Recurrent epicardial ventricular tachycardia following smallpox vaccination

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Introduction

Between 1967 and 1977, a global program of smallpox vaccination resulted in the elimination of the natural disease. Following the eradication of smallpox, routine vaccination in the United States ceased by 1989. However, vaccination among military personnel was renewed in 2002, in response to the imminent Iraq war and fear of bioterrorism.[1] Since the reintroduction of the vaccine, a renewed emphasis has been placed on the risk for vaccine-related adverse events, of which cardiac complications (including sudden cardiac death) have emerged as the most frequent serious adverse events reported.

In this report, we present a patient who developed recurrent episodes of ventricular tachycardia (VT), beginning 1 month after receiving the smallpox vaccine. We present the patient's clinical course, relevant electrocardiograms (ECGs), and epicardial voltage maps. This information helps further our understanding in regard to the possible mechanism for cardiac dysrhythmia, which has been reported to occur following receipt of the smallpox vaccine.[2]

Case report

Four weeks after receiving the smallpox vaccine, a 20-year-old active duty military service member presented to the Emergency Department with a chief complaint of vomiting, as well as 3 weeks of productive cough, headache, subjective fever, fatigue, and general malaise.

An ECG revealed a wide complex tachycardia at a rate of approximately 220 beats per minute and stable systolic blood pressures in the range of 120 mm Hg. After failing to convert to normal sinus rhythm with adenosine, the patient underwent successful synchronized cardioversion. Baseline ECG following cardioversion was normal, with sinus rhythm present and no repolarization abnormality evident. The patient

was discharged with a diagnosis of idiopathic right ventricular outflow tract (RVOT) VT and was provided a prescription for metoprolol succinate.

Approximately 2 weeks after the patient's initial presentation, he presented again with VT and underwent direct current cardioversion for recurrent VT. He then underwent an electrophysiology (EP) study and ablation to the area of the posterior RVOT. Following this procedure, ambulatory rhythm monitoring failed to reveal any recurrence of his tachycardia, and cardiac magnetic resonance imaging (MRI) demonstrated no abnormality. The patient was felt to be safe to return to full duty and was subsequently deployed to an overseas location.

While deployed, the patient did well for 5 months, until he presented again with symptomatic palpitations owing to recurrent VT. A second EP study and repeat ablation for RVOT tachycardia was performed at his overseas duty location.

Unfortunately, despite these measures, the patient experienced a fourth episode of VT. Owing to the recurrent nature of the patient's VT despite repeat ablation procedures, the patient was transferred back to the United States for further EP evaluation.

Upon return to the United States, the patient underwent a third EP study. During the course of this study, a left bundle branch (LBB) morphology, inferior axis VT (Figure 1) was induced. Activation was found to be equally early in both the posterior RVOT and the left coronary cusp of the aorta. During ablation in the left coronary cusp, the outflow tract VT converted to a more apically located VT origin (Figure 1). At this point in the case, based upon the finding of multiple VT morphologies and several failed attempts at endocardial ablation, an epicardial site was suspected to be the source of the patient's recurrent tachycardia.

A fourth EP study using 3-dimensional electroanatomic mapping was performed, using the CARTO mapping system (Biosense Webster, Diamond Bar, CA). Endocardial voltage mapping demonstrated a small region of scar in the posterior free wall RVOT, which was thought to be the site of previous ablations. At the conclusion of the endocardial voltage mapping, isoproterenol was infused and VT with LBB morphology, left superior axis (similar to Figure 1) was induced following a

KEY TEACHING POINTS

- It is important to understand the inherent risk for smallpox vaccine–related adverse events, of which cardiac complications have emerged as the most frequent serious adverse events reported.

- Smallpox vaccine–mediated myocarditis is thought to be an immune-mediated process with a genetic predisposition.

- Cardiac adverse event due to smallpox vaccination is defined as chest pain, dysrhythmia, and electrocardiogram changes (eg, ST-segment and T-wave abnormalities) within 30 days of vaccination, without evidence of other cause.

- The development of ventricular scar as a consequence of vaccine-related myocarditis may serve as a focus for reentrant ventricular tachycardia.

single extrastimulation with a 500-ms drivetrain. Unfortunately, this rhythm led to hemodynamic deterioration and necessitated pace termination.

Next, epicardial access was obtained percutaneously, and epicardial electroanatomic mapping was performed on the left and right ventricles (Figure 2). Extensive mapping with over 1400 data points was obtained, which demonstrated a broad region of low voltage and fractionated electrograms in the lateral-to-posterior right ventricular (RV) free wall, from base to apex, suggestive of scar. Pace mapping revealed a region within the lateral RV epicardial surface with a 96% pace match (PASO algorithm, Biosense Webster) with the left superior axis LBB VT morphology seen in the latter half of Figure 1, but no clear late potentials were evident.

Coronary angiography was performed out of concern regarding the potential proximity of the pace-mapped region
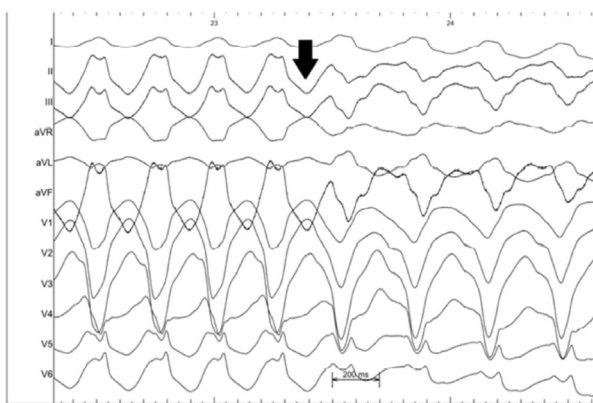
Figure 1 During ablation in the left coronary cusp of the aorta, outflow ventricular tachycardia (VT) terminated and converted to a right ventricular apical VT. The second VT was then pace-terminated. At this point, it became evident that a more extensive process was involved.

with the right coronary artery branches. Unfortunately, a 2-mm RV branch was present coursing across the region of optimal pace match. Based upon an absence of late potentials and close proximity of the RV branch to the optimal pace match location, it was decided that the inherent risk of epicardial ablation outweighed the clinical benefits. The procedure was subsequently concluded.

Discussion

After a brief cessation, smallpox vaccination among military personnel was renewed in 2002 in response to the imminent Iraq war.[1] Since the reintroduction of the vaccine, a renewed emphasis has been placed on the risk of vaccine-related adverse events. Of the possible side effects, myocarditis and pericarditis have emerged as the most frequent serious adverse events among the US Department of Defense and Department of Health and Human Services programs, estimated to occur at a rate of 117.71 per million vaccinations.[1] In a survey conducted by the Centers for Disease Control (CDC), as of 2003 there were 10 cardiac-related adverse events (of which 2 were fatal) detected among the 29,584 civilians who had received the vaccine, and 14 reported cases of myopericarditis and 1 fatal myocardial infarction among military recipients.[2]

This publication documents the development of VT in a previously healthy active duty military service member. The development of this patient's arrhythmia temporally coincides with the administration of the smallpox vaccine. According to the CDC, a cardiac adverse event due to smallpox vaccination is defined as chest pain, dysrhythmia, and ECG changes (eg, ST-segment and T-wave abnormalities) within 30 days of vaccination, without evidence of other cause. The patient reported in this document meets these criteria.[3]

It is plausible that the vaccine administration directly resulted in the development of acute myocarditis with ventricular arrhythmia. As a consequence, the patient developed cardiac scarring, which directly led to the development of recurrent scar-mediated VT not amenable to treatment with endocardial radiofrequency ablation.

In an investigation authored by Murphy and colleagues,[4] endomyocardial biopsy performed on a 29-year-old military recruit with clinical myocarditis following smallpox vaccine administration provides insight into potential mechanisms. The RV endomyocardial biopsy performed on this patient revealed severe eosinophilic-lymphocytic myocarditis and degranulating eosinophils. In addition, polymerase chain reaction for Vaccinia was negative. These findings implicate the possibility of an immune-mediated pathologic process.

In an attempt to better understand possible genetic factors associated with smallpox vaccine–associated adverse events, investigators at Vanderbilt University performed genetic testing on 96 individuals prior to their receiving the smallpox vaccine. Interestingly, there were 3 variant genotypes, which were confirmed to be associated with patients who experienced smallpox vaccine–associated adverse events. These
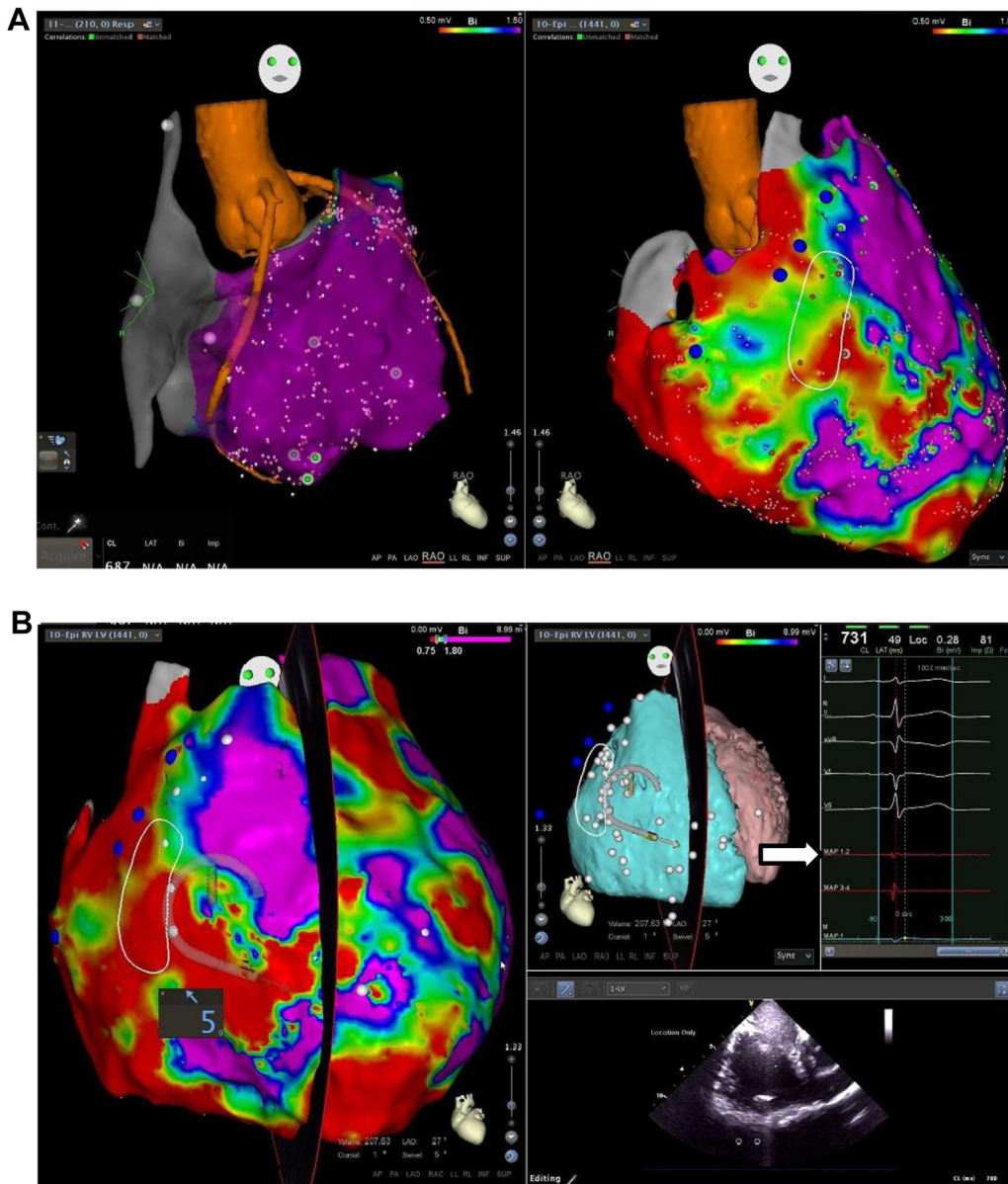
Figure 2   CARTO voltage maps, intracardiac electrogram, and computed tomography integration of aortic root and coronary arteries. **A:** Endocardial (upper left) and epicardial (upper right) voltage maps in the right anterior oblique (RAO) projection with normal tissue (*purple*) reference of 1.5 mV. A small region of endocardial scar is seen on the posterior aspect of the right ventricular (RV) outflow tract over the right coronary cusp corresponding to the region of prior endocardial/aortic root ablation. A significant region of epicardial scar is seen on the lateral RV wall extending to the posterior wall. The *blue dots* delineate atrioventricular groove points; the *white circle* marks a broad site of greater than 90% pace match points to the induced hemodynamically unstable ventricular tachycardia. **B:** Catheter positioning against the RV free wall, along with measured contact force (5 *g*). A large region of low voltage involving the lateral right ventricle is evident on voltage mapping. Simultaneous intracardiac electrogram (right) shows low voltage potentials (*arrow*, 0.28 V) suggesting possible scar. Intracardiac echocardiographic (below right) imaging shows no pericardial effusion. The presence of epicardial scar is not definitive in this region solely by low voltage owing to perivascular and RV epicardial fat in this region, and the absence of late and split potentials suggests the possibility of this being normal. This is equally as likely as there being scarring not detected by magnetic resonance imaging.

variants included 1 single nucleotide polymorphism in the Methylene Tetrahydrofolate Reductase (*MTHFR*) gene and 2 single nucleotide polymorphisms present within the Interferon Regulatory Factor 1 (*IRF1*) gene. These genes are all potentially involved in pathways involving excess stimulation of inflammatory pathways[5] leading to T-cell cytokine stimulation. This study further supports a potential immune-mediated process occurring among genetically susceptible individuals who receive the smallpox vaccine.

An interesting aspect of this case is the manner of presentation, as recurrent episodes of VT that were refractory to endocardial ablation. As a result, epicardial mapping was performed, which demonstrated a broad region of low voltage within the lateral-to-posterior free RV wall from base to apex. This finding suggests the presence of a broad region of myocardial scarring, potentially confirming extensive myocardial damage that may have occurred as a result of a vaccine-related myocarditis.

Other considerations in this case would be a completely unrelated disease process such as arrhythmogenic ventricular cardiomyopathy (ARVC), which can often involve the epicardial surfaces preferentially. However, our clinical suspicion for ARVC was exceedingly low, as there was no evidence on imaging of structural criteria for ARVC, no repolarization abnormality evident on 12-lead ECG to suggest ARVC, and no family history of this condition. In addition, as part of our investigation, genetic testing performed for known ARVC variants demonstrated no known pathogenic mutations.

Cardiac sarcoidosis was also considered unlikely. The patient has no evidence of extracardiac sarcoidosis, normal LV function by echocardiography and MRI, no evidence of late gadolinium enhancement on MRI, and no evidence of heart block on ambulatory rhythm monitoring or serial ECG. Thus the patient does not meet criteria for the diagnosis of this condition.

Ultimately, at this time we cannot exclude the possibility of a separate process from smallpox vaccination–induced myocarditis, as clinical criteria and genetic testing have limited sensitivity in the absence of tissue confirmation; there remains an important percentage of patients who are diagnosed with ARVD or cardiac sarcoid at autopsy, despite an absence of clinical criteria.[6,7]

Superficial RV scar went undetected by MRI in this patient's case, yet was suggested by epicardial voltage mapping, which demonstrated a broad area of low voltage within the right ventricle. This discrepancy may be explained by the findings of several small studies, which demonstrate that voltage mapping consistently outperforms MRI for detecting scar in the right ventricle.[8,9] This is owing to rather limited spatial resolution (as a consequence of the thin RV free wall diameter and significant RV motion artifact), which contributes to a lowered sensitivity. Because of limited sensitivity, RV fat / fibrosis by MRI was removed from the 2010 ARVC task force criteria in favor of quantitative volumes, ejection fraction, and wall motion. Newer data suggest that shorter inversion times (which are normally designed to null LV myocardial signal) may be needed to better image the RV wall and epicardial surface.[10]

Given the inability to eliminate the patient's tachycardia circuits, in part owing to anatomic constraints of his native epicardial vessels, the patient was maintained on sotalol for arrhythmia suppression, and a single-chamber implantable cardioverter-defibrillator was implanted for prevention of sudden death. Unfortunately, this diagnosis and condition were not compatible with continued service in the active duty force, and he was medically retired.

To date, 7 cases of postvaccination cardiac dysrhythmia have been reported to the CDC (supraventricular tachycardia, atrial dysrhythmias, and frequent premature ventricular contractions).[3,11] However, this is the first report, to our knowledge, of recurrent symptomatic, sustained VT in a patient following the administration of the smallpox vaccine, and this report presents a potential case of smallpox vaccine–mediated dysrhythmia.

Acknowledgments

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