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CASE REPORT

A case of vaccine-associated myocarditis following pneumococcal immunization leading to acute mitral regurgitation

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Abstract

Vaccine-associated myocarditis (VAM) is a rare entity but can result in potentially serious sequelae if left untreated. However, the mechanisms of the complications of VAM and its treatment remain unclear. Herein, we report the first case of VAM related to pneumococcal immunization, presenting as a local and systemic inflammatory reaction, in which the patient developed significant secondary mitral regurgitation, resulting in acute heart failure. Finally, the patient recovered completely following corticosteroid treatment. This case highlights the value of cardiac magnetic resonance and the pitfall of endomyocardial biopsy in establishing the definitive diagnosis of VAM and emphasizes the importance of optimal management in understanding the mechanism and instituting the treatment for secondary mitral regurgitation caused by VAM.

Keywords Vaccine-associated myocarditis; Pneumococcal immunization; Heart failure; Cardiac magnetic resonance; Secondary mitral regurgitation

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Introduction

Vaccine-associated myocarditis (VAM) is a potentially serious myocardial inflammatory disease that develops after vaccination and for which no other cause can be identified.[1] Recently, with the worldwide outbreak of the new coronavirus disease 2019, many vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been administered, but unexpectedly, the number of reports of SARS-CoV-2-related VAM is steadily increasing.[2] Therefore, the potential for this rare yet serious side reaction is attracting attention. However, the pathogenesis and mechanical complications following VAM have not been fully elucidated.

Case report

A 69-year-old previously healthy woman with no infectious prodrome was admitted to hospital with dyspnoea 2 days after receiving a pneumococcal immunization a 23-valent pneumococcal polysaccharide vaccine (PPSV23; Pneumovax® NP Merck & Co., Inc., Kenilworth, NJ, USA). She received PPSV23 and developed painful erythema and oedema of the injection site and fever on the next day. The symptoms worsened and were accompanied by dyspnoea on effort. She had a history of hyperlipidaemia, melasma, local reactions after influenza vaccination, and pollen allergy. Pre-admission oral medication included rosuvastatin (2.5 mg/day) and tranexamic acid (500 mg/day). However, she had no recent history of change in medication and foreign travel. In addition, she had no history of underlying cardiac disease. On admission, physical examination results were as follows: blood pressure, 130/67 mmHg; high-grade fever, 39.7°C; heart rate 82 b.p.m.; and oxygen saturation of 89% on ambient air. The left upper arm was swollen and warm, and a painful rash had spread beyond the injection site to the entire upper extremity. Chest radiography and portable echocardiography were unremarkable. The initial

laboratory test results revealed leucocytosis (19 200/μL) with moderate eosinophilia (absolute eosinophilic count: 1632/μL; 8.5% in differential count), elevated C-reactive protein (15.5 mg/dL, normal <0.3 mg/dL), and procalcitonin levels (3.1 ng/mL, normal <0.05 ng/mL), whereas serum total protein and albumin levels were decreased (5.9 g/dL, reference: 6.6–8.1 g/dL, and 2.5 g/dL, reference: 4.1–5.1 g/dL, respectively). Initially, cellulitis and sepsis with subsequent hypoxaemia were considered. Oxygen was administered at 2 L/min along with intravenous sulbactam/ampicillin and intravenous infusion with normal saline. However, repeated blood cultures were sterile. The tentative diagnosis was presumed to be a large local and systemic inflammatory reaction following pneumococcal vaccination.

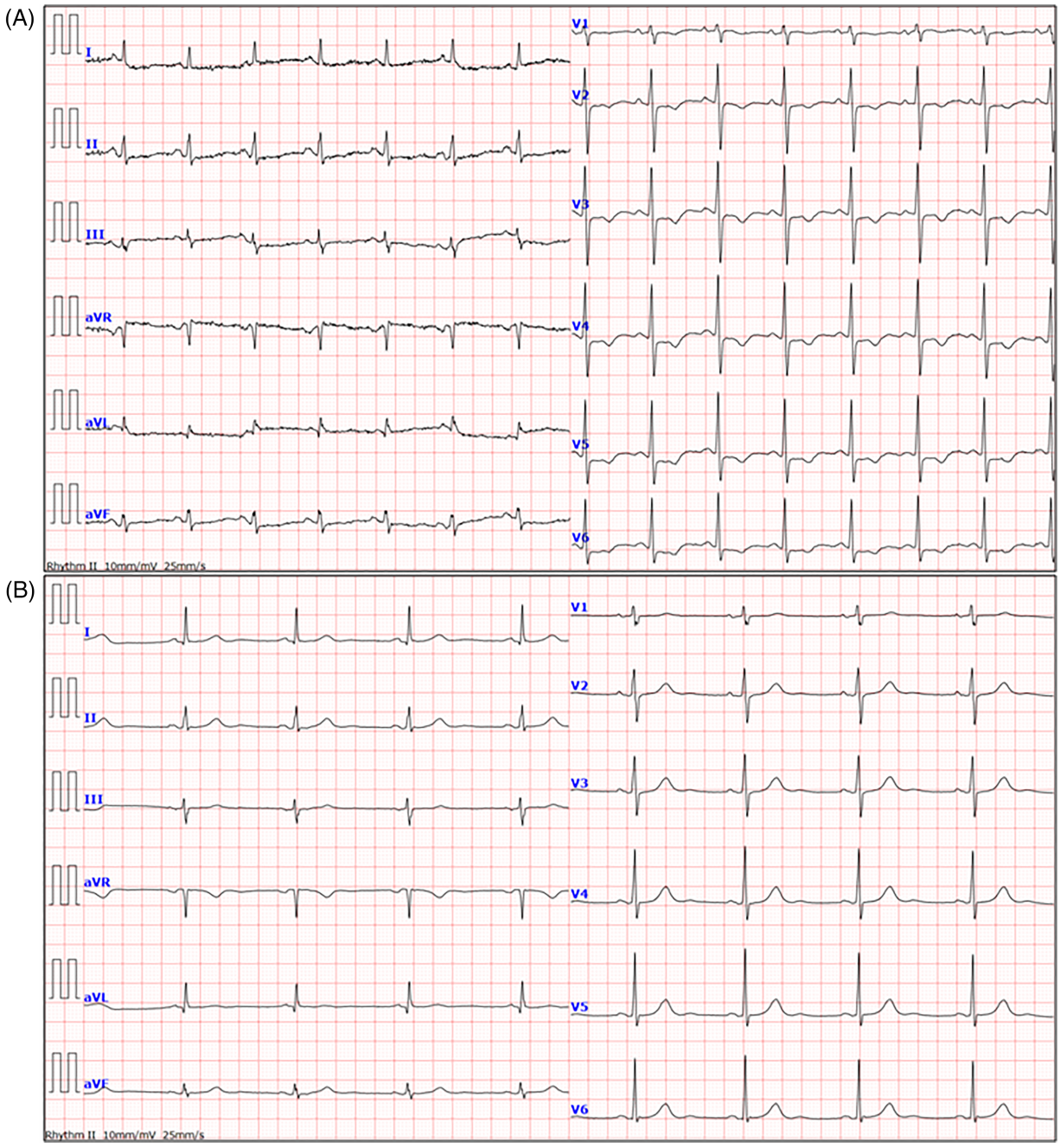
On Day 2, a cardiologist was consulted because the patient complained of worsening dyspnoea. Jugular vein distention and leg oedema were noted. Her vital signs were as follows: blood pressure, 108/62 mmHg; heart rate, 96 b.p.m.; respiratory rate, 28 breaths per minute; and oxygen saturation, 85%. Chest radiography revealed mild cardiomegaly with pulmonary congestion. Electrocardiogram (ECG) showed ST-segment depression with T-wave inversion in the precordial leads (*Figure 1A*). Follow-up echocardiography demonstrated mild left ventricular (LV) basal inferolateral wall motion abnormality with normal LV cavity size and preserved ejection fraction. Colour Doppler echocardiography revealed moderate to severe secondary mitral regurgitation (MR) (*Figure 2A* and *2B* and Supporting Information, *Movies S1* and *S2*). Echocardiographic evaluation of the right heart revealed mildly reduced systolic function with marginal right ventricular (RV) enlargement: RV basal diameter = 41 mm (reference: ≤40 mm), tricuspid annular plane systolic excursion = 20 mm (reference: ≥16 mm), and fractional area change = 30% (reference: ≥35%). Additionally, continuous-wave Doppler revealed a peak tricuspid regurgitation velocity of 3.0 m/s, consistent with a pressure gradient of 36 mmHg and an estimated RV systolic pressure of approximately 46 mmHg. Follow-up laboratory test results revealed elevated levels of liver enzymes, creatine kinase, N-terminal pro-brain natriuretic peptide (1450 pg/mL, normal <125 pg/mL), and cardiac troponin I (736.7 pg/mL, normal <26.2 pg/mL), and thrombocytopaenia. Thus, the patient was diagnosed with acute heart failure (HF) associated with acute MR. She was administered with oxygen at 6 L/min and treated with intravenous infusion of nitroglycerine (2 μg/kg/min) and intravenous loop diuretics (furosemide 20 mg daily). Her condition was haemodynamically stable; however, she was transferred to the intensive care unit for close monitoring. Although the earlier findings raised the suspicion of acute HF caused by myocardial ischaemia, coronary angiography was unremarkable. Subsequent LV endomyocardial biopsy (EMB) showed no evidence of inflammatory infiltrates. Nevertheless, cardiac magnetic resonance (CMR) revealed considerable late gadolinium enhancement (LGE) in the middle layer of the basal inferolateral cardiac wall, ranging from the left ventricle to the more distant wall of the left atrium. T2-weighted image showed a high-signal intensity in the same region (*Figure 3A–3D*). These features fulfilled the Lake Louise criteria for a diagnosis of myocarditis. Considering the peripheral eosinophilia identified during admission, the diagnosis was most likely eosinophilic myocarditis (EM). Differential diagnoses included autoimmune diseases, hypersensitivity, infectious diseases, haematological malignancies, or hypereosinophilic syndrome. Autoimmune profiles, serological tests for cardiotropic virus, and stool examination for ova and parasites were unremarkable. Further laboratory studies using blood samples collected during admission revealed that the serum total immunoglobulin E, T-helper 2 cytokine-related interleukins (ILs), including IL-4 and IL-5, and soluble IL-2 receptor levels were within normal range. Screening for the *FIP1L1–PDGFRA* fusion was negative. Therefore, a final diagnosis of VAM was made based upon the temporal relationship between rash, fever, and peripheral eosinophilia following the vaccine exposure, and myocarditis with no other identifiable cause.

After oral prednisolone (20 mg/day) in combination with esomeprazole (20 mg/day) was initiated, the patient's condition improved steadily, and all the abnormal laboratory findings during admission also improved, resulting in weaning from pharmacological support of HF. Follow-up ECG revealed the resolution of all ECG abnormalities recognized during the initial ECG (*Figure 1B*). On Day 11, she was discharged with a reduced dose of prednisolone (10 mg/day). A significant recovery from LV dysfunction and secondary MR was noted at 3 month follow-up (*Figures 2C*, *2D*, and *3E–3H* and Supporting Information, *Movies S3* and *S4*). Simultaneously, the RV dysfunction has completely recovered (RV basal diameter = 31 mm, tricuspid annular plane systolic excursion = 16 mm, and fractional area change = 40%), and no evidence of pulmonary hypertension was observed. Thereafter, prednisolone was tapered and discontinued over 3 months. The patient remains clinically stable during 1 year follow-up.

Discussion

To our knowledge, this report presents the first case of VAM concurrent with a local and systemic inflammatory reaction following pneumococcal vaccination, in which the patient developed acute HF caused by secondary MR. VAM has been observed sporadically, with the highest incidence reported so far in cases of live-attenuated smallpox vaccination.[1] The Vaccine Adverse Events Reporting System (VAERS) documented 708 cases corresponding to myopericarditis (0.1%) of the 620 195 reports between 1990 and 2018. Among them, smallpox vaccine was the most commonly reported, followed by anthrax and typhoid vaccines (59%, 23%, and 13%, respectively). Furthermore, VAERS reported that the frequency of myopericarditis after pneumococcal vaccination

Figure 1 Electrocardiogram at admission (A) and on Day 11 (B).



(pneumococcal polysaccharide, pneumococcal conjugate, 7-valent or 13-valent) was 0.006%, which was equivalent to 37 out of 620 195 reports. In addition, a cohort study analysing adverse event rates in the elderly aged ≥65 years following pneumococcal vaccination demonstrated that the frequency of acute pericarditis/myocarditis was 0.00256% (six adverse events in 313 136 doses of the 13-valent pneumococcal conjugate vaccine and eight adverse events in 232 591 doses of PPSV23, respectively).[3] These facts suggest that pneumococcal VAM is extremely rare. However, information on detailed clinical features is not available. Our case may provide several clinical pearls.

Firstly, our case highlights the advantages of CMR and the limitations of EMB in the diagnosis of myocarditis.

CMR can define myocardial tissue involvement, such as inflammation, thrombus, and fibrosis, and has an excellent

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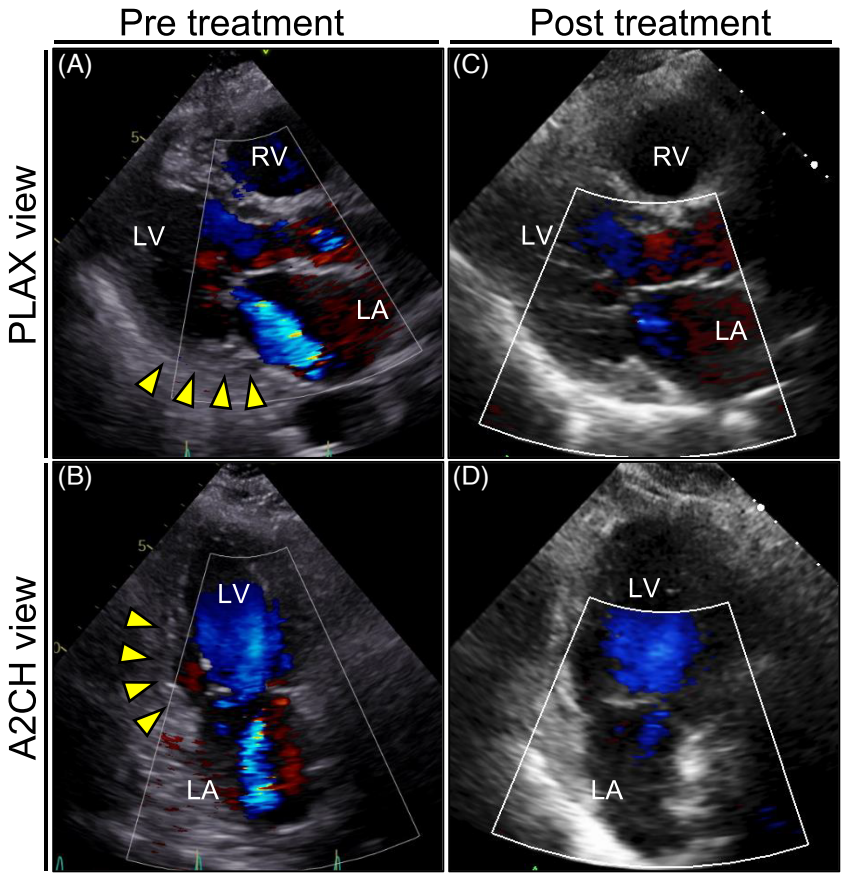
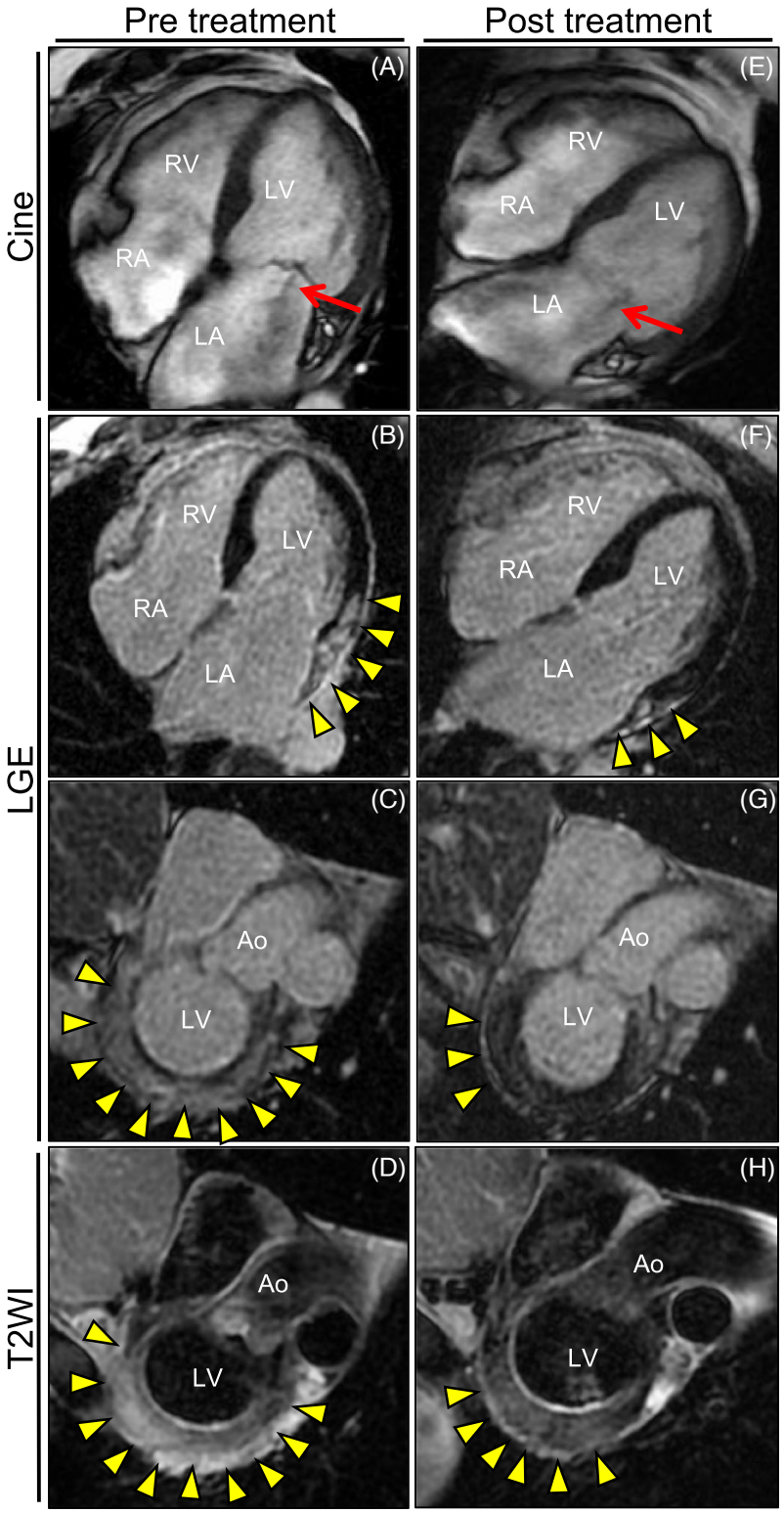
Figure 2 Effects of corticosteroid treatment on echocardiographic parameters and mitral regurgitation (MR). Colour Doppler transthoracic echocardiography (TTE) in parasternal long-axis (PLAX) view (A,C) and apical two-chamber view (A2CH) view (B,D). Initial TTE shows mild regional LV systolic dysfunction (arrowheads) accompanied by moderate to severe MR [left ventricular ejection fraction (LVEF), 57%; left ventricular diastolic diameter (LVDD), 45 mm; mitral annulus diameter, 37 mm; and tenting height, 16 mm] (A,B). A 3 month follow-up TTE shows significant improvement in LV function and MR (LVEF, 60%; LVDD, 41 mm; mitral annulus diameter, 30 mm; and tenting height, 5.5 mm) (C,D). LA, left atrium; LV, left ventricle; RV, right ventricle.



diagnostic ability in identifying patients with stable acute myocarditis (sensitivity 81%, specificity 71%, and accuracy 79%).[4] CMR was also valuable in non-histological diagnosis of VAM and monitoring of treatment response in our case. Moreover, CMR can provide important information on the distribution pattern, extent, and location of inflammatory cell infiltrates. In a multicentre study using CMR, patients with stable acute myocarditis were distributed in four patterns of distribution of LGE in the left ventricle (subepicardial layer of inferolateral wall, 41%; mid-anteroseptal wall, 36%; other segments, 16%; and non-LGE, 7%),[5] explaining the low sensitivity of blind EMB in the diagnosis of myocarditis that is usually taken from either the LV apex or interventricular septum. Similarly, the site of myocardial inflammation in our case was near the atrioventricular groove, which is a biopsy site that carries a high risk of valvular injury, ventricular perforation, or coronary artery injury and hence is strongly considered inadvisable. Given the technical difficulty for biopsy forceps to access the lesion, our EMB result was highly likely to be a sampling error. EMB is an invasive procedure yet remains the gold standard for the definitive diagnosis of VAM. Characterizing the inflammatory infiltrate in the myocardium may provide important clues to determine the respective aetiology; for example, smallpox-related VAM was characterized by a prominent mixed eosinophilic and lymphocytic infiltration with myocyte necrosis; SARS-CoV-2-related VAM shows an inflammatory infiltrate that consists predominantly of T lymphocytes and macrophages; and tetanus toxoid-related VAM showed an independent distribution of eosinophil and lymphocyte infiltrates. These findings suggest that vaccine triggered maladaptive immune-mediated myocardial injury.[6–8] Our case was finally diagnosed as VAM based on evidence of acute myocarditis, and the temporal relationship between pneumococcal vaccination and clinical signs, but the direct causal relationship and detailed mechanism remains unknown. Considering the past allergic diathesis, EM with a severe local and systemic inflammatory reaction after pneumococcal vaccination, and good response

Figure 3 Effects of corticosteroid treatment on cardiac magnetic resonance (CMR) findings. CMR findings at baseline (A–D) and at 3 month follow-up (E–H). Dynamic CMR reveals that severe mitral regurgitation (MR) (arrow) observed at baseline (A) improved significantly at a 3 month follow-up (E). A significant resolution of the late gadolinium enhancement (LGE) areas (arrowheads) at baseline (B,C) is observed at 3 month follow-up (F,G). T2-weighted image (T2WI) shows that diffuse myocardial oedema (arrowheads) observed at baseline (D) improved significantly at 3 month follow-up (H). Ao, aorta; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.



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to steroid therapy, hypersensitivity might be the most plausible mechanism of VAM in this case. Further investigation of the mechanism of pneumococcal VAM is warranted.

Secondly, corticosteroid therapy was effective for secondary MR caused by VAM. In the present case, local myocardial inflammation caused significant acute MR, resulting in acute HF, successfully treated with corticosteroid therapy. The mechanism of secondary MR in this case involves two processes: tenting of mitral leaflets secondary to regional LV remodelling and dilatation of the mitral annulus, and impaired mitral valve closure due to reduced LV and mitral annulus contraction. Interestingly, the site of myocardial inflammation in our case was the basal inferolateral wall, which is near the preferred site for ischaemic MR.[9] In view of the good clinical response to corticosteroid therapy, early detection and prompt treatment are required. Therefore, cardiac evaluation with CMR should be performed for any patient with a recent history of vaccination, presenting with unexplained *de novo* HF. Our case might shed new light on the mechanism and treatment of mechanical complications following VAM.

No evidence-based treatment regimens exist for VAM. Thus, the treatment strategy for VAM follows the guidelines for treatment of acute myocarditis[10] and comprises managing cardiovascular complications and treatment to counteract myocardial inflammation. While most VAMs are mild or resolve spontaneously,[11,12] few patients with applicable HF or arrhythmia should be treated according to the corresponding guidelines. In some cases of fulminant myocarditis or haemodynamic instability, aiding with mechanical circulatory support or cardiac transplantation should be considered as early as possible. In addition, expert consensus recommends refraining from competitive sports for 3–6 months after diagnosing myocarditis to reduce the risk of cardiac remodelling or sudden cardiac death.[10] For disease-specific treatment, apart from anecdotal supportive therapy such as non-steroidal anti-inflammatory drugs or colchicine, although limited to case reports, immunosuppressive therapy, including high-dose corticosteroids, has been suggested for patients with severe VAM given the involvement of an excessive abnormal immune response in myocardial inflammation in VAM.[6–8,13] Because a temporary association between tetanus toxoid immunization and EM has been reported,[8] it was assumed that there were specific VAM cases that can significantly benefit from corticosteroid treatment, as in our case. Further studies are needed to determine which types of VAM are good indications for immunosuppressive drugs and establish specific treatments for each VAM case.

In conclusion, to our knowledge, we encountered the first patient with pneumococcal VAM who developed significant secondary MR, successfully treated with corticosteroid. CMR was useful in reaching a definitive diagnosis and in explaining potential mechanical complications.

Conflict of interest

None declared.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Movie S1. Pre-treatment colour Doppler transthoracic echocardiography: parasternal long-axis view.
Movie S2. Pre-treatment colour Doppler transthoracic echocardiography: apical two-chamber view.
Movie S3. Post-treatment colour Doppler transthoracic echocardiography: parasternal long-axis view.
Movie S4. Post-treatment colour Doppler transthoracic echocardiography: apical two-chamber view.

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