

# A Report of 2 Cases of Myopericarditis after Vaccinia Virus (Smallpox) Immunization

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## ABSTRACT

**Background:** To counter the possibility of smallpox being used as a biological weapon, in 2002 the US government restarted a smallpox vaccination campaign. Myopericarditis is a possible cardiac complication of smallpox vaccination. We report 2 cases of vaccine-associated myopericarditis in military recruits who were treated at our facility. Chest pain, shortness of breath, and electrocardiographic changes of pericarditis, with a recent history of smallpox vaccination, were useful in making the diagnosis of probable post-vaccinial myopericarditis. Nonsteroidal, anti-inflammatory drugs (NSAIDs) were used to manage myopericarditis. Both patients had complete resolution of symptoms and electrocardiographic changes and subsequently returned to active duty.

**Conclusion:** Myopericarditis should be suspected when patients with recent history of smallpox vaccination present with chest pain or shortness of breath. Nonsteroidal anti-inflammatory drugs are useful in the management of post-vaccinial myopericarditis.

## CASE REPORT 1

A 27-year-old male soldier presented with sudden, new onset, sharp, severe left chest pain radiating to his left arm that woke him from sleep. Because the pain lasted for a few hours, he was seen by an on-staff physician and given ibuprofen, which temporarily relieved the chest pain. He continued to have intermittent chest pain throughout the day and was seen at a local emergency department (ED) overnight. A 12-lead electrocardiogram (ECG) revealed sinus rhythm with diffuse ST segment elevations in most of the leads (Figure 1) with a troponin of 4.87 ng/ml and creatinine kinase of 511 units/L. He had received a smallpox vaccine 2 weeks prior to presentation. Two days prior, he also was diagnosed with vaccination-site cellulitis and was started on Bactrim, which was later switched to clindamycin. Thereafter, he developed a facial rash and recur-

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rent chest pain, prompting him to visit the local ED. After myopericarditis was considered likely, the patient was transferred to our facility for further evaluation and treatment.

The patient did not have any past cardiac problems. He was a nonsmoker and did not consume alcohol or recreational drugs. His family history was negative for cardiovascular diseases.

Clinical examination revealed a facial rash, 1 cm-eschar at vaccination site with 0.75 cm-area of surrounding erythema without any active discharge (Figure 2).

He had regular heart sounds with a rub and no murmur. The rest of his clinical examination was unremarkable. The patient was seen by cardiology, who advised that he continue on ibuprofen for presumed myopericarditis. He was started on cephalhexin for arm cellulitis. A transthoracic echocardiogram obtained the following day revealed normal left ventricular size and function, absence of regional wall motion abnormalities, pericardial thickening, and a tiny posterior pericardial effusion. The patient was monitored for 2 days on telemetry floor, where he remained asymptomatic and had resolution of his electrocardiographic changes. He was discharged home with ibuprofen. He continued to stay asymptomatic with no activity limitations and had a normal echocardiogram (ECHO) at a 4-week cardiology clinic follow-up visit.

## CASE REPORT 2

A 41-year-old male soldier visited a local ED with a 2-day history of weakness, reduced exercise tolerance, night sweats, and mid-sternal, nonradiating, nonexertional, dull chest pain. The patient had regular heart sounds without murmurs or rub and no signs of congestive heart failure. ECG revealed diffuse ST segment elevations (Figure 3) with a troponin of 18 ng/ml. He underwent emergent cardiac catheterization for presumed ST elevation myocardial infarction revealing minimal (nonsignificant) coronary artery disease. He had received a smallpox vac-

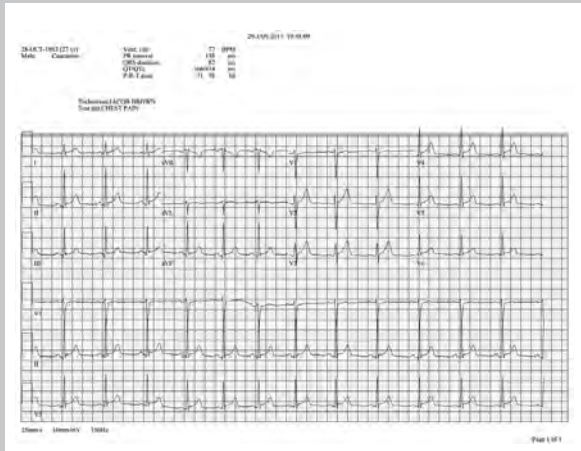


Figure 1. Twelve-lead ECG in Case #1.

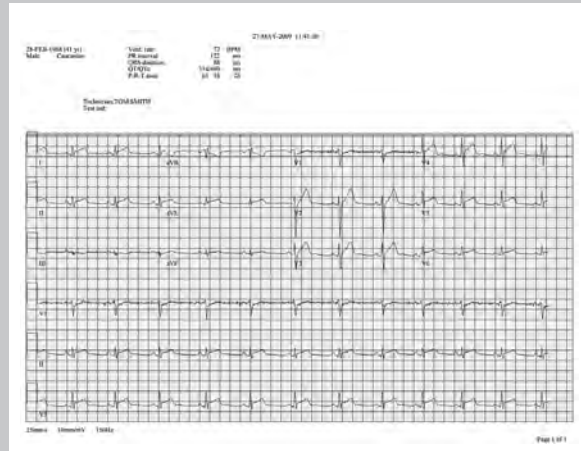


Figure 3. Twelve-lead ECG in Case #2.



Figure 2. Eschar developing on left upper extremity 2 days post-vaccination.



Figure 4. Image of cardiac magnetic resonance imaging (MRI) showing patchy and diffuse myocardial enhancement.

ination 10 days earlier; it was suspected that his symptoms were related to smallpox vaccine-related myopericarditis. He was monitored on telemetry and started on indomethacin. An echocardiogram revealed normal left ventricular ejection fraction with thick pericardium consistent with pericarditis. A cardiac magnetic resonance imaging (MRI) scan revealed patchy diffuse mid-myocardial enhancement consistent with myocarditis (Figure 4). His clinical condition improved in a couple of days. However, he had improved but persistent ST-segment elevations and was discharged home on indomethacin. At a 4-week cardiology clinic visit, the patient had a normal ECG and a satisfactory stress test with improvement in pericardial thickening on echocardiography. He subsequently returned to active duty.

## DISCUSSION

Small pox is a devastating disease that is caused by the variola virus. It has been declared eradicated after an aggressive, widespread vaccination campaign in 1980. In the United States, routine childhood vaccinations were stopped in 1972; they were stopped worldwide in 1982.<sup>1</sup> However, the military did not stop all smallpox vaccinations until 1990.<sup>2</sup> In the last decade, the US military restarted a campaign of smallpox vaccination with vaccinia virus to counteract the threat of bioterrorism using smallpox.<sup>3</sup> More than 540,000 personnel received smallpox vaccines between December 2002 and June 2003.

As a result of these vaccines, there has been 1 case of encephalitis and 67 cases of acute myopericarditis with no clinical case of eczema vaccinatum, progressive vaccinia, or attributed

death.<sup>2,4</sup> In January 2003, voluntary smallpox vaccinations were restarted for health care and public health workers. In the first 2 months, among 25,645 civilians who received vaccine, 7 cardiac-related events, including 2 fatal ones, were reported. Smallpox vaccine-related myopericarditis has been reported among those receiving primary vaccination and revaccination.<sup>5</sup>

Smallpox vaccine is made from vaccinia, a live DNA virus that cross-protects against smallpox. Common side effects include local itching (60%), myalgia (21%), malaise (20%), headache (18%), lymphadenopathy (14%), bandage reaction (7.4%), generalized pruritus (5.5%), fever (5.3%), local rash (5.3%), and generalized rash (1.1%). Rare side effects include generalized vaccinia (80 per million), inadvertent self-inoculation (107 per million), vaccinia transfer to contacts (47 per million), acute myopericarditis (82 per million), and encephalitis (2.2 per million).<sup>3</sup> Other rare adverse effects include eczema vaccinatum, fetal vaccinia, ocular vaccinia, and, rarely, death.<sup>2,3</sup>

Contraindications to smallpox vaccination include history of atopic dermatitis or active skin conditions that disrupt the epidermis, pregnancy, immunosuppressed states, and age >50 years with cardiac and vascular disease.<sup>1,2</sup>

Myocarditis and pericarditis often occur together. The term myopericarditis is indicative of a predominately pericarditic syndrome with minor myocardial involvement. The most common viruses that are known to cause myopericarditis include Coxsackieviruses (especially Coxsackie B), cytomegalovirus, adenovirus, influenza virus, echovirus, parvovirus B19, and, rarely, post-smallpox vaccination.<sup>4,5</sup>

### Clinical Presentation of Myopericarditis

The symptoms of myopericarditis are highly variable but usually include shortness of breath, chest pain, fever, and arrhythmias. A 2004 study by Eckart reviewed 67 cases of myopericarditis among 540,824 vaccinees within 30 days of vaccination.<sup>6</sup> Ninety-one percent of patients exhibited prodromal symptoms, 57.4% of patients exhibited fever and chills, 31.2% had myalgias and/or arthralgias, and 34.4% experienced headache, viral syndrome, and fatigue. A small group, 14.7%, did not have any symptoms besides chest pain. All patients presented with chest pain or substernal pressure.<sup>6</sup>

Sudden cardiac death also has been reported after vaccination, most likely caused by malignant arrhythmias due to dilated cardiomyopathy.<sup>7</sup> Myopericarditis may cause patients to present with symptoms and signs similar to acute coronary syndrome; however, they are more likely to have blunted increase and decrease of cardiac biomarkers and less likely to have regional wall motion abnormality on echocardiogram.<sup>8</sup> A 2007 study by Eckart showed that rates of cardiac ischemic events in the 30-day period following smallpox vaccination

**Table I.** Criteria Used for Diagnosing Myopericarditis

Level of Suspicion	Description of Criteria
<b>Myocarditis</b>	
<b>Suspected myocarditis</b>	
<ol style="list-style-type: none"> <li>Symptoms (palpitations, chest pain, dyspnea)</li> <li>ECG abnormalities beyond normal variants, not documented previously (ST/T abnormality, paroxysmal supraventricular tachycardia, ventricular tachycardia, atrioventricular block, frequent atrial or ventricular ectopy) OR focal or diffuse depressed LV function of uncertain age by an imaging study</li> <li>Absence of evidence of any other likely cause</li> </ol>	
<b>Probable myocarditis</b>	
<ol style="list-style-type: none"> <li>Meets criteria of suspected myocarditis</li> <li>In addition, meets 1 of the following: elevated levels of cardiac enzymes (creatine kinase-MB fraction, troponin T or I) OR new onset depressed LV function on imaging consistent with myocarditis (MRI with gadolinium, gallium-67 scanning, anti-myosin antibody scanning)</li> </ol>	
<b>Confirmed myocarditis</b>	
<ol style="list-style-type: none"> <li>Histopathologic evidence of myocarditis by endomyocardial biopsy or an autopsy</li> </ol>	
<b>Pericarditis</b>	
<b>Suspected pericarditis</b>	
<ol style="list-style-type: none"> <li>Typical chest pain (made worse by supine position, improved with leaning forward, pleuritis, constant)</li> <li>No evidence of alternate cause of such pain</li> </ol>	
<b>Probable pericarditis</b>	
<ol style="list-style-type: none"> <li>Meets criteria of suspected pericarditis</li> <li>Has 1 or more of the following: pericardial friction rub on auscultation, or ECG with diffuse ST-segment elevations of PR-segment depressions not previously documented, or Echocardiogram revealing an abnormal pericardial effusion</li> </ol>	
<b>Confirmed pericarditis</b>	
<ol style="list-style-type: none"> <li>Histopathologic evidence of pericardial inflammation in pericardial tissue from surgery or autopsy</li> </ol>	
<p>Reproduced and adapted from CDC website, CDC. Update: Cardiac-related events during the civilian smallpox vaccination program—United States, 2003;52(21):492-496.<sup>10</sup></p>	

is similar to nonvaccinated military population (140.1 and 143.5 per 100,00 person-years, respectively).<sup>9</sup>

### Diagnosis of Myopericarditis

Criteria used for diagnosis of myopericarditis are summarized in Table 1.<sup>10</sup> Recent history of smallpox vaccination, ECG changes of myopericarditis, and elevated cardiac biomarkers are essential in diagnosis of myopericarditis. Echocardiogram is useful in assessing the left ventricular function and wall motion abnormalities, and in identifying a pericardial effusion or tamponade. Postgadolinium MRI show focal enhancement in acute myocarditis, but within a week the involvement is diffuse. These changes have a specificity and sensitivity of 100%.<sup>11</sup> Cardiac catheterization is indicated to rule out or diagnose isch-

emic heart disease. Endomyocardial biopsy is the gold standard, but it may not be useful due to the patchy nature of the disease; it also carries procedure-related risks.<sup>1</sup> Biopsy reveals patchy or diffuse myocytolysis and intense infiltration with inflammatory cellular products with no evidence of active vaccinia infection, suggesting immune-mediated inflammation.<sup>5,6,12</sup>

US military smallpox vaccination data revealed onset of vaccine-associated myopericarditis about  $10.4 \pm 3.6$  days after vaccination with 57% incidence of ST-segment elevation and a mean troponin of  $11.3 \pm 22.7$  ng/ml. Ninety-six percent of patients had normalization of ECHO and ECG findings around 32 weeks of follow-up.<sup>6</sup>

### Treatment of Myopericarditis

Vaccinia-associated myopericarditis is inflammatory in nature; hence nonsteroidal anti-inflammatory drugs (NSAIDs) are used for symptom relief and usually given for 2 weeks.<sup>6</sup> Rest and avoidance of high-level exertion is advisable for 4 to 6 weeks. Complications like heart failure and arrhythmias need to be managed similar to heart failure/arrhythmias from any other cause. Steroids and immunosuppressive medications have been used in isolated case reports; however, their benefits have not been proven in case-controlled studies. Vaccinia immune globulin inhibits active viral replication and has been used in treatment of noncardiac complication of smallpox vaccine, but is not recommended for treatment of myopericarditis.<sup>1</sup>

### CONCLUSION

Myopericarditis should be suspected when patients present with chest pain or shortness of breath within a month of receiving a smallpox vaccine. Chest pain, typical ECG changes, elevated cardiac biomarkers, and a recent history of smallpox vaccination are essential in diagnosis of myopericarditis. NSAIDs are useful in management of post-vaccinial myopericarditis. Most patients have complete resolutions of symptoms and ECG and ECHO changes, and have full functional recovery. Some

authors suggest electively checking an ECG 10 to 14 days after vaccination especially for those vaccinees >40 years of age.<sup>13</sup>

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