Journal of the American College of Cardiology
© 2004 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 44, No. 1, 2004
ISSN 0735-1097/04/$30.00
doi:10.1016/j.jacc.2004.05.004

EXPEDITED REVIEW

Incidence and Follow-Up of Inflammatory Cardiac Complications After Smallpox Vaccination

Robert E. Eckart, DO,* Suzanne S. Love, MD, MPH,† J. Edwin Atwood, MD,‡ Mark K. Arness, MD,§ Dimitri C. Cassimatis, MD,‡ Charles L. Campbell, MD,‖ Sheri Y. Boyd, MD,* Joseph G. Murphy, MD,¶ David L. Swerdlow, MD,# Limone C. Collins, MD,** James R. Riddle, DVM, MPH,†† David N. Tornberg, MD, MPH,†† John D. Grabenstein, RPH, PHD,‡‡ Renata J. M. Engler, MD,** for the Department of Defense Smallpox Vaccination Clinical Evaluation Team

San Antonio, Texas; Washington, DC; Portsmouth and Falls Church, Virginia; Rochester, Minnesota; and Atlanta, Georgia

OBJECTIVES The purpose of this study was to assess the follow-up of patients with vaccinia-associated myocarditis.

BACKGROUND With the threat of biological warfare, the U.S. Department of Defense resumed a program for widespread smallpox vaccinations on December 13, 2002. One-year afterwards, there has been a significant increase in the occurrence of myocarditis and pericarditis among those vaccinated.

METHODS Cases were identified through sentinel reporting to military headquarters, systematic surveillance, and spontaneous reports.

RESULTS A total of 540,824 military personnel were vaccinated with a New York City Board of Health strain of vaccinia from December 2002 through December 2003. Of these, 67 developed myopericarditis at 10.4 ± 3.6 days after vaccination. The ST-segment elevation was noted in 57%, mean troponin on admission was 11.3± 22.7 ng/dl, and peak cardiac enzymes were noted within 8 h of presentation. On follow-up of 64 patients (96%) at a mean of 32 ± 16 weeks, all patients had objective normalization of echocardiography, electrocardiography, laboratory testing, graded exercise testing, and functional status; 8 (13%) reported atypical, non-limiting persistent chest discomfort.

CONCLUSIONS Post-vaccinial myopericarditis should be considered in patients with chest pain within 30 days after smallpox vaccination. Normalization of echocardiography, electrocardiography, and treadmill testing is expected, and nearly all patients have resolution of chest pain on follow-up. (J Am Coll Cardiol 2004;44:201–5) © 2004 by the American College of Cardiology Foundation

The current U.S. Department of Defense (DoD) Smallpox Vaccination Program began on December 13, 2002, to counter the potential release of variola virus as an act of terrorism against U.S. military forces (1). Through April 2004, the DoD has immunized over 615,000 personnel. This represents the largest smallpox vaccination program since the eradication of smallpox in 1977 (2).

Although sporadic cases of myocarditis and pericarditis were reported with various strains of smallpox vaccine (3), these complications were unexpected with the current strain of smallpox vaccine (New York City Board of Health [NYCBOH] strain) (4,5). The DoD clinicians detected a statistically elevated rate of myopericarditis above background levels after smallpox vaccination (6,7). Between December 2002 and December 2003, a total of 67 cases of myopericarditis within 30 days after smallpox vaccination were identified among 540,824 vaccinees, based on a consensus case definition (8).

From the U.S. Army Medical Command, *Brooke Army Medical Center, Fort Sam Houston, Texas, and ‡Walter Reed Army Medical Center, Washington, DC; Vaccine Healthcare Center, †Naval Medical Center, Portsmouth, Virginia, and **Washington, DC; §Army Medical Surveillance Activity, Washington, DC; ‖Wilford Hall Medical Center, Lackland Air Force Base, San Antonio, Texas; ¶Mayo Clinic and Foundation, Rochester, Minnesota; #Centers for Disease Control and Prevention, Atlanta, Georgia; and ††Office of the Assistant Secretary of Defense for Health Affairs and the ‡‡Military Vaccine Agency, U.S. Army Medical Command, Falls Church, Virginia. The views expressed in this study are those of the authors and do not reflect the official policy or position of the U.S. government.

Manuscript received April 10, 2004; revised manuscript received April 20, 2004, accepted May 4, 2004.

METHODS

Surveillance for adverse events. The DoD Smallpox Vaccination Program emphasized post-vaccination adverse-event surveillance and patient education (1). Vaccinees received full-strength concentration of smallpox vaccine (Dryvax, Wyeth Laboratories, Marietta, Pennsylvania), which contains the NYCBOH strain. Cases of myopericarditis were detected through surveillance methods previously described (1,6). Guidelines were published alerting providers to the diagnostic criteria and encouraging them to report cases using the Vaccine Adverse Event Reporting System. The Vaccine Healthcare Centers Network collected patient data in a centralized registry.

Case identification. Cases were classified by a committee based upon surveillance case definitions for myocarditis and

Report Documentation Page

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
20 APR 2004		**00-00-2004 to 00-00-2004**

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
Incidence and Follow-Up of Inflammatory Cardiac Complications After Smallpox Vaccination	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)	5d. PROJECT NUMBER
	5e. TASK NUMBER
	5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) **Army Surgeon General's Office,Military Vaccine (MILVAX) Agency,5113 Leesburg Pike,Falls Church,VA,22041**	8. PERFORMING ORGANIZATION REPORT NUMBER
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			
unclassified	**unclassified**	**unclassified**	**Same as Report (SAR)**	**5**	

Abbreviations and Acronyms

CK = creatine kinase
DoD = Department of Defense
ECG = electrocardiogram
MI = myocardial infarction
NYCBOH = New York City Board of Health

pericarditis (6,8). These definitions included "possible or suspect myopericarditis" if patients had symptoms without objective pathologic manifestation of disease; "probable myocarditis" if elevated cardiac enzymes were present, and "probable pericarditis" if patients had pathologic electrocardiographic (ECG) changes or pathologic pericardial effusion. "Confirmed" cases had histopathologic evidence of myocardial inflammation (8). Temporal association was defined as occurrence of symptoms or diagnosis within 30 days of vaccination. Suspect cases were excluded from this analysis.

Statistical analysis. Statistical analysis was performed using JMP Professional Software 5.0.1 (SAS Institute Inc., Cary, North Carolina). The Student *t* test was used to compare continuous variables. Yate's corrected chi-square test was used for categorical variables, with the Fisher exact test used if cells had <5 responses in any one group. The p values were considered statistically significant when <0.05.

Clinical follow-up protocol. Standardized guidelines for patient follow-up developed by DoD and first distributed on June 9, 2003, advocated repeat clinical evaluation and laboratory investigation including ECG, echocardiography, and functional stress testing at 6 to 12 weeks, when feasible (9). Patients with persistent symptoms were transferred at the discretion of the clinician to regional military tertiary-care hospitals.

RESULTS

Demographics. The clinical characteristics of all 67 cases of probable or confirmed post-vaccinial myopericarditis reported among 540,824 total vaccinees are summarized in Table 1. The cases were predominantly male (n = 66; 98.5%) and Caucasian (n = 60; 89.6%).

Table 1. Demographics of Patients With Vaccinia-Associated Myopericarditis

	Total Cases (n = 67)
Age (yrs)	26.6 ± 5.2 (18.8–43.0)
Ethnicity	
Caucasian	60 (89.5)
African-American	4 (6.0)
Hispanic	2 (3.0)
Asian	1 (1.5)
Gender	
Male	66 (98.5)
Female	1 (1.5)
Days from vaccination to evaluation	10.4 ± 3.6 (3–25)
Weeks to follow-up	31.0 ± 16.0 (1.6–58.1)

Continuous variables are expressed as mean ± SD (range). Categorical variables are expressed as raw data (percent of column total).

Table 2. Vital Signs and Electrocardiographic Parameters in Patients With Vaccinia-Associated Myocarditis

	Presentation (n = 61)	Follow-Up (n = 44)
Systolic blood pressure, mmHg	114 ± 11	121 ± 13
Diastolic blood pressure, mmHg	73 ± 8	73 ± 10
Heart rate, beats/min	74 ± 17	74 ± 14
Sinus rhythm	61 (100%)	41 (100%)
PR interval, ms	150 ± 22	150 ± 24
QRS duration, ms	90 ± 9	91 ± 9
QT interval, ms	373 ± 43	378 ± 27
Pathologic ST-segment elevation*	35 (57.4%)	0 (0.0%)

$p > 0.05$ for all comparisons. Continuous variables are expressed as mean ± SD. Categorical variables are expressed as raw data (percent of column total). *Pathologic electrocardiogram changes were defined as a new finding of ST-segment elevation ≥1 mm (0.1 mV) elevation in two or more contiguous leads.

Clinical presentation. All 67 cases presented initially with chest pain or substernal pressure. Prodromal symptoms were documented in 61 (91.1%) patients. Fever and chills were noted in 35 (57.4%) patients; myalgias and/or arthralgias in 19 (31.2%) patients; and headache, non-specific viral syndrome, and fatigue reported in 26 (34.4%) patients. Nine patients (14.7%) had no prodromal syndrome until chest pain prompted medical evaluation.

Follow-up data became available on 64 (96%) patients at a mean of 32 ± 16 weeks after presentation (until April 15, 2004). Two of the other three patients self-reported as healthy but voluntarily separated from military service and declined to return for follow-up care; one patient died during hospitalization. Eight (13%) patients reported continued atypical, non-specific chest discomfort, three (5%) patients reported continued fatigue, and two (3%) reported complaints of headache. Except for the single fatality, in no case did symptoms disqualify patients from continued active military service.

The single fatality occurred 33 days after multiple vaccinations. The case was reviewed by two independent groups of physicians, who judged the fatality as possibly associated with vaccination, although a definitive link to smallpox or any other specific vaccine could not be established (1,10–13).

Cardiac catheterization. Catheterization with coronary angiography was performed in 29 (43.2%) patients, with none revealing flow-limiting coronary atherosclerotic lesions. The mean left ventricular end-diastolic pressure was 16 ± 5 mm Hg (range 9 to 22 mm Hg).

Electrocardiography. Electrocardiography during initial presentation was reviewed in 61 (91.0%) patients. Six other patients did not have available ECG data, because initial treatment was in remote locations. Sinus rhythm was present in all 61 ECGs reviewed, and an identifiable abnormality was evident in 46 (75.4%). The most common abnormalities were ST-segment changes, evident in 40 (65.6%) patients; 5 (8.2%) had normal variant early repolarization as defined by Wang et al. (14), and T-wave abnormalities were noted in 11 (18.0%) (Table 2). Two ECGs showed incomplete right bundle branch block, and

Table 3. Echocardiography and Vaccinia-Associated Myopericarditis

	Presentation (n = 57)	Follow-Up (n = 40)
LV ejection fraction	55 ± 8	60 ± 3*
30% to <40%	5 (9.0)	0 (0.0)
40% to <55%	13 (23.0)	1 (2.5)
≥55%	39 (68.0)	39 (97.5)
Pericardial effusion	7 (12.3)	0 (0.0)†
Regional wall motion abnormality	8 (14.0)	0 (0.0)*
$LVID_{ed}$, cm	5.0 ± 0.6	4.9 ± 0.5
$LVID_{es}$, cm	3.4 ± 0.6	3.2 ± 0.5

*$p < 0.05$, †$p = 0.04$ by one-tailed Fisher exact test.
ed = end-diastolic; es = end-systolic; ID = internal dimension; IVS = interventricular septum; LV = left ventricle.

two ECGs showed PR depression. Focal ST-segment elevation was more common than diffuse change, with inferior and inferolateral ST-segment elevation accounting for 45% of pathologic changes.

Forty-four of the 61 patients were matched with a follow-up ECG (72%). These ECGs, obtained from 20 to 362 days (median 108 days) from initial presentation, revealed normalization of pathologic ST-segment elevation and T-wave inversions in all patients; non-specific changes from initial presentation remained evident in only one patient.

Laboratory studies. Cardiac enzymes were elevated in 60 of 61 (98.4%) patients evaluated with this assay. The three cases with troponin-T elevation were excluded from further analysis. Original quantitative laboratory reports (excluding qualitative reports of troponin "positive" or "negative") were available for 54 of 60 cases (81.6%). The mean peak creatine kinase (CK) was 510 IU/l (range 58 to 1,425 IU/l), and mean peak troponin-I was 14.1 ng/ml (range 0.12 to 139.10 ng/ml). Peak CK and troponin-I were collected at a median of 1.5 and 6.9 h, respectively, from presentation with chest pain.

In four cases where myocardial tissue was obtained, there was no evidence of active vaccinia infection by culture or deoxyribonucleic polymerase chain reaction assays. In the three cases of right ventricular biopsy, inflammatory changes were found: one with no clear cellular infiltrate, one with mild lymphocytic infiltrate, and a third with eosinophilic infiltrate predominance (15). In the fatal case, in which prolonged pulmonary illness preceded cardiac enzyme elevation, postmortem examination revealed epicardial inflammation with eosinophilic predominance, but without histopathologic evidence of myocarditis.

Echocardiography. Of 67 patients, 57 (85.1%) were evaluated with echocardiography during acute illness (Table 3). At follow-up echocardiography (n = 40), at 11 to 362 days (median 102 days) after diagnosis, the mean ejection fraction was 61 ± 4% (range 54% to 75%), with no residual evidence of ventricular dilation, diastolic dysfunction, regional wall motion abnormality, or pericardial effusion.

Functional assessment. Graded exercise testing was performed using the Bruce protocol in 41 patients at 18 to 362 days (median 103 days) from the time of diagnosis. The mean exercise duration was 12.2 ± 1.8 min (range 9.0 to 15.5 min). The mean maximum heart rate achieved was 96.0 ± 5.6% age predicted with a rate-pressure product of 30,853 ± 5,203. Testing precipitated no cardiac symptoms or ECG abnormalities.

Persistently symptomatic patients. Unlike the objective normalization of cardiac findings at follow-up, 14% of patients reported continued subjective symptoms (Table 4). No significant difference occurred in follow-up ejection fraction, functional status, or resting ECG abnormalities among these patients, although those with persistent symp-

Table 4. Acute Manifestations in Vaccinia-Associated Myopericarditis Patients, Stratified by Recovery Status

	Full Recovery (n = 50)	Continued Symptoms (n = 14)
Age, yrs	27.1 ± 5.6	25.1 ± 3.6
Time from vaccination to evaluation, days	10.4 ± 3.7	10.0 ± 2.0
Time to follow-up, weeks	30.0 ± 15.6	34.6 ± 15.6
Echocardiography		
Abnormal at presentation	15/43 (34.9%)	8/12 (66.7%)
Ejection fraction at presentation, %	57 ± 8	51 ± 8*
Ejection fraction on follow-up, %	61 ± 4	60 ± 1
Abnormal ECG on presentation	28/46 (61.0%)	7/11 (63.6%)
Cardiac isoenzymes, mean ± SD		
Creatine kinase (IU/l), peak	529 ± 360	484 ± 303
CK-MB (ng/dl), peak	36.0 ± 21.6	31.1 ± 21.7
Troponin-I (ng/dl), peak	13.6 ± 24.3	17.0 ± 28.8
Treadmill testing		
Maximum heart rate, beats/min	183 ± 10	176 ± 9
Percent age-predicted, %	95.2 ± 4.6	93.6 ± 10.3
Duration, min	12.4 ± 1.8	11.3 ± 1.5
Metabolic equivalents	15.0 ± 2.2	13.6 ± 0.5

$p = 0.049$, otherwise, not statistically significant. Continuous variables are expressed as mean ± SD. Categorical variables are expressed as raw data (percent of column total).
CK = creatine kinase; ECG = electrocardiogram.

toms may have had more myocardial depression at presentation.

Follow-up on patients with depressed ejection fractions. Comparing those 18 patients who presented with a depressed ejection fraction (mean 47 ± 6%) to the 39 patients with normal function (61 ± 4%; $p < 0.01$); there was no statistically significant difference in peak troponin-I (17.7 ± 23.1 ng/ml vs. 12.3 ± 25.9 ng/ml; $p = 0.49$) or peak CK (566 ± 353 IU/l vs. 478 ± 343 IU/l; $p = 0.40$). At follow-up, there was no difference in ejection fraction (59 ± 3% vs. 60 ± 3%; $p = 0.06$), or functional capacity (11.6 ± 1.5 min vs. 12.7 ± 1.8 min; $p = 0.41$). No patient on follow-up had an ejection fraction <54%.

DISCUSSION

Clinical myocarditis or pericarditis is an expected rare complication of smallpox vaccination with the NYCBOH strain of vaccinia. All evaluated patients had objective normalization of cardiac function at follow-up. Approximately 20% reported persistent symptoms despite normal testing. Normalization of echocardiography, ECG, and functional status can be expected, even in those with a depressed ejection fraction at presentation.

Pericarditis and myocarditis have been reported after other vaccinations, but they are extremely rare events relative to the millions of individuals immunized; most case reports described self-limited and benign conditions (6). Previous prospective studies identified ECG changes that may have been myocarditis or pericarditis in 1% to 3% of people who received a European strain of vaccinia (3,5). Cardiac involvement has similarly been associated with naturally occurring outbreaks of smallpox in the 1960s (1,6,7).

Viral myocarditis can mimic acute myocardial infarction (MI) clinically, electrocardiographically, and biochemically as suggested by the high rate of diagnostic coronary angiograms in our young cohort (16,17). Coronary events, including angina and MI, have not been causally associated with smallpox vaccination (18,19).

Myocarditis can occur after viral, rickettsial, bacterial, and parasitic disease (20). Whether the underlying myocardial dysfunction in vaccinia-associated myopericarditis is a result of infectious, toxic, or immunologically mediated myocardial damage is unclear. In our four biopsied cases, active vaccinia infection of the heart was excluded. This suggests that vaccinia-associated myopericarditis is immunologically mediated, rather than a result of viral infection of the myocardium. Independent of pathogenesis, the underlying result involves both patchy or diffuse myocytolysis and intense infiltration with inflammatory cellular products (15,20). If the pathogenesis represents eosinophilic injury mediated by autoimmune phenomena, corticosteroids may be efficacious in inflammation, although immunosuppressive therapy is generally considered ineffective in the traditional models of viral-induced myocarditis (21,22).

The strength of this study lies in the large number of generally healthy people vaccinated and the comprehensive nature of adverse event reporting after smallpox vaccination, both of which contribute to study power. This study does not address the occurrence of subclinical myopericarditis. Further investigation is ongoing to better define potential risk factors for post-vaccinial myopericarditis.

Finally, post-vaccinial myopericarditis should be considered in the differential diagnosis of patients who develop chest pain within 30 days after smallpox vaccination, which can be expected to be self-limited.

Acknowledgments

We are indebted to astute clinicians for diligent assistance in case investigation, to our patients in this case series, and to the Vaccine Healthcare Centers for case management.

Reprint requests and correspondence: Dr. Robert E. Eckart, Attn: MCHE-MDC, 3851 Roger Brooke Drive, Brooke Army Medical Center, Fort Sam Houston, Texas 78234-6200. E-mail: Robert.Eckart@us.army.mil.

REFERENCES

1. Grabenstein JD, Winkenwerder W, Jr. U.S. military smallpox vaccination program experience. JAMA 2003;289:3278–82.
2. Ladnyi ID, Jezek Z, Gromyko A. Five years of freedom from smallpox. J Hyg Epidemiol Microbiol Immunol 1983;27:1–12.
3. Ahlborg B, Linroth K, Nordgren B. ECG changes without subjective symptoms after smallpox vaccination of military personnel. Acta Med Scand Suppl 1966;464:127–34.
4. Karjalainen J, Heikkila J, Nieminen MS, et al. Etiology of mild acute infectious myocarditis. Relation to clinical features. Acta Med Scand 1983;213:65–73.
5. Helle EP, Koskenvuo K, Heikkila J, Pikkarainen J, Weckstrom P. Myocardial complications of immunizations. Ann Clin Res 1978;10:280–7.
6. Halsell JS, Riddle JR, Atwood JE, et al. Myopericarditis following smallpox vaccination among vaccinia-naive U.S. military personnel. JAMA 2003;289:3283–9.
7. Arness MK, Eckart RE, Love SS, et al. Myopericarditis following smallpox vaccination of U.S. military personnel. Am J Epidemiol 2004. In press.
8. Centers for Disease Control. Update: Cardiac-related events during the civilian smallpox vaccination program—United States, 2003. MMWR 2003;52:492–6.
9. Establishment of case management guidelines for smallpox-associated myopericarditis. Office of the Assistant Secretary of Defense for Health Affairs, 2003.
10. Institute of Medicine. Review of the Centers for Disease Control and Prevention's Smallpox Vaccination Program Implementation. Letter Report #1. Washington, DC: National Academy of Sciences, 2003.
11. Panels Find Vaccines May Relate to Reservists Illness, Death. News Release: United States Department of Defense, 2003.
12. Review and Assessment of Smallpox Vaccination (Vaccinia) Case 2. United States Department of Health and Human Services, Health Resources and Services Administration, Office of Special Programs, Clinical Expert Immunization Committee (CEIC), 2003.
13. Sentinel Case Review 2004-01. United States Department of the Army, Office of the Surgeon General, Armed Forces Epidemiological Board, 2003.
14. Wang K, Asinger RW, Marriott HJ. ST-segment elevation in conditions other than acute myocardial infarction. N Engl J Med 2003;349:2128–35.
15. Murphy JG, Wright RS, Bruce GK, et al. Eosinophilic-lymphocytic myocarditis after smallpox vaccination. Lancet 2003;362:1378–80.

16. Levi D, Alejos J. Diagnosis and treatment of pediatric viral myocarditis. Curr Opin Cardiol 2001;16:77–83.
17. Dec GW, Jr., Waldman H, Southern J, Fallon JT, Hutter AM, Jr., Palacios I. Viral myocarditis mimicking acute myocardial infarction. J Am Coll Cardiol 1992;20:85–9.
18. Lane JM, Ruben FL, Neff JM, Millar JD. Complications of smallpox vaccination, 1968. N Engl J Med 1969;281:1201–8.
19. Lane JM, Ruben FL, Neff JM, Millar JD. Complications of smallpox vaccination, 1968: results of ten statewide surveys. J Infect Dis 1970;122:303–9.
20. Feldman AM, McNamara D. Myocarditis. N Engl J Med 2000;343: 1388–98.
21. Tomioka N, Kishimoto C, Matsumori A, Kawai C. Effects of prednisolone on acute viral myocarditis in mice. J Am Coll Cardiol 1986;7:868–72.
22. Frustaci A, Chimenti C, Calabrese F, Pieroni M, Thiene G, Maseri A. Immunosuppressive therapy for active lymphocytic myocarditis: virological and immunologic profile of responders versus nonresponders. Circulation 2003;107:857–63.

APPENDIX

The Department of Defense Smallpox Vaccination Clinical Evaluation Team: Scott Wright, MD (Mayo Clinic and Foundation, Rochester, MN), Roger Gibson, DVM, PhD (Office of the Secretary of Defense), Robin Jones-Rogers, MSN, Teresa Riddick, MSN, Denise Chernitzer, MSN (Portsmouth Naval Medical Center), Wayne Scott, BS, Laurie Duran, MSN, Jeannette Williams, MSN, Mary Minor, MSN, Michael Nelson, MD (Walter Reed Army Medical Center), Beth Stanfield, MSN, Marian Gordon, MS, Jeanie Kim, MSN (Fort Bragg Army Medical Center), David Hrncir MD, Sandra Johnson MSN, Catherine Skerrett, MSN, Pam Garwood, MSN (Wilford Hall Medical Center).