DEPARTMENT OF DEFENSE
ARMED FORCES EPIDEMIOLOGICAL BOARD
5109 LEESBURG PIKE
FALLS CHURCH VA 22041-3258

AFEB

June 20, 2003

MEMORANDUM FOR

The Assistant Secretary of Defense (Health Affairs)
The Surgeon General, Department of The Army
The Surgeon General, Department of The Navy
The Surgeon General, Department of The Air Force

SUBJECT: DoD Immunization Program for Biological Warfare Defense – 2003 - 11

1. References:

a. Department of Defense Directive 6205.3, "DoD Immunization Program for Biological Warfare Defense," dated November 26, 1993.

b. Department of Defense Directive 6200.2, "Use Of Investigational New Drugs for Force Health Protection," dated August 1, 2000.

c. Memorandum, OASD(HA)/FHP&R, March 13, 2002, Therapeutics Against Biowarfare Agents.

d. Memorandum, AFEB 2002 - 09, August 12, 2002, Therapeutics Against Biowarfare Agents.

2. The Armed Forces Epidemiological Board (AFEB) annually provides recommendations to the Assistant Secretary of Defense for Health Affairs and the DoD Executive Agent on vaccines and immunization protocols necessary to enhance protection against validated biological warfare threat agents. Specifically, DoD Directive 6205.3 requires that "on an annual basis the President of the Armed Forces Epidemiological Board (AFEB) shall identify to the Assistant Secretary of Defense for Health Affairs "vaccines available to protect against validated biological warfare threat agents, and recommend appropriate immunization protocols".

3. On 20 and 21 May 2003 the AFEB met to consider the biological threat agents designated by the Chairman of the Joint Chiefs of Staff. The current Chairman of the Joint Chiefs of Staff validated threat list was last updated in September 2002. The Board received briefings on international biowarfare vaccine production capabilities, the current intelligence based biological warfare threat, the current U.S. military vaccination program for anthrax and smallpox, the Medical Biological Defense Research Program, and the Joint Vaccine Acquisition Program.

4. The proponent office for the current DoD Directive, DoDD 6205.3, DoD Immunization Program for Biological Warfare Defense, dated November 26, 1993, briefed the Board on current efforts to revise this directive. The revision would broaden its focus from vaccines to all medical countermeasures, including pharmaceuticals, available for prophylaxis and treatment of biowarfare agents. The Board endorsed the concepts presented as part of the planned revision of this document.

5. The Board would like to recognize the outstanding performance of the staff of the Military Vaccine (MILVAX) Agency, particularly Colonel John Grabenstein, in coordinating DoD's Smallpox Vaccination Program in support of military operations in the Central Command area of responsibility. Over a highly compressed time frame, MILVAX coordinated a multi-Service effort that developed educational materials, policies, and procedures that facilitated the vaccination of almost 500,000 active duty and reserve personnel. This was accomplished through a screening process that reduced the occurrence of the well-recognized complications of smallpox vaccination below historical rates. As a result, no cases of progressive vaccinia or eczema vaccinatum were reported or identified, nor were any fatalities that could be attributed directly to the use of the vaccine. Although cases of generalized vaccinia were seen, these were mild, did not require the use of vaccinia immune globulin (VIG), and occurred at or below the expected frequency. Efforts to minimize the risk for secondary inoculation appear to have been successful; no cases were identified in health care settings and only one episode of ocular inoculation in a contact required VIG administration.

6. The Board has had a longstanding interest in force protection against biowarfare agents such as anthrax and smallpox, and in recent years has issued a number of statements concerning use of the vaccines. These previous AFEB statements have supported the use of the vaccines when indicated to protect individuals being deployed to areas where analysis has determined that there is a credible risk of exposure.

a. Previous AFEB recommendations on administration of anthrax vaccine remain current. In regard to the anthrax vaccination program, the Board acknowledges efforts made to address previously stated concerns and to share publicly the findings of research efforts. We have seen no data that leads us to conclude that the vaccine is unsafe when administered according to the package insert. The range of reported side effects experienced by recent recipients of the anthrax vaccine are in line with previously published reports. There are no convincing data demonstrating long-term adverse health impacts to recipients of anthrax vaccine.

b. The Board is concerned about two issues related to the smallpox vaccination program:

(1) The first is an unexpectedly high number of myopericarditis cases occurring in a 2-week period following vaccination (1). This complication was infrequently identified

during previous vaccination programs in the U.S., although it was reported to occur in approximately one in 10,000 Finnish military recruits (2). Currently available data indicate a 6-fold increase in risk during the 2-week post-vaccination period, even though most cases have been transient and mild with apparent recovery. All cases have occurred in white males between the ages of 21 and 33 years, despite the fact that 25-30% of vaccinees are members of minority groups and 13% of vaccinees are female. There also appears to be variation in the rates of myopericarditis recognized by the various uniformed Services, with higher rates seen in the Coast Guard, Army, and Air Force, and few cases recognized among Navy and Marine Corps personnel. This suggests that the number of myopericarditis cases may be higher than reported to date.

(2) The second concern relates to the number of pregnancies occurring among personnel at the time of, or shortly after, receipt of smallpox vaccine. Although rare, fetal vaccinia is a recognized complication of smallpox vaccination. The Board acknowledges that a significant proportion of these pregnancies could not have been identified at the time of vaccination either because they were too early or because conception took place post-vaccination. However, the rapid operational tempo surrounding deployment to Southwest Asia is likely to have been a contributing factor. The Board notes that additional screening measures have been instituted to assure that such avoidable complications can be minimized in the future. The efforts undertaken to enroll these women into the smallpox pregnancy registry so that appropriate monitoring can occur and any complications documented are noteworthy.

Weaponized anthrax spores remain a potential threat to U.S. military personnel. Although impossible to quantify, there does appear to be an ongoing concern that the virus that causes smallpox is also a legitimate concern for U.S. military personnel. Use of either agent as a biological warfare weapon can result in significant morbidity, mortality, and operational disruption. In light of the success of vaccination efforts to date, it appears reasonable to continue both anthrax and smallpox prophylaxis for those personnel and in those deployments in which there is a perceived potential risk of exposure.

7. Regarding available vaccines and immunization protocols necessary to enhance protection against validated biological warfare threat agents, the Board makes the following recommendations:

a. The Board continues to strongly endorse efforts to develop new generation anthrax vaccines that are potentially less reactogenic and could require less frequent dosing to afford protection. We also support efforts within the Departments of Defense and Health and Human Services to explore alternative dosing schedules and administration routes to minimize localized reactions with the currently available vaccine.

b. Uniform criteria for evaluation and follow-up of patients with myopericarditis following smallpox vaccination should be developed. Individuals diagnosed with smallpox vaccine associated myopericarditis should be evaluated clinically in the mid- and long-term to ascertain the consequences of this clinical manifestation following smallpox vaccination. Analytic studies should be undertaken to examine risk factors for myopericarditis after smallpox vaccination in military personnel. Consideration should be given to case-control studies, genetic and other laboratory analyses that may help define why this complication occurs in the patterns currently seen. These studies might also help determine the optimal environment and timing for vaccine administration prior to deployment to a designated threat area. Enhanced clinical awareness and uniform criteria for evaluation should help address the discrepancy in case recognition among the various uniformed Services. It is also important to conduct longitudinal studies to ascertain any long-term consequences among recognized cases of myopericarditis and among all smallpox vaccinees compared to non-vaccinees. Such data are necessary to factor into risk-benefit analyses regarding future use of this vaccine and these data should be part of the criteria used in making decisions about the current smallpox vaccination program.

c. Measures should be strengthened to further reduce the potential for vaccinating pregnant women and for educating females about the importance of avoiding conception in the peri-vaccination period. Consideration should be given to development of policies that minimize just-in-time vaccinations prior to deployment so that adequate time is available for education, screening and vaccination deferral as appropriate.

d. As long as vaccine supplies are adequate, the current risk-based approach for anthrax vaccination and capabilities-based approach for smallpox vaccination, focused on deployments to high threat theaters of operations, should be retained as the basis for decisions about the need for pre-exposure vaccination against biowarfare threats such as anthrax and smallpox. Such approaches should also take into consideration the need for adequately vaccinated emergency response personnel and the feasibility of alternative pre- and post-exposure therapeutic interventions. Results of the recommended studies on current smallpox vaccine recipients diagnosed with myopericarditis will need to be evaluated on an ongoing basis.

e. The Board supports the proposed rewording of DoDD 6205.3 to include annual review of all available medical countermeasures for biowarfare threat agents.

f. The Board is disappointed that a joint requirements document has not been developed for therapeutics against biowarfare agents as recommended in AFEB 2002-09, dated August 12, 2002. Because of the recent re-organization of the Chemical/Biological Defense Program and the establishment of the Joint Requirement Office – Chemical, Biological, Radiological and Nuclear (JRO-CBRN), the Board recommends that JRO-CBRN address the 2002-09 Board recommendation.

8. The above recommendations were unanimously approved.

FOR THE ARMED FORCES EPIDEMIOLOGICAL BOARD:

STEPHEN M. OSTROFF, M.D.
AFEB, President

JAMES R. RIDDLE, D.V.M., M.P.H.
Colonel, USAF, BSC
AFEB Executive Secretary

2. Enclosures
1. Halsell JS, Riddle JR, Atwood JE, et al. Myopericarditis Following Smallpox Vaccination Among Vaccinia-Naïve US Military Personnel. *Jama.* Jun 25 2003;289(24):3283-3289.
2. Karjalainen J, Heikkila J, Nieminen MS, et al. Etiology of mild acute infectious myocarditis. Relation to clinical features. *Acta Med Scand.* 1983;213(1):65-73.

CF:
Board Members and Consultants (w/o Encls)
USD(AT&L) (w/o Encls)
DATSD(CBD) (w/o Encls)
USAMRMC (w/o Encls)
J4-MRD (w/o Encls)
AMEDD(C&S) (w/o Encls)
USAMRIID (w/o Encls)
JVAP (w/o Encls)
DASG-HCF (w/o Encls)
JRO-CBRN (w/o Encls)

ORIGINAL CONTRIBUTION

Myopericarditis Following Smallpox Vaccination Among Vaccinia-Naive US Military Personnel

Jeffrey S. Halsell, DO
James R. Riddle, DVM, MPH
J. Edwin Atwood, MD
Pierce Gardner, MD
Robert Shope, MD
Gregory A. Poland, MD
Gregory C. Gray, MD, MPH
Stephen Ostroff, MD
Robert E. Eckart, DO
Duane R. Hospenthal, MD, PhD
Roger L. Gibson, DVM, PhD
John D. Grabenstein, RPh, PhD
Mark K. Arness, MD, MTM&H
David N. Tornberg, MD, MPH
and the Department of Defense Smallpox Vaccination Clinical Evaluation Team

Context In the United States, the annual incidence of myocarditis is estimated at 1 to 10 per 100000 population. As many as 1% to 5% of patients with acute viral infections involve the myocardium. Although many viruses have been reported to cause myopericarditis, it has been a rare or unrecognized event after vaccination with the currently used strain of vaccinia virus (New York City Board of Health).

Objective To describe a series of probable cases of myopericarditis following smallpox vaccination among US military service members reported since the reintroduction of vaccinia vaccine.

Design, Setting, Participants Surveillance case definitions are presented. The cases were identified either through sentinel reporting to US military headquarters surveillance using the Defense Medical Surveillance System or reports to the Vaccine Adverse Event Reporting System using *International Classification of Diseases, Ninth Revision*. The cases occurred among individuals vaccinated from mid-December 2002 to March 14, 2003.

Main Outcome Measure Elevated serum levels of creatine kinase (MB isoenzyme), troponin I, and troponin T, usually in the presence of ST-segment elevation on electrocardiogram and wall motion abnormalities on echocardiogram.

Results Among 230734 primary vaccinees, 18 cases of probable myopericarditis after smallpox vaccination were reported (an incidence of 7.8 per 100000 over 30 days). No cases of myopericarditis following smallpox vaccination were reported among 95622 vaccinees who were previously vaccinated. All cases were white men aged 21 years to 33 years (mean age, 26.5 years), who presented with acute myopericarditis 7 to 19 days following vaccination. A causal relationship is supported by the close temporal clustering (7-19 days; mean, 10.5 days following vaccination), wide geographic and temporal distribution, occurrence in only primary vaccinees, and lack of evidence for alternative etiologies or other diseases associated with myopericarditis. Additional supporting evidence is the observation that the observed rate of myopericarditis among primary vaccinees is 3.6-fold (95% confidence interval, 3.33-4.11) higher than the expected rate among personnel who were not vaccinated. The background incidence of myopericarditis did not show statistical significance when stratified by age (20-34 years: 2.18 expected cases per 100000; 95% confidence interval [CI], 1.90-2.34), race (whites: 1.82 per 100000; 95% CI, 1.50-2.01), and sex (males: 2.28 per 100000; 95% CI, 2.04-2.54).

Conclusion Among US military personnel vaccinated against smallpox, myopericarditis occurred at a rate of 1 per 12819 primary vaccinees. Myopericarditis should be considered an expected adverse event associated with smallpox vaccination. Clinicians should consider myopericarditis in the differential diagnosis of patients presenting with chest pain 4 to 30 days following smallpox vaccination and be aware of the implications as well as the need to report this potential adverse advent.

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WE REPORT THE FIRST 18 cases of probable myopericarditis following smallpox vaccination among otherwise healthy, young adult members of the US military who were vaccinated between mid-December 2002 and March 14, 2003 (N=326356; 230734 primary vaccinees and 95622 revaccinees). Despite decades as the standard vaccine for US civilian and military populations, the New York City Board of Health (NYCBOH) strain of vaccinia virus (Dryvax, Wyeth Laboratories, Marietta, Pa) has only rarely

See also pp 3278, 3290, 3295, and 3306.

Author Affiliations are listed at the end of this article. **Corresponding Author and Reprints:** James R. Riddle, DVM, MPH, Armed Forces Epidemiological Board, Skyline Six, Suite 682, 5111 Leesburg Pike, Falls Church, VA 22041-3206 (e-mail: James.Riddle@otsg.amedd.army.mil).

Box. Myopericarditis Following Smallpox Vaccination: Adverse Event Surveillance Case Definitions

Confirmed Myopericarditis Following Vaccination

Patient with acute myocarditis* with or without pericarditis with symptom onset 4 to 30 days after vaccinia exposure and absence of another causal infection, disease or toxic agent and, virus culture or detection† of vaccinia DNA by polymerase chain reaction identification of vaccinia virus infection from myocardial tissue or pericardial fluid (detection of viral nucleic acid in the myocardium is regarded as indicative of virus infection)

Probable Myopericarditis Following Vaccination

Patient with acute myocarditis* with or without pericarditis with symptom onset 4 to 30 days after vaccinia exposure and absence of another causal infection, disease, or toxic agent

*Clinical diagnosis of myocarditis is confirmed by detection of elevated serum levels of creatine kinase (MB isoenzyme), troponin I, and troponin T, usually in the presence of ST-segment elevation on electrocardiogram and abnormal findings on echocardiogram.
†Whether vaccinial myopericarditis is a direct viral cytopathogenic effect or an immune-mediated disease remains unclear.

been associated with myopericarditis following vaccination. Only 5 cases were reported in the medical literature between 1955 and 1986.[1-8]

Myocarditis and pericarditis following vaccination have been reported more commonly with other vaccinia virus strains,[9-17] may be associated with other adverse events following vaccination,[2] and may be asymptomatic.[10,18-20] In 1968, Price and Alpers[14] noted that minor cardiac complications after smallpox vaccination may be more common than is generally reported. Six years earlier, MacAdam and Whitaker[21] reported 3 cases of cardiac complications 5 to 14 days following smallpox vaccination and suggested that cardiac complications had been previously overlooked. In 1983, the incidence of myocarditis following vaccination among Finnish military conscripts who were hospitalized with mild myocarditis following vaccination with the Finnish strain of smallpox had been estimated to be as high as 1 per 10 000.[22] As early as 1953, Mathieu and Hadot[23] recommended screening for cardiac risk factors before vaccination, especially in individuals aged 50 years or older.

METHODS

Surveillance for Adverse Events

A program to vaccinate up to 500 000 US military personnel was launched mid-December 2002.[24] To detect adverse events after vaccination, the Department of Defense and the US Coast Guard require reporting to the Vaccine Adverse Event Reporting System (VAERS) using established guidelines. Additionally, the Department of Defense encourages clinicians to report all other clinically relevant adverse events after administration of any vaccine or medication to VAERS or MedWatch (US Food and Drug Administration Safety Information and Adverse Event Reporting Program). To heighten awareness of potential adverse events, including cardiac events, clinicians were provided extensive education and vaccinees were individually counseled and provided educational material. An Internet site providing access to a comprehensive array of materials and ongoing program status was established (http://www.smallpox.army.mil/).

A 3-pronged approach was implemented for surveillance and patient safety following vaccination, as described by Grabenstein and Winkenwerder[24] elsewhere in this issue of THE JOURNAL. Standard documentation was used to record screening results, vaccination delivery, vaccination response, and adverse event management. Vaccination was recorded electronically as a component of the individual's longitudinal health record, which was maintained as part of the Defense Medical Surveillance System (DMSS).[25] This system integrates data from sources worldwide in a continuously expanding relational database that documents the military and medical experiences of service members throughout their careers. The DMSS allows nearly instantaneous assessments of the morbidity experiences of service members who share common characteristics, such as vaccination. Statistical analysis was performed using SAS version 8.02 (SAS Institute, Cary, NC).

Case Identification

The cases presented herein were identified either through sentinel reporting to military headquarters and/or to the VAERS or through diagnostic surveillance among vaccinees at military treatment facilities using *International Classification of Diseases, Ninth Revision (ICD-9)*[26] coded diagnoses (420.90, 420.99, other and unspecified acute pericarditis; 422.90, 422.91, other and unspecified acute myocarditis; and 429.0 myocarditis unspecified) obtained from the DMSS. Fifteen cases were first identified from surveillance of military treatment facilities, and only 3 cases were first identified from the VAERS. The cases were classified based on surveillance case definitions shown in the BOX. Clinical diagnosis of myocarditis was based on detection of elevated serum levels of creatine kinase (MB isoenzyme), troponin I, and troponin T, usually in the presence of ST-segment elevation on electrocardiogram and wall motion abnormalities on echocardiogram.

RESULTS

Clinical and diagnostic details for the 18 cases of probable myopericarditis following smallpox vaccination reported among 230 734 primary vaccinees (71% of vaccines) are presented in the TABLE. No cases were detected among 95 622 vaccinees who were previously vaccinated. All cases were military personnel in active duty who received vaccination with the NYCBOH strain of vaccinia

Table. Relevant Findings Among 18 Primary Vaccinee Cases With Probable Myopericarditis Following Smallpox Vaccination Among US Military Personnel

Case	After Vaccination, d	Smallpox and Other Vaccines Administered Within 30 d	Viral Prodrome	Chest Pain	ECG Findings	ECHO Findings	Cardiac Enzymes Positive Peak Levels*	Infectious Disease Laboratory Evaluation Results†
1	11	1/25/03: smallpox 1/23/03: meningococcal and anthrax 1/29/03: MMR	Myalgias, arthralgias, lymphadenopathy	Substernal	ST-segment elevation	Low normal LV systolic function; EF, 50%-55%	CK-MB, 48.6; troponin I, 14.76	Serum: hepatitis panel negative; CBC and metabolic panel normal; elevated liver enzymes: AST, 94 (normal, 5-45 IU/L); ALT, 66 (normal, 7-56 IU/L); ESR elevated: 30 (normal, 0-15 mm/h) CSF: none Other: none
2	7	1/31/03: smallpox	Fever (38.5°C), chills, headache, stiff neck, myalgias	Better with bending forward	Normal	EF, 50%; improved later to 59%	CK-MB, 8.0; troponin I, 1.31	Serum: coxsackie A and B virus, HIV, hepatitis A, B, and C, Lyme Ab, ANA, RF, ASO: negative, acute, and convalescent; Adenovirus CF Ab unremarkable; DNAse B Ab unremarkable CSF: viral culture negative, Shell vial culture for Enterovirus, HSV, and CMV negative Other: nasal wash viral culture negative
3	8	2/05/03: smallpox, anthrax, influenza, typhoid (parenteral)	Fever (subjective), sore throat, myalgias	Squeezing, pleuritic, reproduced by touch	ST-segment elevation	Normal	CK-MB, 22.3; troponin I, 3.0	Serum: influenza A and B, RPR, ANA, HIV, hepatitis profile, RF, viral cultures, PPD, CBC, metabolic panel normal, C-reactive protein, 1.1 (normal <1 mg/dL), ESR, 26 (normal 0-15 mm/h) CSF: none Other: none
4	11	2/08/03: smallpox	Fever (subjective), myalgias, arthralgias, headache	Radiation to neck	ST-segment elevation	Pericardial effusion = 4 mm	CK-MB, 133	Serum: baseline laboratory results (chem7, CBC, LFT, and coagulation studies) normal; C-reactive protein, 42 (normal 0-1 mg/dL) CSF: none Other: normal cardiac catherization
5	10	2/13/03: smallpox 2/07/03: anthrax 2/26/03: anthrax	Recent upper respiratory tract symptoms	Pleuritic	ST-segment elevation	Normal	CK-MB, 33; troponin T, 1.3	Serum: CBC, ESR, and metabolic panel normal; PCRs and cultures for enteroviruses and vaccinia negative CSF: none Other: none
6	7	2/27/03: smallpox and anthrax	Chills, night sweats	Worse with movement	ST-segment elevation	Mild global hypokinesis: LVEF, 50%-55%	CK-MB, 55; troponin I, 97.2	Serum: C3/C4, CH_{50} levels, C1q assay, Raji cell assay for circulating immune complexes, RF, ANA, all normal; PCRs and cultures for enteroviruses and vaccinia, negative CSF: none Other: none
7	11	2/27/03: smallpox	Fever (subjective), chills, sweating	Pleuritic	ST-segment elevation	Small pericardial effusion	CK-MB, 46.4	Serum: hepatitis panel negative except for HBs Ab positive (previous hepatitis B vaccine); CBC normal CSF: none Other: none
8	10	2/13/03: smallpox 2/06/03: anthrax 2/20/03: anthrax	Myalgias, fever (subjective), arthralgias	Pleuritic	ST-segment elevation	Normal	Troponin I, 7.7	Serum: C-reactive protein and ANA normal, Lyme titers negative CSF: none Other: none

(continued)

Table. Relevant Findings Among 18 Primary Vaccinee Cases With Probable Myopericarditis Following Smallpox Vaccination Among US Military Personnel (cont)

Case	After Vaccination, d	Smallpox and Other Vaccines Administered Within 30 d	Viral Prodrome	Chest Pain	ECG Findings	ECHO Findings	Cardiac Enzymes Positive Peak Levels*	Infectious Disease Laboratory Evaluation Results†
9	12	2/28/03: smallpox, anthrax, hepatitis B, hepatitis A, influenza, polio (IPV), meningococcal, typhoid (parenteral)	Recent upper respiratory tract symptoms	Pleuritic	ST-segment elevation	Mild LV dysfunction; LVEF, 45%	Troponin I, 22.5	Serum: metabolic panel, CBC, C1q assay, C3/C4, CH50 levels, ANA, RF, all normal; C-reactive protein, 3 (normal, 0-1 mg/dL) CSF: none Other: none
10	12	3/05/03: smallpox	None reported	Pleuritic and positional	ST-segment elevation	Normal	Troponin T, 0.395	Serum: CBC, metabolic panel, LFTs, TSH, all normal; ESR, 35 (normal, 0-15 mm/h) CSF: none Other: none
11	19	3/08/03: smallpox, anthrax, hepatitis B, hepatitis A, influenza, typhoid (ViCPs) 3/24/03: anthrax	Fever, arthralgias, dry cough	Positional	ST-segment elevation	Low EF, 37%	Troponin T, 9.2	Serum: multiple heart biopsy specimens negative by PCR for vaccinia CSF: none Other: cardiac biopsy pathological results consistent with eosinophilic myocarditis
12	12	3/13/03: smallpox 1/16/03: typhoid (ViCPs)	Myalgias	Pleuritic	ST-segment elevation	Low normal LVEF, 50%-55%	CK-MB, 76.6; troponin I, 150	Serum: acute and convalescent viral titers negative; C3/C4, C1q assay, CH_{50}, interleukin-6, Raji cell assay, C-reactive protein, negative CSF: none Other: none
13	14	1/30/03: smallpox 1/17/03: anthrax	Recent upper respiratory tract symptoms	Substernal	ST-segment elevation	Normal	Troponin I, 30	Serum: CBC, metabolic panel, INR, lipid panel, protein electrophoresis, TSH, normal; C-reactive protein, 12 (normal, 0-1 mg/dL) CSF: none Other: none
14	7	3/06/03: smallpox	None reported	Left axillary	Normal	Normal	Troponin I, 0.73	Serum: none CSF: none Other: none
15	7	3/14/03: smallpox	Headache, fatigue	Substernal	ST-segment elevation	Low normal LVEF, 50%	Troponin I, 15	Serum: CBC normal CSF: none Other: none
16	8	3/14/03: smallpox	Chills, adenopathy	Substernal with radiation down both arms	ST-segment depression	Inferior wall hypokinesis	Troponin I, 1.99	Serum: CBC, metabolic panel, lipid panel, drug assays/toxicology, normal CSF: none Other: none
17	12	3/04/03: smallpox 2/18/03: anthrax 2/06/03: anthrax 2/03/03: meningococcal	None reported	Substernal	ST-segment elevation	Normal	Troponin I, 139; CK-MB, 93	Serum: CBC, metabolic panel, normal CSF: none Other: none
18	11	2/14/03: smallpox and anthrax	Muscle aches, elevated temperature	Substernal with radiation to right scapula	ST-segment elevation	Small pericardial effusion with mild inferior hypokinesis	Troponin I, 3.23	Serum: CBC, metabolic panel, ANA, anti-DNA, anti-cardiolipin, serum electroimmunoelectrophoresis, normal; C-reactive protein, 8.03 (normal, 0-0.94 mg/dL) CSF: none Other: none

Abbreviations: ALT, alanine aminotransferase; ANA, antinuclear antibody; ASO, anti-streptolysin O; AST, aspartate aminotransferase; C3/C4, complement factor 3/complement factor 4; CBC, complete blood cell count; CFS, cerebrospinal fluid; CF, complement fixation; CK-MB, creatine kinase MB isoenzyme; CH_{50}, total hemolytic complement; ECG, electrocardiogram; ECHO, echocardiograph; EF, ejection fraction; ESR, erythrocyte sedimentation rate; HBsAg, hepatitis surface antigen; HIV, human immunodeficiency virus; INR, international normalized ratio; IPV, injectable polio vaccine; LFT, liver function tests; LV, left ventricular; LEVF, left ventricular ejection fraction; MMR, measles-mumps-rubella; PCR, polymerase chain reaction; RF, rheumatoid factor; TSH, thyrotropin; ViCPs, Vaccine Injury Compensation Programs.

*Troponin I and troponin T activity and CK-MB are reported in ng/mL.

†Metabolic panel includes serum sodium, potassium, chloride, CO_2, blood urea nitrogen, creatinine, glucose, and calcium concentrations. Hepatitis panel includes hepatitis B surface antigen, hepatitis C antibody, hepatitis B surface antibody, and hepatitis B core antibody. Chem 7 includes sodium, potassium, chloride, CO_2, blood urea nitrogen, creatinine, and glucose.

virus in various regions of the United States, Europe, and the Middle East. All cases were white (73% of total vaccinees), men (78% of total vaccinees), aged 21 years to 33 years (mean age, 26.5 years; 59% of total vaccinees were aged 21-35 years), with disease onset 7 to 19 days following vaccination (mean, 10.5 days). Typical clinical presentation involved prodromal myalgias; arthralgias; subsequent pleuritic, precordial chest pain; and variable shortness of breath and/or dry cough. All vaccinees had elevated serum cardiac enzyme levels; 15 of the 18 cases had ST-segment elevation changes on electrocardiogram, and 11 of the 18 cases had abnormal echocardiogram findings (ie, wall motion abnormalities). Biopsy of myocardial tissue was performed in only 1 case; the results revealed histological evidence of eosinophil infiltration of the myocardium, eosinophil degranulation, secretion of major basic protein in close apposition to myocyte necrosis, and IL-5 generation. No cases were confirmed by viral diagnosis. All cases had a characteristic primary vaccination response at the inoculation site as defined by the World Health Organization.[27] Results of serologic laboratory tests, when done, did not indicate the presence of other infectious etiologies or host conditions predisposing to myopericarditis. All cases survived and all returned to duty or are on short-term convalescent leave. Longer-term follow-up to detect possible sequelae is underway.

The 18 cases among 230 734 primary vaccinees represent an incidence of 7.80 per 100 000 over a 30-day observation window. The background incidence of myopericarditis in all service members on active duty is 2.16 cases (95% confidence interval, [CI], 1.90-2.34; Poisson distribution) per 100 000 over any 30-day period. This incidence was calculated using 2002 calendar year DMSS data for all services for the above described 5 myopericarditis *ICD-9* diagnoses among a population of 1 399 739 persons. When stratified by age, race, and sex, the background incidence rates in all service members of myopericarditis were not statistically significant, with 2.18 expected cases per 100 000 for ages 20 years to 34 years (95% CI, 1.90-2.34); 1.82 expected cases per 100 000 for whites (95% CI, 1.50-2.01), and 2.28 expected cases per 100 000 for males (95% CI, 2.04-2.54).

The expected number of myopericarditis cases in the population of 230 734 primary vaccinees was calculated by applying the background rate estimate of 2.16 to this population, which yielded 4.98 expected cases (95% CI, 4.38-5.40). The 18 cases reported herein represent an unadjusted estimate of relative risk (RR) of 3.61 (95% CI, 3.33-4.11; Poisson distribution) over the expected incidence of myopericarditis.

Etiologic Summary of Cases

The lack of clinical suspicion for myopericarditis following vaccination, no standard evaluation protocol, and the varied capability of the medical sites where these cases presented resulted in variable diagnostic workup for etiologic causes. In none of the cases was infection of myocardial tissue or pericardial fluid with the vaccinia virus confirmed using virus culture or by detection of vaccinia DNA by polymerase chain reaction. Among this case series, when serologic testing was done, findings have been negative for coxsackie A and B viruses, as well as hepatitis B and C, HIV, *Borrelia burgdorferi*, and *Streptococcus pyogenes* (by antistreptolysin O and anti-DNAse B). Viral cultures of nasal wash from 1 patient recovered no adenovirus or influenza viruses. Results of cerebrospinal fluid viral cultures from the same patient were negative, including a shell viral culture that tests specifically for enteroviruses, herpes simplex viruses, and cytomegalovirus. Results of serum antinuclear antibody from 6 patients and rheumatoid factor from 4 patients also were negative. To address the variability in etiologic diagnosis given the unexpected occurrence of these probable cases of myopericarditis following vaccination, the Department of Defense Vaccine Healthcare Center Network is developing clinical guidelines for evaluating patients and clinical policy to increase clinician awareness.

COMMENT

Viral myocarditis is an inflammatory disorder of the myocardium characterized by injury of myocytes with associated inflammatory infiltrate.[28] Often pericarditis and myocarditis are observed in tandem, hence the term *myopericarditis*.[29] Clinical diagnosis is suggested by detection of elevated serum levels of myocardial enzymes (creatine kinase-MB isoenzyme, troponin I, and troponin T), usually in the presence of nonspecific electrocardiographic changes and/or focal or generalized wall motion abnormalities on echocardiography.[18,30] In most cases, an etiology is not determined, but in cases in which a causative infectious agent has been identified, viral agents are most common, particularly the enterovirus group (predominantly coxsackie B virus), adenoviruses, and influenza A.[31] Diagnosis may be confirmed using histopathological and/or viral identification by polymerase chain reaction from endomyocardial biopsy or autopsy specimens.[28,30] Whether myopericarditis following smallpox vaccination is a direct viral cytopathic effect or an immune-mediated phenomenon remains unclear.

Association of Myopericarditis With Vaccinia Virus

Vaccinia virus has long been associated with myopericarditis.[28,29,32] However, only 1 previous report has described the pathological characteristics of myopericarditis following smallpox vaccination; the histological changes included a mixed mononuclear infiltrate.[33] This case series of probable myopericarditis associated with the New York City Board of Health strain of vaccinia virus serves to establish an expected baseline rate for myopericarditis following vaccination in primary vaccinees. The cases reported herein occurred only in otherwise healthy, young, white adult men who were carefully screened for conditions that might

preclude vaccination. The cases reported were moderate to severe in clinical presentation, and our observed incidence of myopericarditis likely represents a minimum, with milder cases unrecognized.

The close temporal clustering following vaccination (7 to 19 days; mean 10.5 days), the wide geographic and temporal distribution during the vaccination program, and the lack of alternative diagnoses, provide epidemiologic evidence for an association between smallpox vaccination and myopericarditis. Additional supporting evidence is the absence of myopericarditis in revaccinees and the observation that the observed rate of myopericarditis among primary vaccinees is 3.6-fold higher than the expected rate among personnel on active duty who were not vaccinated. However, some covariates could confound this rate comparison, and a multivariate statistical model in a case-control study design is needed. Myopericarditis due to a synergistic inflammatory effect of multiple vaccines cannot be excluded. Exertion may have predisposed these military personnel to viral myocarditis, as exertion has been associated with increased viral titer and inflammation of the heart in experimental animal models.[34,35] It is possible that the occurrence of myopericarditis following vaccination may represent coincidental outcomes; however, the data linking myopericarditis with smallpox vaccine seem the most likely explanation.

Clinicians should be alert to the potential occurrence and implications of myopericarditis among adult primary vaccinees after receiving smallpox vaccination, and they should report these adverse events to the VAERS. Patients with a clinical suspicion of myopericarditis based on decreased ventricular function on echocardiography, a markedly elevated troponin levels suggestive of significant myocyte injury or a cardiac magnetic resonance imaging positive scan for myocarditis may be indicated to undergo endomyocardial biopsy. Biopsy specimens should be tested for the presence of vaccinia virus.

Study Limitations

Potential bias exists for both underreporting and overreporting of cases. Although extensive efforts have been made to identify all cases, underreporting bias may result from incomplete ascertainment of cases with myopericarditis following smallpox vaccination, considering the reported mild-to-moderate acute presentation and clinical course,[10] and the necessity of an index of suspicion to pursue an association. The generalized lack of clinical suspicion, exemplified by only 3 cases initially being reported through the VAERS, argues against overreporting of myopericarditis among vaccinees resulting from a case-ascertainment bias of clinicians. Ascertainment bias among vaccinees that resulted in overreporting (eg, the inference that individuals with chest pain after smallpox vaccination may be more likely to seek care) also is unlikely, given the moderate-to-severe clinical presentation of the reported cases. The absence of cases in this study among revaccinees, females, and nonwhite males is difficult to explain from a purely epidemiologic perspective. The Centers for Disease Control and Prevention (CDC) has reported myopericarditis following smallpox vaccination in females, although the CDC case definition differed from that used to classify the cases reported herein.[36] Although revaccinees might be expected to be more aware of the potential adverse effects from this vaccine and thus be less likely to seek care, given the extended time (decades) from their initial vaccination, and the acutely ill presentation of the reported cases, this seems to be an unlikely explanation.

These cases were diagnosed prior to the press release from the CDC on March 25, 2003, which changed the vaccine eligible screening criteria and highlighted the concerns for potential cardiac adverse effects after smallpox vaccination.[37] Recognition of potential cardiac adverse events led to development of a case definition for myocarditis and pericarditis and increased awareness by clinicians of this potential adverse event following smallpox vaccination.[38] Future reports will include additional cases recognized subsequent to the change in case definition along with follow-up of these cases and a case-control study examining risk factors among the cases reported herein.

The generalizability of these findings from young adult military vaccinees to the general US population is limited. Similar populations, such as police, firefighters, or other first-responders, are prescreened and periodically evaluated for good overall health and therefore may be the most appropriate comparison group. Further investigation is ongoing to better define the occurrence of myopericarditis following smallpox vaccination. It also will be important to closely monitor the longer-term health of these cases, as studies have indicated that viral myocarditis may result in long-term or permanent damage to the heart.[29,30]

Implications

Implications of these findings for older individuals, or individuals with preexisting cardiac morbidity, are unclear.[39] Clinicians treating patients with other complications from smallpox vaccination (eg, encephalitis, generalized vaccinia, or eczema vaccinatum) may want to evaluate patients for occult myopericarditis.[2] Based on reports of cardiac events following smallpox vaccination among military and civilian vaccinees, the CDC has recommended additional exemptions based on known cardiac disease or potential risk factors for cardiac disease.[40]

These findings are relevant to current policies and guidelines for vaccinating military and civilian populations against smallpox. Although these cases all recovered clinically from their acute illness, the potential long-term consequences must be evaluated to know the true significance of myopericarditis following vaccination. Furthermore, these findings suggest that myopericarditis following smallpox vaccination is an expected adverse event. We project a morbidity estimate of at least 78 cases of clinical myopericarditis per million primary vaccinees in com-

parable adult populations. Myopericarditis following vaccination should be considered in the differential diagnosis of patients with chest pain 4 to 30 days following smallpox vaccination.

Author Affiliations: The University of Virginia, Charlottesville (Dr Halsell); Office of the Assistant Secretary of Defense for Health Affairs, Falls Church, Va (Drs Riddle, Gibson, and Tornberg); Walter Reed Army Medical Center, Washington, DC (Dr Atwood); Military Vaccine Agency, US Army Medical Command, Falls Church, Va (Dr Grabenstein); National Institutes of Health, Fogarty International Center, Bethesda, Md (Dr Gardner); College of Public Health, University of Iowa, Iowa City (Dr Gray); University of Texas Medical Branch, Center for Tropical Disease, Department of Pathology, Galveston (Dr Shope); National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Ga (Dr Ostroff); Mayo Clinic and Foundation, Rochester, Minn (Dr Poland), Brooke Army Medical Center, Fort Sam Houston, Tex (Drs Eckart and Hospenthal); Army Medical Surveillance Activity, Washington, DC (Dr Arness). Additional authors are listed at the end of this article.

Author Contributions: *Study concept and design:* Halsell, Riddle, Poland, Ostroff, Gibson, Grabenstein, Arness, Tornberg.
Acquisition of data: Halsell, Riddle, Eckhart, Hospenthal, Grabenstein, Arness.
Analysis and interpretation of data: Halsell, Riddle, Atwood, Gardner, Shope, Poland, Gray, Eckhart, Hospenthal, Gibson, Grabenstein, Arness, Tornberg.
Drafting of the manuscript: Halsell, Riddle, Atwood, Gardner, Gibson, Grabenstein, Arness.
Critical revision of the manuscript for important intellectual content: Halsell, Riddle, Atwood, Gardner, Shope, Poland, Gray, Ostroff, Eckhart, Hospenthal, Grabenstein, Arness, Tornberg.
Statistical expertise: Riddle, Gibson, Arness.
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Administrative, technical, or material support: Halsell, Riddle, Gardner, Shope, Poland, Ostroff, Eckhart, Gibson, Grabenstein, Arness.
Study supervision: Riddle, Atwood, Ostroff, Hospenthal, Grabenstein, Arness, Tornberg.

Additional Authors/The Department of Defense Smallpox Vaccination Clinical Evaluation Team: George W. Christopher, MD, Louis C. Coyle, DO, MS, Randolph E. Modlin, MD (Landstuhl Regional Medical Center, Germany), Bradley A. Lloyd, DO (39th Medical Group, Incirlik, Turkey), Renata J. M. Engler, MD, Limone C. Collins, MD (Vaccine Healthcare Center Network, Walter Reed Army Medical Center, Washington, DC), Michael R. Nelson, MD, PhD, Bryan L. Martin, DO (Allergy-Immunology, Walter Reed Army Medical Center, Washington, DC), J Russell Bowman, DO, MS (US Coast Guard Air Station Sitka, Sitka, Alaska), Donald Lehmann, MD (Sitka Medical Center, Sitka, Alaska), Matthew J. Hepburn, MD, Robert F. Setlik, MD, PhD, David P. Dooley, MD (Brooke Army Medical Center, Fort Sam Houston, Tex), Steven J. Brewster, MD (Guthrie Ambulatory Clinic, Fort Drum, NY), Jonathan D. Beck, MD (Ambulatory Health Care Center, McGuire Air Force Base, NJ), Michael G. Stanley, DO, (US Army Hospital Heidelberg, Heidelberg, Germany), Michael R. Brumage, MD (Madigan Army Medical Center, Wash), Carol Alley, MD (US Coast Guard Base Clinic, Ketchikan, Alaska), Joseph G. Murphy, MD, Larry M. Baddour, MD (Mayo Clinic and Foundation, Rochester, Minn), Jeffrey S. Sartin, MD (Gundersen Lutheran, La Crosse, Wis), Cynthia Perry, DO, Chris C. Highley, DO (Reynolds Army Community Hospital, Fort Sill, Okla) Gorman Thorp, MD, FACC (Hendrick Medical Center, Abilene, Tex) and Marsha F. Lopez, PhD, Jeffrey L. Lange, PhD (Army Medical Surveillance Activity, Washington, DC).

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Etiology of Mild Acute Infectious Myocarditis

Relation to Clinical Features

Jouko Karjalainen, Juhani Heikkilä, Markku S. Nieminen, Hannu Jalanko, Marjaana Kleemola, Kaisa Lapinleimu and Timo Sahi

From Central Military Hospital 1, First Department of Medicine, University Central Hospital, the Department of Bacteriology and Immunology, University of Helsinki, Central Public Health Laboratory, and the Medical Division of the Finnish Defence Forces, Helsinki, Finland

ABSTRACT. The etiology of mild myocarditis, diagnosed on the basis of serial ECG changes during an acute infection, was studied in 126 consecutive conscripts. A fourfold rise in the antibody titers in the paired serum samples was required for a positive etiologic diagnosis. An etiologic diagnosis was made probable in 47% of the patients. Adenovirus was incriminated in 19 patients, vaccinia in 12, influenza A in eight, β-hemolytic Streptococcus in six, mononucleosis in five and Mycoplasma in three. Chlamydia, influenza B and Coxsackie B4 were each found in two patients; parainfluenza, mumps and adult Still's disease were each found in one patient. The incidence of vaccinia myocarditis was 1/10 000 smallpox vaccinations. Clear-cut myopericarditis was usually noted during vaccinia, mononucleosis, Mycoplasma, Chlamydia and Coxsackie B4 infections. Adenovirus and influenza A myocarditis was most often subclinical, being mostly detected only because of ECG screening of patients without cardiac symptoms. Frequent recent ventricular extrasystoles were most often triggered by a β-hemolytic Streptococcus infection. The etiology of infectious myocarditis seems to reflect the overall profile of viruses and other infective agents in the study population at that particular time. Cardiotrophic viruses such as Coxsackie B only rarely cause myocarditis outside epidemics.

Key words: adenovirus, β-hemolytic Streptococcus, Chlamydia, Coxsackie, Influenza, mononucleosis, Mycoplasma, myocarditis, myopericarditis, vaccinia.

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Myocarditis due to causes other than acute rheumatic fever or diphteria was practically undiagnosed before the report by Gores and Saphir in 1947 on 1 402 autopsied myocarditis cases (1). They found that only about 10% of the myocarditis cases were due to rheumatic fever and another 10% due to diphteria, while rickettsial and viral diseases were incriminated in 24% of the cases. Since then, a viral cause of myocarditis, with or without pericarditis, has become increasingly recognized. In fact, most virus infections may involve the heart (2).

The incidence and clinical picture of myocarditis have been surveyed during epidemics caused by such viruses as Coxsackie B (3, 4) and influenza A (5–7). However, few studies have been made of myocarditis emerging during a specific period (8–11). It is generally believed that Coxsackie B viruses are the most common agents responsible for infectious myocarditis (12, 13). The carditis of acute rheumatic fever, on the other hand, is rare nowadays in the developed countries, and its clinical picture is usually mild (14).

Clinical studies of myocarditis are embarrassed by the difficulty of a diagnosis, especially in mild cases. The ECG criteria are vague; even very high incidence figures of myocarditis (≥40%, during specific viral infections) have been published, as reviewed by Woodruff (15). However, all ECG abnormalities noted in connection with acute infectious diseases, such as vasoregulatory asthenia, should not be explained as indicating myocardial involvement (16).

We have proposed a new ECG classification for patients with various ECG abnormalities which suggest myocardial involvement in connection with.

Address for reprints: J. Heikkilä, M.D., Cardiovascular Laboratory, University Central Hospital, SF-00290 Helsinki 29, Finland.

infectious diseases. This classification is based on serial ECG recordings and on the effect of a β-blocking drug on these changes (17). Here we report our experience with the etiology of myocarditis, with or without pericarditis, and its correlation with clinical features in consecutive patients hospitalized because of ECG changes suggesting myocardial involvement.

PATIENTS AND METHODS

One hundred and eighty-seven patients, young men performing military service, were thoroughly examined at Central Military Hospital 1 in Helsinki. The patients had been admitted due to ECG abnormalities which were observed in the course of an acute infectious disease. This consecutive series of 187 patients, aged 18–38 years (median 20), was collected during the period Dec. 1976–Jan. 1981. The patients' ECGs were taken systematically because of symptoms or signs suggesting acute infectious heart disease, or as a screening examination during an acute infection, even though cardiac symptoms were not present (7, 17). None of the patients had a history of heart disease or other major medical problems.

Diagnosis of myocarditis

On the basis of serial ECG tracings and the effect of a β-blocking drug on the ST-T changes, 162 of the 187 patients could be classified into the following seven ECG groups:

Group 1. The myopericarditis type ST-T pattern showed serially changing ECG ST segment elevations and T wave inversions characteristic of the well established changes in "acute pericarditis" (18). This ECG course was noted in 34 patients. *Group 2.* Myocarditis T wave inversion. A gradual pattern of T wave inversions occurred in at least two ECG leads, where the T wave is normally positive, and the inversions subsequently gradually reversed to normal. The T wave inversions had to last for four days or more. β-Blockade did not normalize inverted T waves in any of these 23 patients. *Group 3.* Thirty-five patients showed a pattern of gradual T wave changes similar to that described in group 2. In fact, the only difference was that no β-blockade test was available for this group. *Group 4.* Ventricular extrasystoles were first noted during or soon after an acute infection as a presenting symptom in this patient group: serial ECGs at the same time showed minor T waves in five patients. Extrasystoles had an occasional frequency of at least 10 beats/min. Further, the patient himself had to feel that this cardiac irregularity was a new symptom. This group comprised 14 patients. *Group 5.* Short-term myocarditis-type T wave inversions, which were gradually changing but did not last longer than three days, were noted in 17 patients. No β-blockade test was available. No vacillating, functional T wave behaviour took place after the ECG pattern had returned to normal. *Group 6.* Functional T wave changes did not show the gradually changing pattern in the serial ECGs described above, but instead vacillated irregularly between a normal and an abnormal stage. T wave inversions were always augmented orthostatically, and were completely normalized by β-blockade. This group included 25 patients initially suspected of having acute myocarditis. *Group 7.* Stable T wave inversions occurring in 14 patients did not show serial alterations, nor were they normalized by β-blockade.

Groups 1 and 2 were considered to have definite myocarditis, groups 3 and 4 probable myocarditis. Myocarditis was possible but uncertain in group 5, while groups 6 and 7 did not have acute myocarditis.

The relevance of this ECG classification was discussed in our previous report (17). The diagnosis of myocarditis was based on this ECG classification. Supplementary echocardiographic and serial X-ray studies were made on each patient while serum enzyme analyses were carried out mainly if the patient was seen in the early stage of the disease. These data have been published separately (17).

Twenty-five of the 187 patients could not be classified into any of the seven groups presented above. Three of these 25 patients were suspected of having myocarditis. One of the three patients developed right bundle branch block and prolongation of the PQ interval during an acute infection. This patient is presented in the Results section in the group of patients with extrasystoles (group 4). Two others had ST-T changes in their ECGs only during exercise. They are presented in the Results section together with group 5 patients (possible myocarditis). The remaining 22 patients were not considered to have acute myocarditis and the majority of them just presented with "early repolarization" variant ST changes or supraventricular benign arrhythmias without signs of acute myocarditis.

Thus, this series consists of 57 patients with definite myocarditis, 50 with probable myocarditis and 19 with possible myocarditis. Acute myocarditis was considered unlikely in the remaining 61 patients.

Etiologic microbiological diagnosis

In an attempt to establish the etiology, serum specimens were taken as soon as possible after a symptomatic infection and in the convalescent stage 2–3 weeks later. A complement fixation test was carried out on a microscale using antigens for the adenovirus group, influenza A and B, parainfluenza 1 and 3, parotitis V-antigen, herpes simplex, respiratory syncytial virus, cytomegalovirus, Coxsackie B5 (representing the enterovirus group), Mycoplasma pneumoniae, and Chlamydia group antigen in 117 of the 126 patients in ECG groups 1–5. The antibodies to Coxsackie B 1–6 viruses were determined by means of a neutralization test in Vero cells in 72 of the 126 patients. A positive etiologic diagnosis was made when at least a fourfold rise was detected in antibody titers in the paired serum samples. A merely high or falling titer was not accepted as indicating a positive diagnosis.

Other serological tests were performed according to the clinical picture of the infection. Antibodies to streptolysin O were measured in 40% of the patients with suspected myocarditis. A changing titer of 400 U/ml or more, or a positive throat culture for β-hemolytic Streptococcus group A with an antistreptolysin titer of 2

Table I. *Etiology of myocarditis related to the ECG patterns*

	Group					
	1	2	3	4	5	Total
ECG definition	Myoperi-carditis	Myocarditis T wave in-versions	Myocarditis T wave in-versions	Extra-systoles	Short-term T wave in-versions	
Diagnosis of myocarditis	Definite	Definite[b]	Probable[c]	Probable	Possible	
Etiology[a]						
Adenovirus	3	4	6	0	6	19
Vaccinia	10	1	1	0	0	12
Influenza A	1	2	3	0	2	8
Streptococcus	1	1	0	4	0	6
Mononucleosis	3	1	1	0	0	5
Myocoplasma	2	0	0	0	1	3
Chlamydia	1	1	0	0	0	2
Coxsackie B4	1	0	1	0	0	2
Influenza B	0	0	1	1	0	2
Parainfluenza	1	0	0	0	0	1
Mumps	0	1	0	0	0	1
Adult Still's disease	1	0	0	0	0	1
Unknown	12	12	22	10	11	67
Total no. of pats.	34	23	35	15	19	126

[a] Double infections occurred twice in group 1 and once in group 5.
[b] β-Blockade did not normalize inverted T waves.
[c] β-Blockade test not performed.

titral or more was required for a positive diagnosis of recent streptococcal disease. A laboratory diagnosis of infectious mononucleosis was based on a positive Paul-Bunnel test and on differential blood cell counts. Antibodies against toxoplasma, yersinia, and corona virus as well as nuclear antibodies or rheumatoid factors were determined in appropriate patients.

Vaccinia virus was considered as an evident etiologic agent in myocarditis or myopericarditis supervening 8–14 days after a smallpox vaccination when all serological studies for other agents were negative. Isolation of the virus from stools and/or throat swabs was attempted in 10% of the myocarditis patients.

RESULTS

A microbiological etiology was established for 59 of the 126 patients (47%) with definite, probable or possible myocarditis, as presented in Table I. The etiology was most often identified in myopericarditis patients (group 1) (65%), while the success rate was lowest (33%) in patients with cardiac arrhythmias only (group 4).

Of the 59 patients with a positive microbial etiology, 47 had a viral diagnosis, six showed evidence of a recent infection with β-hemolytic Streptococcus and are potential cases of acute rheumatic fever carditis, three showed evidence of Mycoplasma pneumoniae infection and two of chlamydial infection, and one had obvious adult Still's disease (19) with myopericarditis as a major symptom.

In three patients, at least fourfold rises were detected in two antibody titers. One patient with myopericarditis had rises both in chlamydia and in parainfluenza titers and another in Coxsackie B4 and adenovirus titers. One patient with short-term ECG T wave inversions had simultaneous increases in antibodies against Mycoplasma pneumoniae and adenovirus.

One myopericarditis patient with typical clinical features of infectious mononucleosis and a positive Paul-Bunnell test (mononucleosis group, Table I) had a concomitant rise in antistreptolysin titer to 6 400 U and a fourfold rise in influenza A antibodies.

The ECG changes suggesting acute myocarditis were present during the very first days after the onset of respiratory or gastrointestinal infections. The changes were usually present already in the first ECG recorded. In 74% of the cases (84/114), the ECG was abnormal in the course of the first week of the disease; in 53% (60/114) the changes were evident already during the three first days (vaccinia patients excluded). No differences were observed between the five groups.

Table II. *Clinical features of vaccinia myocarditis*

EF = ejection fraction, ST↑ = elevation of ST segment, T↓ = inversion of T waves

Pat. no.	Days from vaccination	Cardiac pain	Pericardial rub	Asynergy and/or S_3-gallop	ECG changes			Heart size[a]	Returned to full duty (d.)	Cardiac enzymes[b]	Echocardiography	
					ST↑	Site of T↓	Duration (d.)				EF (%)	Site of asynergy
104	9	+	0	+	+	Inf-apic	50	N	120	N	64	Anteroseptal
106	13	+	0	+	+	Ant-lat	60	↑	95	. .	62	Inferoseptal
108	8	+	0	0	+	Ant-lat	58	N	150	. .	42	Extensive anterior
121	9	0	+	+	+	Inf	12	N	35	. .	66	Apical
122	12	0	0	0	+	Inf-apic	50	N	110	. .	60	Anteroseptal
124	11	+	+	+	+	Ant-lat	45	↑	200	++	70	Anteroseptal
125	14	+	+	+	+	Inf-apic	50	↑	200	++	58	Anterolateral
126	9	+	+	+	+	Ant-lat	66	↑	200	. .	55	Anterior
127	8	+	0	0	+	Inf-apic	30	N	60	. .	62	Uncertain, anterior
130	13	+	+	+	+	Ant-lat	40	N	95	+	63	Diffuse
220	12	+	+	0	0	Inf-apic	10	N	40	N	55	Anterior, posterior
302	12	0	0	0	0	Inf-apic	5	N	40	N	71	Uncertain, diffuse

[a] N = normal, ↑ = enlarged. [b] N = normal, . . = not done, + = modest rise, ++ = marked rise.

Vaccinia myocarditis

Myocarditis was detected in 12 patients 8–14 days (mean 10.8) after a smallpox vaccination without any other infectious agent being incriminated serologically. Eight of these 12 patients presented with other infectious symptoms, in the upper respiratory tract ($n = 7$) and the gastrointestinal tract ($n = 1$), but none had signs of encephalitis or eczema vaccinatum although the local vaccination reaction was usually strong. Vaccinia virus was the most common etiologic agent (10/34) in the patients presenting with myopericarditis-type ECG changes. Clinical data on these patients are given in Table II.

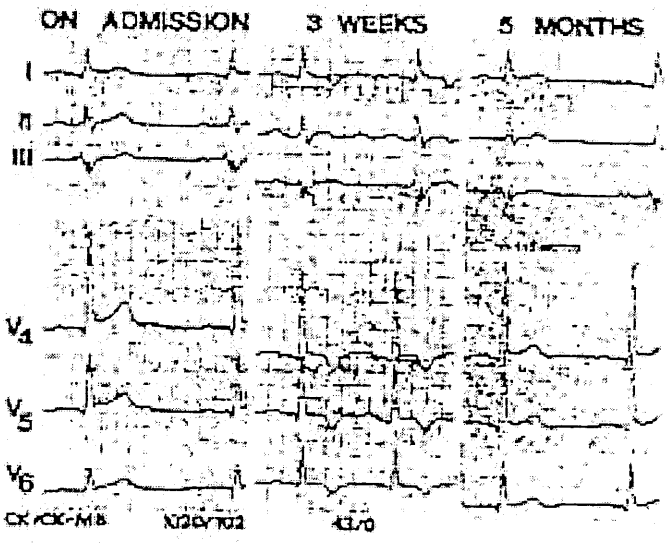

Fig. 1. Case 124. A 20-year-old man developed myopericarditis 11 days after smallpox vaccination. He had chest pains, pericardial rub, palpable paradoxical cardiac pulsation, loud S_3-gallop and cardiac enlargement. ECGs showed characteristic serial ST-T changes of myopericarditis. Serum enzyme pattern was similar to acute myocardial infarction. Echocardiography revealed anteroseptal akinesia. All abnormalities were completely normalized within one year.

Vaccinia myocarditis often started with severe chest pains (Table II). Serum enzymes were studied during the first days of the disease when the ST segments were elevated in four myopericarditis patients. The pattern was similar to acute myocardial infarction in three patients. A cardiac specific creatine kinase MB fraction as high as 102 IU/l (normal 0, total CK 1020 U/l, normal <220) was observed in one vaccinia myopericarditis patient (Fig. 1). During the later stage with T wave inversions only, these enzymes were always normal. In spite of the often dramatic onset of symptoms and signs of acute myopericarditis, the patients recovered quickly, and none developed final cardiac failure. After three months, all vaccinia patients had a normal ECG. In one patient, however, inversion of the T waves occurred during exercise even after one year's follow-up.

Mononucleosis, mycoplasma and chlamydia myocarditis

Myocarditis was associated with glandular fever in five (4%) of the 126 patients; Mycoplasma pneumoniae was responsible in three of them and a fourfold increase in antibodies against the ca-

Table III. *Clinical features of adenovirus myocarditis*

Two patients with double infections and one patient with mere exercise-induced T wave changes excluded
EF = ejection fraction, ST↑ = elevation of ST segment, T↓ = inversion of T waves

Pat. no.	Days to positive ECG	Cardiac pain	Pericardial rub	Asynergy and/or S_3-gallop	ECG changes: ST↑	ECG changes: Site of T↓	ECG changes: Duration (d.)	Heart size*	Returned to full duty (d.)	Echocardiography: EF (%)	Echocardiography: Site of asynergy
Definite myocarditis											
120	2	0	0	+	+	Inf-apic	6	N	60	56	Anterior
129	5	0	+	0	+	Inf-apic	90	N	120	54	Anterolateral
205	2	0	0	0	0	Inf-apic	19	N	60	50	Inferoseptal
211	2	0	0	+	0	Inf-apic	6	N	60	63	Inferoapical
218	2	0	0	+	0	Inf-apic	7	N	60	67	Inferoseptal
221	Vague	0	0	0	0	Ant	5	N	30	69	Anterior
Probable myocarditis											
311	1	0	0	0	0	Inf	10	N	40	76	Inferior
323	1	0-	0	0	0	Ant	7	N	25	60	Uncertain
327	3	0	0	+	0	Inf-	7	N	70	59	Anterolateral
331	7	0	0	+	0	Inf-apic	7	↑	100	..	Uncertain
332	6	0	0	+	0	Ant	5	N	60	81	Anterior
334	2	0	0	+	0	Inf	5	N	25	66	Low anterior
Possible myocarditis											
306	1	0	0	+	0	Ant	3	N	10	68	0
307	2	0	0	+	0	Inf	1	N	20	58	Uncertain
314	3	0	0	0	0	Inf-apic	1	N	10	70	0
315	Vague	0	0	0	0	Ant	2	N	30	62	0

*N = normal, ↑ = enlarged.

mydia group antigen was detected in two. Heart involvement during these infections resembled that found in association with vaccinia virus, clear-cut myopericarditis being the typical presentation. ECG changes were detected 4–11 days after the onset of infectious mononucleosis, 2, 3 and 6 days after the onset of symptoms of acute mycoplasma infection, and 2 and 6 days after chlamydia infection. The mean duration of ECG changes was 24 days in the two chlamydia patients. The heart became enlarged in two mononucleosis patients and in one chlamydia patient, while pericardial friction rub was heard in two mycoplasma patients and in both chlamydia patients.

Coxsackie B4 myocarditis

Remarkably, only two patients (2%) displayed evidence of an acute Coxsackie infection, due to the B4-type virus in both. Both patients had a "flu-like" syndrome. ECG changes were present from the second day of the infection in the patient with myopericarditis-type ST-T changes, while in the other patient with T wave inversions these were not detected until the seventh day of the disease, when an ECG was recorded for the first time (the initial ST segment elevation phase may have been missed). ECG changes lasted for 19 and 55 days, respectively. Both patients recovered completely.

High stable titers of 256 or more against Coxsackie B viruses were established in 6% of the determinations among the myocarditis patients (groups 1–5), and in 7% of the determinations among the non-myocarditis patients (groups 6–7).

Myocarditis caused by adenovirus and influenza

Twenty-nine patients with adenovirus or influenza virus infections usually had mild, subclinical myocarditis. Clinically definite acute myopericarditis with ECG changes present for at least six weeks was noted in four of the 29 patients. Myocarditis was mainly detected only because of routine ECG screening of the infectious patient. For instance, all but one of the nine patients showing only short-term T wave inversions suggesting possible myocarditis were patients with an acute adenovirus or influenza virus infection (Tables I and III). An adenovirus infection was established in 19 myo-

carditis patients, excluding those with double infections. None had heart-type chest pains, only one had radiological enlargement of the heart and only two had gradual ECG ST segment or T wave changes lasting for more than 10 days. Clinical and ECG findings in the 10 patients with influenza A or B infections were fairly similar.

Myocarditis associated with streptococcal infection

Table IV gives the data on six patients with definite ($n=2$) or probable ($n=4$) streptococcal myocarditis. Five patients had diagnostic changes in antistreptolysin O titers. One patient, moreover, had a positive throat culture for β-hemolytic Streptococcus.

Three of the 14 patients with frequent ventricular extrasystoles, developing in connection with an acute infection, had had a recent streptococcal infection and one patient had acute right bundle branch block and prolonged PQ time. In one patient, myocarditis was detected when a pericardial rub appeared eight days after the onset of streptococcal tonsillitis. Two patients had apical systolic murmurs, transient in one and persistent in the other, suggesting mitral regurgitation. Four of the six patients with streptococcal disease showed enlargement of the heart in an X-ray taken during follow-up. None of these patients, who could potentially have rheumatic fever, displayed any other major symptoms of this disease, such as arthritis, chorea or erythema marginatum.

Myocarditis with another positive microbiological diagnosis

One myopericarditis patient had a fourfold rise in both parainfluenza and chlamydia antibody titers. The elevation of mumps antibody titers in a patient with myocarditis and upper respiratory infection was due to a vaccination against mumps just before the acute myocarditis episode, leaving open a possible connection between the mumps vaccination and myocarditis.

A 20-year-old man had characteristic clinical and laboratory features of adult Still's disease (19). Pericardial friction rub appeared after the patient had suffered for two days from a sore throat and severe myalgia, and was present for one month. ECG showed an ST-T pattern typical of myopericarditis. The patient had for several weeks a high, spiking fever which was resistant to antibiotics and also, in the early phase, to prednisone. Other features were the typical rash, pneumonitis, hepatic dysfunction, leucocytosis of 20 000 cells/mm³ and an ESR of up to 122 mm/h. Extensive virological and serological studies were all negative. Virus isolation was successful only once: adeno 7 virus was cultured from stools.

DISCUSSION

In this report we have sought the etiology of mild myocarditis in 126 consecutive patients admitted to the hospital during a period of four years. An infective agent was incriminated in 47% of the cases. The etiology was viral in 47 cases, chlamydia infection was responsible in two cases and Mycoplasma pn. infection in three. Streptococcus was the causative agent in six patients. Apart from the vaccinia and infectious mononucleosis cases, the viral etiology must be considered probable on the basis of at least a 4-fold change in the antibody titers in the paired serum samples; virus was isolated only once and no viral antigen was demonstrated by immunofluorescence or other immunological techniques. The success rate was fairly high in the myopericarditis subgroup: the etiology was established in 65% of the cases. Myocarditis during vaccinia, mononucleosis, mycoplasma, chlamydia and Coxsackie B4 infections was usually clinically clear-cut myopericarditis, with serum enzyme patterns during the early stage of ST segment elevation simulating minor acute myocardial infarction. On the other hand, adenovirus and influenza myocarditis were most often subclinical, being detected only because of serial ECG screening of patients without cardiac symptoms.

In earlier studies, figures for patients with a positive etiologic diagnosis have been: 23/82 (28%) (8), 18/60 (30%) (11), 22/45 (49%) (10), and 8/15 (53%) (9). A high percentage of positive diagnoses was established in an elegant study by Engle et al. (20) concerning viral infection in the specific post-pericardiotomy syndrome in children: 70% of the patients had at least a fourfold rise in at least one of eight viruses (adenovirus, cytomegalo, Coxsackie B 1–6).

In the majority of our patients (53%), ECG changes suggesting viral myocarditis were detected during the very first three days of the onset of respiratory or gastrointestinal infectious symptoms. This would suggest a direct viral involvement of the

Table IV. *Patients with presumptive acute rheumatic fever carditis after streptococcal infection*

AST = antistreptolysin titer, EF = ejection fraction, MI = mitral incompetence, ST↑ = elevation of ST segment, T↓ = inversion of T waves, VES = ventricular extrasystoles, RBBB = right bundle branch block

Pat. no.	Days to positive ECG	Cardiac pain	Pericardial rub	Asynergy and/or S_3-gallop	Murmur	ECG findings	Duration (d.)	Heart size*	Throat culture*	AST (U/ml)	Echocardiography EF (%)	Echocardiography Site of asynergy
124	?	0	+	+	MI	ST↑, inf-apic T↓	>100	↑	..	50–1 250	53	Anteroseptal
125	..	0	0	+	–	Inf-apic T↓	60	↑	..	800–400	55	Inferolateral
409	20	+	0	+	MI	VES	~90	N	+	3 200–400	64	Anterior
412	25	0	0	0	–	VES	>100	N	–	1 100–3 200	70	Diffuse
411	14	0	0	+	–	VES	170	↑	+	200–200	62	Anteroseptal
415	2	0	0	+	–	1° AV block, RBBB	40	↑	–	800–400	69	Diffuse

*N = normal, ↑ = enlarged. †.. = not done, + = positive, and – = negative for group A β-hemolytic Streptococcus.

heart tissue, instead of the immunopathogenetic mechanisms more evident in acute rheumatic fever.

Surprisingly, the most usual presumptive agent incriminated in our series in definite myocarditis (groups 1–2) was vaccinia virus. Every Finnish conscript was vaccinated against smallpox at the beginning of his military service until the end of 1979. We detected 12 myocarditis cases associated with the smallpox vaccination during a three-year period, giving an incidence of about 1/10 000 vaccinations. Occasional myocardial and pericardial complications have been reported to occur 1–3 weeks after a smallpox vaccination (21–24), but only one systematically studied series has been published (23). Myocarditis after a vaccinia inoculation may be severe, and even fatal (21, 22).

The mean interval between the inoculation of the vaccinia virus and the appearance of the heart involvement was 10.8 days. Viremia occurs 9–13 days after vaccination (25). This points to the direct viral involvement of the heart tissue even in cases of vaccinia myocarditis. This assumption is further supported by the isolation of vaccinia virus from the heart of a patient who succumbed to vaccinia myocarditis (26). Virus has also been cultured from the synovial fluid in arthritis, a rare complication of smallpox vaccination (27). It was typical of our vaccinia myocarditis patients that, after an often dramatic onset with chest pain, a complete recovery quickly took place following the first week of the cardiac disease, as also pointed out by Bengtsson et al. (23). Though vaccinia myopericarditis could be clinically conspicuous, only minor heart "irritation" may occur as well. A recent prospective study showed minor ECG changes in eight (3%) of 234 patients vaccinated against smallpox; none had other signs of heart involvement, however (28).

Coxsackie B viruses have been the agents most commonly incriminated in viral myocarditis. However, this etiology was observed in only 2% of our patients. There are two obvious reasons for this discrepancy: 1) No Coxsackie B epidemics occurred in Finland during the study period, 1977–1980. In contrast, during the widespread epidemic of 1965, many patients were hospitalized because of Coxsackie myocarditis in Finland (3). 2) In two earlier series, in which Coxsackie B viruses were incriminated as agents in 15% (11) and in 44% (12) of the cases, even stable high or falling titers of the antibodies against Coxsackie B were accepted as proof of acute infection. In recent reports on the possible role of these viruses in acute myocardial infarction, high titers (256 or more) were common both in patients with myocardial infarction (28%) and in control patients (24%) (29). Although Coxsackie viruses are known to be highly myotrophic (4), our results suggest that they play a minor role as an etiologic agent during periods when Coxsackie epidemics are not evident. Virus diagnostic laboratories had not established widespread epidemics due to other enteroviruses in Finland during the study period, so they were hardly responsible for many cases in this series.

Adenovirus was the most common agent in the serological analysis when all our patients are taken in account. The study population of military troops largely explains this. Adenovirus typically causes continual epidemics among military personnel.

Adenovirus was one of the agents in two of three double infections in this series. In our earlier report on an influenza A epidemic in conscripts (7), we found a simultaneous rise in adenovirus titers in 7.3% of the influenza patients. Thus, some of the myocarditis cases with rising adenovirus antibody titers may have had another unidentified infection, perhaps responsible for the heart involvement, the adenovirus infection being coincidental. Myocarditis during an adenovirus infection is usually mild and subclinical. Its diagnosis therefore depends largely on ECG recordings during the first days of the infection. The same is true of influenza A myocarditis (7).

Acute rheumatic fever is becoming rare and its clinical picture is changing (14). On the basis of our ECG classification, two of our six patients with evidence of a recent streptococcal infection had definite and four probable myocarditis. If these cases are accepted as having had rheumatic fever, the incidence will be about 0.4/10 000 among Finnish conscripts. During the study period, no case with the classic picture of rheumatic fever, with both arthritis and carditis, came to our attention. The incidence of rheumatic fever in the Finnish defence forces was 53/10 000 in 1945 and 5/10 000 in 1963 (30). Six per cent of the definite or probable myocarditis cases were associated with a β-hemolytic Streptococcus infection, while the figure was 49% in a study undertaken by Bengtsson and Lamberger in 1950–55, (31).

The two chlamydia infections deserve some comment. The complement fixation test utilizes a group antigen common to all Chlamydiae, and it is not possible to distinguish between Chlamydia psittaci and C. trachomatis with this test. We have therefore called these infections simply "chlamydial". Evidence is accumulating that even C. trachomatis is able to cause a wide range of clinical conditions beyond the well known oculogenital ones; these are meningoencephalitis (32), pneumonitis in children (33) and adults (34), and endocarditis (35). Because the specific method for the serodiagnosis of chlamydial infections (the microimmunofluorescence test) was not available to us, it seemed wiser not to use the term ornithosis, as has been done in some other studies.

The spectrum of infectious agents recorded in other studies has been much the same as that in the present study: Coxsackie B (8, 9, 11, 20), vaccinia (9, 10), mononucleosis (9–11), Mycoplasma (10), ornithosis (10), adenovirus (11, 20), influenza A (8, 11), mumps (8, 10) and Streptococcus (10, 11). The relative role of each agent varies from study to study, obviously depending on the time of sampling, the study population, and the diagnostic methods and criteria. The pattern of the etiologic agents in myocarditis evidently reflects the overall profile of viruses and other infectious agents in that particular study population at the particular time. However, the above mentioned agents are repeatedly being linked with heart involvement. Thus they must be considered especially cardiotrophic.

Our series does not include any patient with severe myocarditis causing intractable congestive heart failure and showing marked histological inflammatory changes (11, 36). Infectious etiology of this presentation of acute myocarditis has usually remained enigmatic (11, 36).

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