S protein such as Defensin 5 is settled, and a complex of high molecular weight and antigenicity attached to the heart [9].

Testing Hypothesis

Several basic science and clinical steps are needed for advancing my hypothesis: Intensive follow-up of people immunized with RNA vaccine against SARS-CoV-2 S protein, identify signs and symptoms of myocarditis (chest pain, arrhythmias, ECG changes), diagnose the disease (high troponin, elevated CRP, positive cardiac echocardiogram, MRI). Then investigate the acquired immune system (antibodies, populations of B and T lymphocytes) and characterize their targets (S1 protein, S1-ACE2 complex or other antigen complexes).

Discussion

Acute myocarditis is a rare complication of COVID-19 disease, an inflammation of the myocardium due to the viral direct attack followed by over reaction of the acquired immune system. RNA vaccine may cause myocarditis in a similar process. Activating the immune system by SARS-CoV-2 S protein which acts as a super-antigen, triggers escalation of the cytotoxic adaptive immune response by binding to T cell receptors or major histocompatibility complex class II molecules. In almost every case the recovery is complete and mortality reported in a very few cases. The incidence of myocarditis after the first or second vaccine injection has not been reported and should be carefully studied.

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