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Letters to the Editor

Rare cases of myocarditis after COVID-19 vaccination: searching for diagnosis, type, treatment and prevention

Casos raros de miocarditis tras la vacunación contra la COVID-19: búsqueda de diagnóstico, tipo, tratamiento y prevención

To the Editor,

Myocarditis following COVID-19 vaccination has been reported recently, especially among young men. The median age was 25 years. Most cases occurred after the second dose with a median onset of symptoms approximately 3 days after vaccination. Nearly 1300 cases of probable myocarditis, confirmed myocarditis, or acute pericarditis were reported among more than 350 million doses in the United States Vaccine Adverse Events Reporting System (VAERS). So far, attempts to clarify the type of myocarditis, the potential cause, and how to avoid such types of myocarditis have not yielded results.

In the interesting case published in *Revista Española de Cardiología*,[1] a 39-year-old male physician, with a history of asthma, autoimmune hypothyroidism, chronic atrophic gastritis, and recurrent spontaneous pneumothorax with left apical lobectomy developed increased fever, intermittent chest and interscapular pain, tachycardia, diffuse ST-segment elevation, and raised high-sensitivity troponin 6 hours after the second dose of BNT162b2 (Pfizer-BioNtech, United States) vaccine. Cardiac magnetic resonance imaging showed edema on T2-STIR sequences with subepicardial enhancement in the lateral mediastinal region compatible with acute myocarditis. Serological examination was positive for nonspecific immunoglobulin M and positive for immunoglobulin G but endomyocardial biopsy was not performed due to the patient's low-risk profile and favorable progress.

This report raises important issues on the diagnosis, type, causes and prevention of such events following current vaccination against the COVID-19 pandemic.

Myocarditis after COVID-19 vaccination was initially reported with microRNA vaccines but recently the Medicines and Healthcare Products Regulatory Agency (MHRA) adverse event report have revealed 31 cases of myocarditis related to the AstraZeneca vaccine.[2] The gold standard for diagnosing myocarditis is histological or immunohistological evidence of an inflammatory cell infiltrate with or without myocyte damage. So far, only 6 cases of myocarditis associated with COVID-19 vaccines have undergone endomyocardial biopsies. In 3 cases, the biopsies did not demonstrate myocardial infiltrate or any evidence of myocarditis. In another 2 cases, in which myocarditis had developed within 2 weeks after COVID-19 vaccination, the endomyocardial biopsies revealed eosinophils and other interacting inflammatory cells such as macrophages, T-cells, and B cells compatible with hypersensitivity or drug-induced myocarditis. In a case diagnosed as lymphocytic myocarditis, the endomyocardial biopsy revealed only macrophages and T cells. In this case, however, staining with hematoxylin-eosin, suitable for detecting eosinophils, was not used.

Hypersensitivity or drug-induced myocarditis (HM) is caused by an allergic or hypersensitivity reaction and is neither necrotizing nor fibrotic but with eosinophilic infiltration.[3] One third of patients may not have peripheral eosinophilia and most patients respond well to steroids and drug cessation. The culprits are vaccines, antibiotics, antitubercular, central nervous system and other drugs. Cardiac explants and ventricular assist devices are associated with HM. Eosinophilic myocarditis is necrotizing and includes hypereosinophilic syndrome (Loeffler endomyocarditis), eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) and other undefined complex hypereosinophilic syndromes.

The currently available COVID-19 vaccines contain ingredients and excipients able to induce HM.[4,5] The mRNA vaccines Pfizer-BioNTech and Moderna contain polyethylene glycol (PEG) and polyethylene glycol plus tromethamine, also known as trometamol, respectively. The viral vector vaccines Johnson&Johnson, AstraZeneca, also known as Covishield, and Sputnik-V contain polysorbate 80 (the first), polysorbate 80, disodium edetate dihydrate (ethylenediaminetetra-acetic acid [EDTA]) and aluminium hydroxide (the second) and polysorbate 80 with disodium EDTA dehydrate (the third). The classic Sinovac (Coronavac) vaccine manufactured in China contains disodium hydrogen phosphate, sodium dihydrogen phosphate monohydrate, and sodium chloride. These ingredient-excipients are also contained in creams, ointments, lotions, other cosmetics, anticancer drugs and various dental materials, which could have sensitized their users. Indeed, it is estimated that 1% to 5.4% of the population is already sensitized to cosmetics, cosmetic ingredients, and dental materials.[6]

Free polysorbate medications, used in oncology, have already been on the market. Alternatives in vaccine manufacturing have been also suggested. Alkylsaccharides are promising agents because they can reduce immunogenicity, improve stability, suppress oxidative damage, and may prevent thrombotic and cardiovascular events.[7] We believe that COVID-19-free allergenic vaccines would be more suitable, more beneficial, and would not induce myocarditis.

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AUTHORS' CONTRIBUTIONS

All authors contributed equally to the manuscript.

CONFLICTS OF INTEREST

None.

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How to reduce the risk of residual shunt during percutaneous treatment of ventricular septal defects

Cómo reducir el riesgo de cortocircuito residual durante el cierre percutáneo de comunicación interventricular

To the Editor,

It was with great interest that we read the study by Solana-Gracia et al., published in *Revista Española de Cardiología* in July 2021.[1] In that interesting article, the authors reveal the feasibility, safety, and effectiveness of the Nit-Occlud Lê VSD (pmf medical, Germany) in the treatment of ventricular septal defects (VSD), although this procedure has frequent and serious complications (residual shunt) that should not be tolerated after VSD closure, especially in the elderly and children.[2,3] Unfortunately, in some patients, residual shunts do not disappear in the short-term and may continue to destroy blood cells.[4] Interestingly, recent studies by Bu et al.[3,5] and Hu et al.[6] have shown that residual shunts may affect the stability of the device and aggravate mechanical hemolysis, so that if any residual shunt (width $>$ 2 mm; flow rate $>$ 3.0 m/s) are identified, it may be recommended to withdraw the device and convert to conventional surgical closure before release to avoid the high risk of persistent hemolysis. Excitingly, transesophageal echocardiography (TEE), performed immediately after deployment of the device, has been considered as a standard technique for the VSD closure procedure.[3,5,6] TEE can provide beneficial information for occlusion and a repeat image can also be obtained to assess the effectiveness of VSD closure, including the device position and the presence of a residual shunt. Therefore, the use of TEE is generally recommended to optimize information on the shape and size of the defect and to evaluate the effect of the procedure.[5] Consideration of these issues may help to decrease the incidence of residual shunt. In addition, it would be better to provide basic information on all residual shunt patients, such as defect diameter, the device diameter used in procedures, and the width and flow rate of the residual shunt to analyze the factors related to the incidence of residual shunt and hemolysis. Moreover, hemolysis may have been aggravated by multiple-exit VSD or the larger size of VSD and could have been resolved by additional device implantation or a VSD coil.[7] To reduce the high risk of foreseeable persistent hemolysis and residual shunt, we suggest that patient selection should be meticulous, with the exclusion of multiple-exit and large VSD, which may help to improve the effectiveness and safety of this procedure. Altogether, we believe that paying full attention to the above problems and formulating appropriate strategies may help to reduce the incidence of hemolysis and residual shunt with Nit-Occlud Lê VSD coil closure of VSD.

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AUTHORS' CONTRIBUTIONS

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CONFLICTS OF INTEREST

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