CASE REPORT

Myocarditis secondary to smallpox vaccination

Kyle Keinath,[1] Tyler Church,[1] Benjamin Kurth,[1] Edward Hulten[2]

[1]Internal Medicine, Walter Reed National Military Medical Center, Bethesda, Maryland, USA
[2]Cardiology, Walter Reed National Military Medical Center, Bethesda, Maryland, USA

Correspondence to
Dr Kyle Keinath, kyleke@pcom.edu

Accepted 10 March 2018

SUMMARY

The development of vaccines ushered in the most profound advancement in 20th century medicine, and have widely been regarded as the one of the most important scientific discovery in the history of mankind. However, vaccines are not without risk; reactions can range from injection site reactions to life-threatening anaphylaxis. Among the more serious vaccine-related sequela is myocarditis. Although myocarditis has been reported following many different vaccines, the smallpox vaccine has the strongest association. We report a case of a 36-year-old active duty service member presenting with progressive dyspnoea, substernal chest pain and lower extremity swelling 5 weeks after receiving the vaccinia vaccination. The aetiology of his acute decompensated heart failure was determined to be from myocarditis. Although the majority of cases of myocarditis resolve completely, some patients develop chronic heart failure and even death. Vaccine-associated myocarditis should always be on the differential for patients that exhibit cardiopulmonary symptoms after recent vaccinations.

BACKGROUND

Vaccination is an integral part of primary care medicine by preventing common and sometimes life-threatening diseases.[1] Among US armed service members, vaccines are specifically used to counter bioterrorism threats such as anthrax and smallpox.[2] Like any medical intervention, vaccination is not without risk. Smallpox vaccination frequently leads to minor injection site reactions, fever, fatigue and lymphadenopathy.[2–4] More concerning is myocarditis, a known side effect of the smallpox vaccine. Initially thought to be a rare occurrence, subsequent studies have shown a higher incidence.[3–5] Retrospective studies confirmed with prospective studies show that >10% of patients receiving the smallpox vaccine develop new-onset dyspnoea, chest pain or palpitations.[3 4] Myocarditis can range from an influenza-like illness with subtle ECG changes to acute decompensated heart failure and death. It is essential not only to recognise and treat this condition, but also to properly counsel patients on all the important side effects of vaccination.

CASE PRESENTATION

A previously healthy 36-year-old Caucasian man presented after several days of palpitations, dyspnoea on exertion, paroxysmal nocturnal dyspnoea, orthopnoea and lower extremity swelling. The patient had neither personal nor family history of heart failure, premature coronary artery disease or sudden cardiac death. Of note, the patient received the smallpox vaccination 5 weeks prior to presentation, while serving in Kuwait and Iraq.

Physical examination revealed a man in mild distress. Vital signs were significant for tachypnoea and tachycardia, and oxygen saturation of 93% on ambient air. Heart sounds were distant and rate was tachycardic. Jugular venous distension was noted with prominent hepatojugular reflux. Pulmonary examination was significant for bibasilar inspiratory crackles, and examination of his extremities showed 1+ pitting oedema to the knee joints.

INVESTIGATIONS

ECG was significant for atrial flutter with 2:1 atrioventricular block, normal voltage and no ischaemic changes or T-wave abnormalities. Chest radiography revealed air space opacification and an enlarged cardiac silhouette. Laboratory studies revealed elevations in brain natriuretic peptide (549 pg/mL, normal range 0–100 pg/mL) and troponin T (10.4 ng/mL, normal <0.01). A transthoracic echocardiogram revealed global myocardial hypokinesis, depressed ejection fraction (19%), large left ventricular apical thrombus, trivial pericardial effusion and moderate mitral and tricuspid regurgitation. Computed tomographic angiography of the coronary arterial system showed no signs of coronary artery disease. Cardiac MRI with gadolinium showed elevated early global relative enhancement ratio and multiple focal areas of subepicardial, midmyocardial and transmural late gadolinium enhancement, satisfying two of the three Lake Louise tissue criteria for myocarditis.[6] The Lake Louise criteria on MRI represents oedema, hyperaemia and necrosis/scarring, that is intrinsically occurring in the myocardium secondary to an insult. Additionally, prominent subendocardial fibrosis was appreciated, a finding consistent with eosinophilic myocarditis secondary to smallpox vaccination.[7] The extensive fibrosis also suggests a subacute/chronic process opposed to the oedema seen with a more acute myocarditis.

DIFFERENTIAL DIAGNOSIS

The differential for new-onset heart failure is broad. However, given his age and lack of comorbid conditions, the typical aetiologies of cardiomyopathy were less likely (ischaemic, hypertensive, alcoholic, metabolic, etc). Ischaemia-induced heart failure was ruled out with a normal coronary CT angiogram (CTA). Evaluation with cardiac MRI confirmed myocarditis as the likely aetiology. Viral studies, including Coxsackie, adenovirus, parvovirus,

To cite: Keinath K, Church T, Kurth B, *et al*. *BMJ Case Rep* Published Online First: [*please include* Day Month Year]. doi:10.1136/bcr-2017-223523

human herpesvirus 6, herpes simplex virus and HIV, all returned negative. Patient did not report the use of medications nor excessive alcohol intake, and routine military urine drug screens were negative. The patient's myocarditis was attributed to his vaccinia exposure, as the temporal relationship to his vaccination and presentation falls within the expected time frame, of 2 to 6 weeks.[2–5]

TREATMENT

Smallpox vaccine-induced myocarditis, and myocarditis in general, is a self-limiting entity that requires supportive care (ie, guideline-directed medical therapy for heart failure, anti-arrhythmic therapy). Permanent debility and death are rarely reported.[2–4] There are only a handful of reports in which patients were given therapies aimed at the underlying cause to limit the extent of the disease. One of the proposed treatment options was prednisone with either cyclosporine or azathioprine.[5] This one randomised study of 111 myocarditis cases concluded that immunosuppression (prednisone with cyclosporine/azathioprine) was of no clinical benefit; in fact, some patients had higher rates of mortality. Intravenous immunoglobulin has also been proposed as a possible treatment modality for viral myocarditis, with some success.[8] This modality has yet to be explored in smallpox-associated myocarditis. Currently, there is insufficient evidence to support alternative therapies for myocarditis, let alone postvaccinia myocarditis, beyond the recommended supportive care.

OUTCOME AND FOLLOW-UP

The patient's arrhythmia on presentation was treated emergently with synchronised cardioversion, returning him to normal sinus rhythm. The patient's heart failure was treated with furosemide, lisinopril and carvedilol and the patient was discharged after several days with resolution of his dyspnoea on exertion and lower extremity oedema. However, carvedilol was stopped as an outpatient, due to symptomatic bradycardia. Weight-based enoxaparin was initiated for the left ventricular thrombus and bridged to warfarin for 6 months. The apical thrombus has since resolved and there has been no evidence of systemic embolisation. Most recent cardiac MRI demonstrated subendocardial, midmyocardial, transmural and posteromedial papillary muscle late gadolinium enhancement which are not significantly changed as compared with prior examinations. No new areas of late gadolinium enhancement are identified. Although the patient has minimal residual symptoms of heart failure (New York Heart Association class II), his cardiac function remains diminished after 8 months of treatment, with an ejection fracture of 30%. The patient was referred to cardiac electrophysiology for a subcutaneous implantable cardiac defibrillator implantation.

DISCUSSION

Smallpox once claimed 10% of all the deaths in the world.[8] The smallpox vaccine is a testament to the advances in medicine, eradicating one of the most deadly diseases. The risks of the vaccinia vaccine clearly outweigh the risks of smallpox infection as smallpox infection carries up to a 50% mortality rate in patients that are unvaccinated.[8] Since 2002, approximately 2 million US armed service members have been vaccinated against smallpox.[3 4] The incidence of confirmed myocarditis secondary to smallpox vaccination is estimated to be 16.1 per 100 000 service members, with a recent Department of Defense study estimating 12 per 100 000 in a review of 730 000 service members.[3–5]

As there has been only one report of viraemia in a patient with vaccinia vaccine-associated myocarditis, the pathophysiology is more likely an autoimmune phenomenon rather than an infectious process.[2] The prevailing theory suggests that the viral antigen resembles proteins on the myocardium of the patients, and their immune system cannot distinguish between the two. This 'molecular mimicry' is an immunological theory and is the best possible explanation for smallpox vaccine-associated myocarditis or any postvaccination myocarditis.[9]

Myocarditis can present in many ways. In general, one should suspect myocarditis in patients that present with new-onset heart failure, cardiogenic shock or arrhythmias. Patients are usually between the ages of 20 and 50, and may have a history of recent upper respiratory viral infection and chest pain with pleuritic variation.[10] It is imperative to rule out other possible causes of the presentation, specifically acute ischaemia (In this case given the relatively young age and no risk factors for coronary arterial disease, a coronary CTA was performed to investigate for any ongoing ischaemia; in other cases left heart catheterisation may be performed acutely).[10] After ischaemia, restrictive and hypertrophic cardiomyopathies and valvular lesions are ruled out, further investigation can be accomplished to diagnose myocarditis. The gold standard is currently cardiac biopsy. However, biopsy is not always necessary. The 2007 American Heart Association/American College of Cardiology Foundation/European Society of Cardiology issued a scientific statement on biopsy, stating class I indications for cases of (1) new-onset heart failure of less than 2 weeks duration associated with a normal size or dilated left ventricle and haemodynamic compromise; (2) new-onset heart failure of 2 weeks to 3 months duration associated with a dilated left ventricle, and new ventricular arrhythmias, second-degree or third-degree heart block or failure to

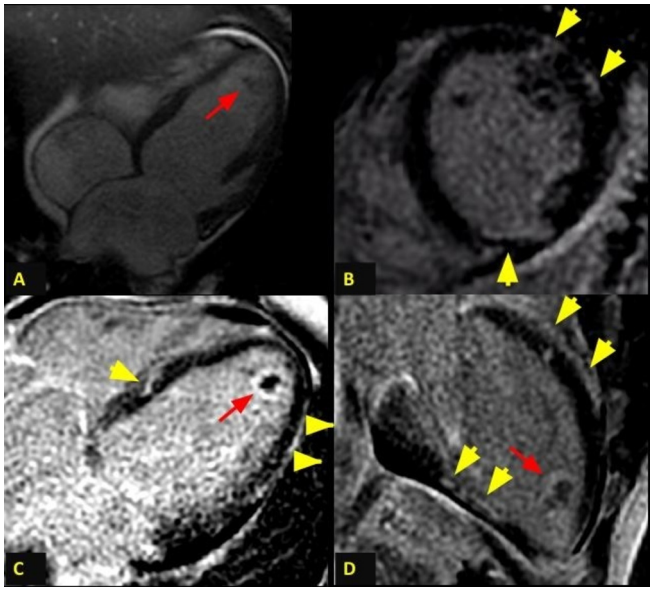

Figure 1 Four chamber cardiac MRI cine (A) with small pericardial effusion and left ventricular apical thrombus (red arrow). Late gadolinium enhancement short axis (B), four chamber (C) and two chamber (D) view demonstrating subendocardial enhancement (yellow arrows) in the midinferior segment and subepicardial enhancement (yellow arrows) in the basal to midanterior, basal anteroseptal and midanterolateral segment. There was no acute oedema indicating chronic process. Early gadolinium enhancement was abnormal. Two of three MRI criteria for myocarditis were met.[6]

respond to usual care within 1–2 weeks. Our patient did not meet the class I indication criteria.[11]

We had a strong clinical suspicion for myocarditis, given the objective data and subjective presentation. In order to confirm our suspicion, we relied on cardiac MRI rather than biopsy, given that he was not a suitable candidate for biopsy. There are specific indications for cardiac MRI in a suspected myocarditis case including currently symptomatic cases, evidence of myocardial damage and suspected viral or autoimmune aetiologies.[12] The diagnosis of myocarditis is confirmed if the imaging fulfils two out of three Lake Louise criteria defined as (1) regional or global myocardial signal intensity increase on T2-weighted images; (2) increased global myocardial early gadolinium enhancement ratio; (3) at least one focal, non-ischaemic lesion at inversion recovery late gadolinium enhancement.[12] As demonstrated in figure 1, the patient satisfied the criteria, with the additional finding of subendocardial fibrosis found in cases of eosinophilic myocarditis.[5]

In the review of the literature, the vast majority of cases are self-limiting without residual cardiac dysfunction.[2 5 13–16] Our patient significantly deviates from the majority, as evidenced by his continued reduced ejection fraction. There is a strong association with myocarditis and smallpox vaccination.[2–4] However, it is known that other vaccines can lead to cardiac disease, with reports of DTaP (diphtheria, tetanus, acellular pertussis) and influenza vaccine-associated myocarditis, although at a lower incidence.[3 17] Although vaccinations remain the cornerstone of preventative medicine, we recognise the rare, potentially life-threatening side effects such as myocarditis and its severe sequela, secondary to not only smallpox, but all vaccinations. Clinicians must remain vigilant for cardiac symptoms after vaccinations, particularly smallpox vaccinations, as this may herald the onset of myocarditis.

Learning points

- Cardiac symptoms reported after vaccination, particularly smallpox, should be investigated regardless of severity of the complaint.
- Cardiac MRI is excellent in differentiating myocarditis from other causes of myocardial dysfunction and can be used with certainty if satisfying certain criteria.
- Myocarditis secondary to smallpox vaccination is usually self-limiting, but rarely can be debilitating and life-threatening.

Contributors KK and TC wrote the case report with the guidance and mentorship of BK. The radiographic imaging was performed and interpreted by EH.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Centers for Disease Control and Prevention. *Achievements in public health, 1900-1999 impact of vaccines universally recommended for children - United States, 1990-1998 [Internet]*: Centers for Disease Control and Prevention, 2017. https://www.cdc.gov/mmwr/preview/mmwrhtml/00056803.htm
2 Cassimatis DC, Atwood JE, Engler RM, *et al*. Smallpox vaccination and myopericarditis: a clinical review. *J Am Coll Cardiol* 2004;43:1503–10.
3 Engler RJ, Nelson MR, Collins LC, *et al*. A prospective study of the incidence of myocarditis/pericarditis and new onset cardiac symptoms following smallpox and influenza vaccination. *PLoS One* 2015;10:e0118283.
4 Halsell JS, Riddle JR, Atwood JE, *et al*. Myopericarditis following smallpox vaccination among vaccinia-naive US military personnel. *JAMA* 2003;289:3283.
5 Mora LF, Khan AH, Sperling LS. Cardiac complications after smallpox vaccination. *South Med J* 2009;102:615–9.
6 Friedrich MG, Sechtem U, Schulz-Menger J, *et al*. Cardiovascular magnetic resonance in myocarditis: A JACC White Paper. *J Am Coll Cardiol* 2009;53:1475–87.
7 Syed IS, Martinez MW, Feng DL, *et al*. Cardiac magnetic resonance imaging of eosinophilic endomyocardial disease. *Int J Cardiol* 2008;126:e50–e52.
8 Mason, O'Connell H. Immunosuppressive Therapy for Myocarditis. *New England Journal of Medicine* 1995;333:1713–4.
9 Fenner F, Henderson DA, Arita I, *et al*. Smallpox and its eradication, World Health Organization. *Geneva* 1988.
10 Kohm AP, Fuller KG, Miller SD. Mimicking the way to autoimmunity: an evolving theory of sequence and structural homology. *Trends Microbiol* 2003;11:101–5.
11 Blauwet LA, Cooper LT. Myocarditis. *Prog Cardiovasc Dis* 2010;52:274–88.
12 Cooper LT, Baughman KL, Feldman AM, *et al*. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. *Circulation* 2007;116:2216–33.
13 Stouffer GA, Sheahan RG, Lenihan DJ, *et al*. The current status of immune modulating therapy for myocarditis: a case of acute parvovirus myocarditis treated with intravenous immunoglobulin. *Am J Med Sci* 2003;326:369–74.
14 Murphy JG, Wright RS, Bruce GK, *et al*. Eosinophilic-lymphocytic myocarditis after smallpox vaccination. *Lancet* 2003;362:1378–80.
15 Saurina G, Shirazi S, Lane JM, *et al*. Myocarditis after smallpox vaccination: a case report. *Clin Infect Dis* 2003;37:145–6.
16 Sharma U, Tak T. A report of 2 cases of myopericarditis after Vaccinia virus (smallpox) immunization. *WMJ* 2011;110:291–4.
17 Amsel SG, Hanukoglu A, Fried D, *et al*. Myocarditis after triple immunisation. *Arch Dis Child* 1986;61:403–5.