Scientific Research Publishing

Case Reports in Clinical Medicine, 2024, 13, 309-314
https://www.scirp.org/journal/crcm
ISSN Online: 2325-7083
ISSN Print: 2325-7075

Refractory Ventricular Fibrillation with Underlying Coronary Artery Disease after COVID-19 Vaccine-Kounis Syndrome or Coincidence

Elaine M. C. Chau

Cardiology Centre, Hong Kong Sanatorium & Hospital, Hong Kong SAR, China
Email: echau@hksh.com

How to cite this paper: Chau, E.M.C. (2024) Refractory Ventricular Fibrillation with Underlying Coronary Artery Disease after COVID-19 Vaccine-Kounis Syndrome or Coincidence. *Case Reports in Clinical Medicine*, **13**, 309-314.
https://doi.org/10.4236/crcm.2024.138037

Received: July 12, 2024
Accepted: August 23, 2024
Published: August 26, 2024

Abstract

A 63-year-old man with diabetes and asymptomatic coronary artery disease developed refractory ventricular arrhythmia at 20 hours at rest after his second COVID-19 vaccine. Despite significant stenosis in the coronary arteries, there was no evidence of acute or old myocardial infarction, heart failure, myocarditis or structural abnormalities on post-mortem to account for the substrate for the fatal arrhythmia. The refractory and incessant nature of the ventricular fibrillation and post-mortem finding of a grossly elevated unexplained IgE level (in the absence of acute myocardial infarction) suggested the possibility of Kounis Syndrome or allergic acute coronary syndrome.

Keywords

Refractory Ventricular Fibrillation, COVID-19 Vaccine, Kounis Syndrome

1. Introduction

COVID-19 vaccines were widely used during the pandemic for the prevention of COVID-19 infection as a public health measure. Patients with pre-existing cardiac disease who develop acute fatal cardiac events after COVID-19 vaccines were often dismissed as natural deaths from their pre-existing illness and not as a possible consequence of the vaccine. However, a meta-analysis of self-controlled case series studies showed that COVID-19 vaccination may be associated with a small increase in cardiac-related mortality, especially among males [1]. I report here a case who died with refractory ventricular defibrillation and was found to have elevated unexplained IgE levels and previously unknown coronary artery

disease. The cause of death was determined to be a natural cause of death due to ventricular arrhythmia related to significant coronary artery disease. However, the possibility of an acute allergic coronary syndrome (Type II Kounis Syndrome) cannot be excluded.

2. Case Report

The deceased was a 63-year-old Chinese male with an 8-year history of diabetes mellitus when he died in August 2021. His diabetes control was suboptimal with documented evidence of diabetic retinopathy and maculopathy. The patient had not complained of any exertional chest discomfort or dyspnoea or symptoms suggestive of angina. He received his first dose of the COVID-19 vaccine Sinovac-CoronaVac (a whole inactivated virus vaccine) one month before and his second dose of Sinovac-CoronVac on the day before his death. On both occasions, the patient was observed for 30 minutes after the injection and did not report any discomfort. On the next day after the second vaccination, approximately 20 hours later, the patient complained of feeling tired and was resting in his room at home when he was found by his family members to be gasping and he quickly became unconscious. Ambulance crew arrived at the scene soon after and cardiopulmonary resuscitation was started. The patient was found to be in ventricular fibrillation. Repeated shock was delivered but was unsuccessful. The Patient was taken to the nearest hospital with continuous resuscitation, was intubated and given intravenous amiodarone. After 50 minutes, the ventricular fibrillation turned into asystole and he was certified dead soon afterwards.

Autopsy showed a normal-sized heart and no ventricular hypertrophy. There was extensive calcification in the coronary arteries with severe atheromatous stenosis with 90% occlusion of the major arteries in multiple areas. Importantly there was no evidence of coronary thrombosis, acute myocardial infarction, acute pericarditis, or old infarcts or scars. Viral study of the major organs (lungs, kidney, liver and heart) was all negative. Toxicology study showed therapeutic levels of hypoglycaemic drugs (gliclazide and metformin) and anti-arrhythmic drugs (amiodarone). IgE level was grossly elevated at 746 - 913 IU/ml (normal < 100 IU/ml). The cause of death was ventricular arrhythmia (resistant ventricular fibrillation) with underlying significant coronary artery disease.

3. Discussion

At first glance, the post-mortem appeared to suggest that the silent coronary artery disease was the culprit for the refractory and eventually fatal ventricular arrhythmia. However, there were several issues of concern.

3.1. No Obvious Substrate for Ventricular Arrhythmia

If the patient had been exerting himself when the ventricular arrhythmia occurred with subsequent acute myocardial infarction due to plaque rupture, that could easily explain a) the ventricular arrhythmia because of ongoing ischaemia

and b) the grossly elevated IgE level. But the ventricular arrhythmia occurred during rest and the post-mortem ruled out any acute thrombosis in the coronary arteries and any evidence of an acute myocardial infarction due to plaque rupture. The heart was normal-sized and there was no ventricular hypertrophy or heart failure or evidence of myocarditis or pericarditis, i.e. there is no obvious ischaemia or inflammation or substrate for ventricular arrhythmia.

3.2. Refractory and Incessant Nature of the Ventricular Fibrillation

Despite resuscitation and repeated electrical shocks, the ventricular fibrillation did not return to normal sinus rhythm. The patient remained in ventricular fibrillation for at least 50 minutes before the asystole. Causes of refractory and incessant ventricular fibrillation include ongoing ischaemia in acute myocardial infarction, persistent inflammation in myocarditis, severe heart failure, structural abnormalities in cardiomyopathies, significant electrolyte abnormalities, congenital QT abnormalities, Brugada syndrome and allergy to pro-arrhythmic drugs or herbal medicine such as herbal aconite tea, etc. Although sudden cardiac death can occur in asymptomatic patients with coronary artery disease, the risk of sudden cardiac death is increased in patients with heart failure due to reduced ejection fraction. There was no evidence of heart failure in this patient. Congenital QT abnormalities and Brugada syndrome usually present at an earlier age and there was apparently no previous history or family history of syncope or dizziness in this patient to suggest a congenital or hereditary cause of ventricular arrhythmias. The remaining possible cause of refractory ventricular arrhythmia is allergy to an unknown allergen such as drugs, herbal medicine, vaccine, etc. A recent review on arrhythmias after COVID-19 vaccination published in 2023 showed a series of case reports from different countries reporting ventricular arrhythmias [2]. It was postulated that these ventricular arrhythmias occur as an allergic or adverse reaction to the vaccine in patients with genetic arrhythmic predisposition.

3.3. Unexplained Elevated IgE Level

Elevated IgE levels occur in atopic disease, systemic anaphylaxis and acute myocardial infarction. Acute myocardial infarction is associated with a consistent early rise in serum IgE level, followed by sustained elevation and a drop to initial levels by the end of the third week [3]. The grossly elevated IgE level in the absence of acute myocardial infarction was suggestive of atopy or some kind of allergic reaction in this patient.

According to the review of allergic reactions to COVID-19 vaccinations by Dr Nicholas G Kounis, patients may become IgE-sensitized by previous exposure to antigens. Therefore, atopic patients could be more vulnerable in the second dose of vaccination [4]. The IgE level before the second vaccination was unknown and could already be elevated even before the second vaccination. Since the patient had no evidence of acute myocardial infarction on post-mortem, the ele-

vated IgE level suggested some kind of atopy or allergic reaction. The combination of an allergic reaction and an unexplained acute coronary event raised the possibility of an allergic acute coronary syndrome or Kounis Syndrome.

3.4. Kounis Syndrome or Coincidence?

Kounis Syndrome is an acute coronary syndrome associated with allergic reactions to any allergen, including drugs, bee stings, snake bites, vaccines, etc. It is rare and not well recognised. Diagnosis of Kounis Syndrome requires a high index of suspicion and knowledge of the pathophysiologic mechanisms. This syndrome may occur in patients with normal coronary arteries (type I) [5], with underlying coronary artery disease (type II) [6], with coronary stents (type III) and with coronary grafts (type IV). It is interesting that Dr Kounis commented in his review that in any unexpected death and allergic reactions associated with current COVID-19 vaccinations, allergic acute coronary syndrome or Kounis Syndrome should not be excluded. Symptoms of allergic reactions may range from mild to severe. Examples of mild allergic reactions include hives, nasal congestion, rash, scratchy throat, watery or itchy eyes. These mild symptoms may often be overlooked and not reported by the patient. On the other hand, examples of severe allergic reactions include angioedema, cardiovascular collapse, cerebral manifestations, chest tightness, flushing, hives, laryngeal oedema, loss of consciousness, low blood pressure, swelling of mouth, lips, tongue, throat or wheezing, which usually lead to the patient seeking urgent medical attention. In severe anaphylaxis associated with sudden death, cutaneous manifestations could be absent and cardiovascular investigations are difficult to obtain [4].

3.5. Timing of Allergic Reaction after Vaccination

Although anaphylaxis through mast-cell activation and interaction between IgE antibodies against a particular vaccine component acting as antigen usually occurs within minutes or up to 4 hours of exposure to the relevant antigen, in some instances the manifestation of anaphylactic reactions may be delayed. Other non-IgE-mediated pathophysiological mechanisms (non-IgE-mediated mast cell degranulation via complement activation or MRGPRX2 activation) may produce indistinguishable symptoms from IgE-mediated mechanisms [7]. Type IV hypersensitivity or delayed reactions can take even longer—from 2 to 4 days post-vaccination. In a 2017 case report of an atypical clinical case of Kounis syndrome involving a 70-year-old male with known coronary artery disease with previous coronary bypass graft surgery, the acute coronary event (a non-ST elevation myocardial infarction) occurred 48 hours after the allergic reaction [8]. The angiogram revealed patent coronary grafts. It was concluded that many other mediators, especially slow mediators of inflammation during allergic reactions, played a role in the delayed development of acute coronary events. Therefore, an acute coronary syndrome presenting as ventricular arrhythmia 20 hours after vaccination may still be related to the vaccine through non-mast cell activation mechanisms.

3.6. Other Cases of Ventricular Arrhythmia after COVID-19 Vaccine

Our case bears striking similarity to a case of refractory ventricular tachycardia 12 hours after a booster COVID-19 vaccine (reported in 2022). In this particular case report, polymorphic ventricular tachycardia in the form of Torsades de Pointes occurred in a 65-year-old lady with pre-existing heart disease (namely hypertension and a mildly impaired left ventricular function) within 12 hours of receiving a third booster COVID-19 vaccination. She received 14 defibrillation shocks for refractory ventricular arrhythmia over the course of resuscitation. It is of note that she did not report any significant side effects after receiving the first 2 doses of the same COVID-19 vaccine. Although Torsades de Pointes was not a known side effect of COVID-19 vaccination, infection with COVID-19 viruses had been associated with QT prolongation due to excessive inflammation modulating potassium and calcium channels that can lead to ventricular arrhythmias. It was proposed that an excessive immune response following vaccination for COVID-19 may lead to Torsades de Pointes via a similar mechanism to that seen in patients during active COVID-19 infection [9].

4. Conclusion

As more cases of arrhythmias after COVID-19 vaccination worldwide are reported, this raised the possibility of ventricular arrhythmia being triggered by the vaccine in an atopic or genetically susceptible patient with coronary artery disease being a contributing factor in his rapid demise. The alternative explanation would be the vaccine being a coincidental event in a patient with refractory ventricular fibrillation due to significant but stable coronary artery disease, no acute trigger or precipitating factors for a fatal arrhythmia and unexplained elevated IgE level. Like other cases of rapid demise, it was impossible to prove a causal relationship between the vaccine and the refractory ventricular arrhythmia. According to the principle of Occam's razor, the explanation that makes the least assumptions is likely to be the preferred one. It is postulated that the patient (who may have been IgE-sensitized after the first vaccine) had an allergic reaction to the second vaccine, resulting in elevated IgE level (due to IgE-mediated mast cell activation) and stimulation of other non-IgE-mediated mechanisms. The allergic reaction or excessive immune response resulted in an acute coronary event (Kounis Syndrome) with refractory ventricular fibrillation which caused the patient's demise. The time span of 20 hours would be compatible with other reported cases of COVID-19 vaccine-related Kounis Syndrome or refractory ventricular arrhythmia and could be explained by the different pathophysiological mechanisms underlying vaccine-related allergic reactions. Continued data collection and adverse event reporting after any new drug or vaccine is important for future research on the safety of the drug/vaccine.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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