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LETTER TO EDITOR

First Identified Case of Fatal Fulminant Eosinophilic Myocarditis Following the Initial Dose of the Pfizer-BioNTech mRNA COVID-19 Vaccine (BNT162b2, Comirnaty): an Extremely Rare Idiosyncratic Necrotizing Hypersensitivity Reaction Different to Hypersensitivity or Drug-Induced Myocarditis

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To the Editor

We read with interest the report published in **the Journal of Clinical Immunology** [1] describing an extremely rare vaccine-related fatal fulminant necrotizing eosinophilic myocarditis, in a female patient, following the initial dose of the Pfizer-BioNTech mRNA COVID-19 Vaccine (BNT162b2, Comirnaty) with abundant eosinophils and focal myocyte necrosis at autopsy and we like to comment on the confusion related to classification of myocarditis following COVID-19 vaccination.

So far, the published reports concerning myocarditis following COVID-19 vaccination have not clarified the type, the cause, and the potential measures of how to prevent such myocarditis. The gold standard for diagnosing myocarditis is the histological or immunohistological evidence of an inflammatory cell infiltrate with or without myocyte damage. Such procedure has not been performed routinely due to the mild clinical course of COVID-19 vaccine-associated myocarditis. Myocardial biopsy has been performed only in one patient with BNT162b2 vaccine, among 54 cases, and demonstrated perivascular infiltration of eosinophils and lymphocytes [2]. Moreover, in one fatal case [3] of post BNT162b2 mRNA COVID-19 vaccination myocarditis, the Masson's trichrome staining demonstrated dense eosinophilic intracellular strips of myocytes, consistent with contraction band necrosis and in 2 additional patients [4] with again BNT162b2 vaccine, myocardial biopsy in the first patient demonstrated myocardial infiltration by eosinophils and other inflammatory cells and in the second, who died 3 days after presentation, an autopsy showed again eosinophils and other inflammatory cells.

The presence of eosinophils and other interacting inflammatory cells in biopsy is compatible with eosinophilic myocarditis. There are several sub-types of eosinophilic myocarditis which include hypersensitivity myocarditis or drug induced myocarditis that may well respond to drug cessation, corticosteroids and immunosuppressives [5] and is differentiated from hypereosinophilic syndrome, eosinophilic granulomatosis with polyangiitis, undefined complex hypereosinophilic syndrome (HES), or malignancies. Hypersensitivity myocarditis is neither necrotizing nor fibrotic and its recognition is often rendered difficult as non-specific skin rash, malaise, fever, and eosinophilia may be absent in most cases [5]. Vaccines including conjugate meningococcal C, hepatitis B vaccine, smallpox, and tetanus toxoid can induce this type of myocarditis. All COVID-19 vaccines, rarely, can induce hypersensitivity reactions and therefore myocarditis of this type should not been excluded. Myocarditis is an inflammatory disease of the myocardium in the absence of acute or chronic coronary artery disease. It can be classified by causative (viral, bacterial, protozoal, trypanosomal, toxic, hypersensitivity or drug induced), histological (eosinophilic, giant cell, granulomatous, lymphocytic), and clinicopathological (fulminant, acute, chronic active, chronic persistent, myopericarditis) criteria. The authors of the above report [1] correctly characterized this unique case of fulminant eosinophilic myocarditis as an extremely rare idiosyncratic necrotizing hypersensitivity reaction because it is clearly

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differentiated from hypersensitivity myocarditis. It seems that the combination of fulminant, eosinophilic, necrotizing, hypersensitivity, and idiosyncratic elements of this myocarditis constitute a new type of the disease that follows COVID-19 vaccination. However, myocarditis after vaccination is much less common, and much milder, than other more severe cardiac complications of COVID-19 infection including cerebral and body thrombosis and myocardial infarction. Therefore the benefits of vaccination should be taken into account and continue to be recommended to all those eligible.

Declarations

Conflict of Interest The authors declare no competing interests.

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