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Hypersensitivity Myocarditis and the Pathogenetic Conundrum of COVID-19 Vaccine-Related Myocarditis

Nicholas G. Kounis[a] Ioanna Koniari[b] Virginia Mplani[c] Panagiotis Plotas[a] Dimitrios Velissaris[d]

[a]Department of Cardiology, University of Patras Medical School, Patras, Greece; [b]Department of Cardiology, University Hospital of South Manchester NHS Foundation Trust, Manchester, UK; [c]Intensive Care Unit, University of Patras Medical School, Patras, Greece; [d]Department of Internal Medicine, University of Patras Medical School, Patras, Greece

Introduction

Myocarditis is a rare side effect of the mRNA vaccines with uncertainty around its pathogenesis and frequency. Its incidence varies from 1.4 to 4.2 per 100,000 vaccinated individuals. The incidence in Denmark was found to be 1.4 per 100,000 individuals vaccinated with BNT162b2, and in an analysis using a 14 day post-exposure window the vaccine was associated with myocarditis only in female, not male, participants, a fact inconsistent with international data and difficult to explain [1, 2]. In the important review published in *Cardiology* [3], the authors correctly referred to active vaccine component as a possible cause of myocarditis and speculated on mRNA immune reactivity, antibodies to SARS-CoV-2 spike glycoproteins cross-reacting with myocardial contractile proteins, hormonal differences depending on age, sex and immune-genetic background [3, 4]. This report raises issues on type, pathogenesis, causality, and new therapeutic perspectives.

Types of Myocarditis

Myocarditis is an inflammatory disease of the myocardium in the absence of acute or chronic coronary artery disease. Confusion still exists on the proper definition and differentiation of myocarditis caused by vaccines, drugs, or substances. The types of myocarditis [5] classified by causative, histological, and clinicopathological criteria are sown in Table 1. Histological evidence of an inflammatory cell infiltrate with or without myocardial damage is the gold standard for diagnosing myocarditis. However, due to its mild initial clinical course, the pathogenesis of COVID-19 vaccine-associated myocarditis is poorly understood because myocardial biopsies are not routinely performed (Table 1).

Eosinophilic Myocarditis

Eosinophilic myocarditis has been associated with hypersensitivity reactions and constitutes a rare form of myocardial inflammation. It is characterized by eosinophilic myocardial infiltration and is usually accompanied by eosinophilia and rarely by myocyte fibrosis and/or ne-

Karger@karger.com
www.karger.com/crd

Correspondence to:
Nicholas G. Kounis, ngkounis@otenet.gr

Karger

Table 1. Classification of myocarditis

Causal	Histological	Clinicopathological
Viral: enteroviruses (e.g., Coxsackie B), erythroviruses (e.g., Parvovirus B19), adenoviruses, and herpes viruses	Eosinophilic: Hypersensitivity or drug induced	Fulminant
Bacterial: *Corynebacterium diphtheriae*, *Staphylococcus aureus*, *Borrelia burgdorferi*, *Ehrlichia* species	Eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome)	Acute
Drug induced or hypersensitivity	Hypereosinophilic syndrome Malignancies	Chronic active
Protozoal: *Babesia*	Parasitic infections	Chronic persistent
Toxic: alcohol, radiation, chemicals (hydrocarbons and arsenic), drugs, e.g., doxorubicine	Idiopathic acute necrotizing eosinophilic myocarditis	Myopericarditis
Trypanosomal: *Trypanosoma cruzi*	Giant cell	
	Granulomatous	
	Lymphocytic	

crosis [6]. Several subtypes of eosinophilic myocarditis have been described, including hypersensitivity myocarditis that is differentiated from immune-mediated disorders [7], such as eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome), hypereosinophilic syndrome or its myeloproliferative variant, infections, malignancies, and idiopathic acute necrotizing eosinophilic myocarditis.

Hypersensitivity or Drug Induced Myocarditis

This discrete subtype of eosinophilic myocarditis constitutes the most common form. It is caused by a hypersensitivity reaction, usually to drugs [8], most commonly antibiotics (36.5%) and is neither necrotizing nor fibrotic. Other drugs include vaccines (7.7%), central nervous system agents (21.1%), antituberculars (1.9%), and a variety of other drugs (32.8%). The incidence of hypersensitivity myocarditis is 2%–7%, in patients waiting for cardiac transplantation who are often taking multiple medications as diagnosed histologically in the explanted heart or left ventricular apex removed at time of assist device insertion [9]. Hypersensitivity myocarditis is particularly difficult to recognize because the clinical features characteristic of a drug hypersensitivity reaction – including non-specific skin rash, malaise, fever, and eosinophilia – are absent in most cases. One-third (36.5%) of patients may not have peripheral eosinophilia. Most patients with hypersensitivity myocarditis respond well to steroids and drug cessation and only few may need immunosuppressives. The diagnosis is confirmed by endomyocardial biopsy that shows diffuse interstitial infiltrates rich in eosinophils. Since the disease is usually generalized, biopsy of the right ventricle is regarded as adequate [10]. The mechanism of the cardiac reaction seems to be a delayed hypersensitivity reaction [10, 11].

Is COVID-19 Vaccine-Related Myocardidis Hypersensitivity Myocarditis?

Whereas myocardial biopsies have not been performed routinely due to the mild clinical course of COVID-19 vaccine-associated myocarditis, there are few reports where myocardial biopsy has demonstrated eosinophilic infiltration, lymphohistiocytic infiltration where histiocytes have eosinophilic cytoplasm, and giant cell infiltration where giant cells are formed by histiocytes and eosinophils, compatible with hypersensitivity myocarditis. Paradoxically, in these reports, the myocarditis has not been diagnosed as hypersensitivity myocarditis and in others has been diagnosed as such in the absence of myocardial biopsy [12]. So far, myocardial biopsies have been performed and reported only in 8 patients worldwide with myocarditis following COVID-19 vaccine. In 3 patients, the biopsy and in the 4th patient the autopsy demonstrated eosinophilic myocardial infiltration. These reports were 2 from the USA [13], one from Israel [14] and a fatal case from Korea [15], respectively. All 4 cases had received BNT162b2 COVID-19 vaccines. The rest 4 patients had undetermined causes of myocarditis. Previous history of atopic childhood asthma, pollen, and pet allergy [16] could be aggravating factors for myocarditis. All above support our view that COVID-19 vaccine-associated myocarditis seems similar to hypersensitivity myocarditis.

Perspectives

BNT162b2 COVID-19 vaccines contain the excipient polyethylene glycol also known as macrogol or PEG that could potentially induce hypersentitivity reactions [17]. Creams, ointments, lotions, cosmetics that are used frequently by females and young individuals and dental ma-

terials contain also PEG that is able to sensitize its users. Indeed, 1–5.4% of the general population is sensitized to cosmetics or dental materials [18] and 2%–5% of the population, in USA, have experienced hypersensitivity or anaphylaxis, to drugs, food, or insect stings [19]. Therefore, hypersensitivity myocarditis could be induced by the vaccine excipient. However, recent reports [20] have demonstrated that most individuals after first-dose mRNA COVID-19 vaccine reactions, regardless of excipient skin testing result, were able to receive the second mRNA COVID-19 vaccine dose safely. Others [19] have suggested alternative excipients in vaccine manufacturing if vaccine component-induced hypersensitivity is confirmed by systematic future investigations. In a recent report [21], the authors concluded that hypersensitivity to such excipients constitutes risk to patients with allergy to PEG or polysorbates. After diagnostic evaluation, safe COVID-19 vaccines could be offered to most patients, "the remainders will await new vaccines containing different excipients." Myocarditis after vaccination is much milder than other more severe cardiac complications and benefits of vaccination should be taken into account and continue to be recommended to all those eligible.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Nicholas G. Kounis wrote the first draft of the article, which was subsequently revised by Panagiotis Plotas and Dimitrios Velissaris. Virginia Mplani did literature search. Ioanna Koniari edited the manuscript and revised the manuscript for the English language. All authors approved the final submission.

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