STATE-OF-THE-ART PAPER

Smallpox Vaccination and Myopericarditis: A Clinical Review

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Smallpox is a devastating viral illness that was eradicated after an aggressive, widespread vaccination campaign. Routine U.S. childhood vaccinations ended in 1972, and routine military vaccinations ended in 1990. Recently, the threat of bioterrorist use of smallpox has revived the need for vaccination. Over 450,000 U.S. military personnel received the vaccination between December 2002 and June 2003, with rates of non-cardiac complications at or below historical levels. The rate of cardiac complications, however, has been higher than expected, with two confirmed cases and over 50 probable cases of myopericarditis after vaccination reported to the Department of Defense Smallpox Vaccination Program. The practicing physician should use the history and physical, electrocardiogram, and cardiac biomarkers in the initial evaluation of a post-vaccination patient with chest pain. Echocardiogram, cardiac catheterization, magnetic resonance imaging, nuclear imaging, and cardiac biopsy may be of use in further workup. Treatment is with non-steroidal anti-inflammatory agents, four to six weeks of limited exertion, and conventional heart failure treatment as necessary. Immune suppressant therapy with steroids may be uniquely beneficial in myopericarditis related to smallpox vaccination, compared with other types of myopericarditis. If a widespread vaccination program is undertaken in the future, many more cases of post-vaccinial myopericarditis could be seen. Practicing physicians should be aware that smallpox vaccine-associated myopericarditis is a real entity, and symptoms after vaccination should be appropriately evaluated, treated if necessary, and reported to the Vaccine Adverse Events Reporting System.   (J Am Coll Cardiol 2004;43:1503–10) © 2004 by the American College of Cardiology Foundation

Smallpox is a devastating viral illness that was eradicated after an aggressive widespread vaccination campaign. Routine U.S. childhood vaccinations ended in 1972, and routine military vaccinations ended in 1990. Recently, the threat of bioterrorist use of smallpox has revived the need for vaccination. Over 450,000 U.S. military personnel received the vaccination between December 2002 and June 2003, with rates of non-cardiac complications at or below historical levels (1). The rate of cardiac complications, however, has been higher than expected, with two confirmed cases and over 50 probable cases of myocarditis after vaccination reported to the Department of Defense (DoD) Smallpox Vaccination Program. Halsell et al. (2), in an analysis of the first 230,734 primary vaccinees, recently reported a rate of 1 case of myopericarditis per 12,819 primary vaccinees. As military and civilian vaccination programs continue and more people are vaccinated, it will be important for practicing cardiologists and primary-care physicians to be aware of the potential for cardiac complication.

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HISTORICAL PERSPECTIVE

Smallpox was a highly contagious viral disease, spread by respiratory droplet, endemic in every country in the world, which at times decimated populations and disfigured millions. It was described in Asia as far back as the first century A.D., and since then has been described in Europe, Africa, and the Americas. At one time it may have accounted for 10% of all deaths in the world (3).

Smallpox is caused by the variola virus, which enters via the respiratory tract to infect local lymph nodes. The clinical course of smallpox has been recently well described by Breman and Henderson (4). In brief, it causes a generalized pustular rash and fever after a 7- to 17-day incubation period. Death, if it occurs, is believed to be secondary to toxemia and shock (5). Five types of smallpox infection have been described, of varying severity (6). The most common, accounting for about 90% of cases, is variola major and has a mortality of about 30% in adults, and even higher in infants and children. A milder form of variola infection, described as variola minor, rarely occurred in unvaccinated persons but made up approximately 25% of smallpox infections in those who had been vaccinated and was usually well tolerated. The worst types, hemorrhagic and flat, accounted for 10% or less of cases and were almost always fatal. Previously infected or vaccinated people could also get a

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Abbreviations and Acronyms
CDC    = Centers for Disease Control and Prevention
CRP    = C-reactive protein
DoD    = Department of Defense
ECG    = electrocardiogram
ESR    = erythrocyte sedimentation rate
MRI    = magnetic resonance imaging
NSAID  = non-steroidal anti-inflammatory drug
VIG    = vaccinia immune globulin
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mild form called variola sine eruptione, which was <1% fatal and almost never contagious.

Early attempts at vaccination to prevent smallpox used the actual virus itself in a process called variolation. Dried scab material from pustular wounds of mildly infected persons was intentionally scratched into the skin of uninfected persons. However, this led to approximately 1% of vaccinees contracting severe systemic infections (6,7). In 1796, Edward Jenner observed that a nurse caring for his son had contracted swinepox and appeared to be immune. He infected three other people from the swinepox lesions and then variolated them with smallpox with no subsequent infection occurring. He later demonstrated better protective immunity with cowpox rather than with swinepox. This observation led to the successful vaccination of an eight-year-old boy using material from a cowpox lesion. The process was repeated in others and found to be safer than variolation. The practice of vaccination was slow to catch on, but after considerable effort by Jenner it became a common procedure in Europe and America (3,8).

Current vaccines utilize another poxvirus, vaccinia virus. Vaccinia, cowpox, and variola virus are all poxviruses, of the same subfamily Chordopoxvirinae and genus *orthopoxvirus* (4,6). The origin of vaccinia virus is unclear, but because of the ease with which it is cultivated on many different animals, it became the vaccine of choice to prevent smallpox.

In 1959, the World Health Organization set out to eradicate smallpox from the earth. They capitalized on the availability of an effective vaccine, the absence of any non-human reservoir for variola, the lack of an asymptomatic carrier state, and a long incubation period enabling vaccination to modify the course of the illness (6). Through an aggressive program of case detection, quarantine of the infected, and vaccination of contacts, the World Health Organization was eventually successful. The eradication of smallpox was declared in 1980 (9).

Routine childhood vaccinations in the U.S. were stopped in 1972, and worldwide by 1982. There is now a large population of never vaccinated persons who would be susceptible to infection, and an older population with waning immunity from their vaccinations received over 20 years ago (6). In addition, there is a population of immunocompromised individuals, from those with human immunodeficiency virus infection to transplant survivors, who are at significantly greater risk for mortality and largely did not exist during the smallpox era before its eradication in 1980. This, combined with the concern that smallpox could be used as a bioterrorism weapon, has renewed interest in vaccination, especially in military personnel who might face exposure during the performance of their duties and in health care workers who might care for the ill.

Vaccination of military personnel resumed in December 2002 in many centers across the U.S. Since that time, over 468,000 military personnel and 38,000 civilians have received the smallpox vaccine (10). The Vaccine Healthcare Center Network, a collaborative effort between the DoD and the Centers for Disease Control and Prevention (CDC), developed initially at Walter Reed Army Medical Center, has facilitated the surveillance and case management of vaccine-associated events (Vaccine Adverse Events Reporting System) experienced by service members (1).

The DoD commitment to close surveillance of adverse events has identified an increased rate of pericarditis and myocarditis in temporal association with smallpox vaccination compared with rates seen in comparable unvaccinated populations within the DoD in 2002. In addition, questions have been raised regarding other cardiac events, such as myocardial infarctions and arrhythmias occurring after immunization. To date, ischemic cardiac events have not occurred at a frequency exceeding expected population rates (1).

CARDIAC COMPLICATIONS OF SMALLPOX VACCINATION

Cardiac complications were reported in Europe during the first wave of vaccinations of the 1950s and 1960s. A review of the worldwide literature reveals at least 7 fatal (11–13) and 59 non-fatal cases of post-vaccinial myocarditis among adults (13–25) using autopsy, symptoms, and/or electrocardiogram (ECG) changes to diagnose myocarditis and/or pericarditis. Estimates of incidence range from as high as 2% to 3%, based on the number of Swedish military recruits with asymptomatic T-wave changes after vaccination (14,20), to 1 in 10,000, a number calculated in a 1983 Finnish study on the basis of 12 reported cases divided by the number of military vaccinees in that interval (21). Recovery was most common and within three weeks in those cases that received follow-up.

Of the seven fatal cases, five are from a 1953 French report of five fatal myocardial infarctions occurring after smallpox vaccination (13). All had been stable before vaccination, and two of the five had known coronary artery disease. The authors concluded that those with known coronary artery disease or over the age of 50 with risks for vascular disease should not be vaccinated, even though they had not proven that their cases went beyond expected background rates. The other two fatal cases reported in Europe both showed lymphocytic infiltration of the heart on autopsy (11,12).

Table 1. Case Definition of Myo/Pericarditis for Use in Smallpox Adverse Events Monitoring*

Level of Suspicion	Description of Criteria
Suspected myocarditis	1) Symptoms (dyspnea, palpitations, or chest pain) 2) ECG abnormalities beyond normal variants, not documented previously (ST/T abnormality, paroxysmal supraventricular tachycardia, ventricular tachycardia, atrioventricular block, frequent atrial or ventricular ectopy) OR focal or diffuse depressed LV function of uncertain age by an imaging study 3) Absence of evidence of any other likely cause
Probable myocarditis	1) Meets criteria for suspected myocarditis 2) In addition, meets one of the following: elevated levels of cardiac enzymes (creatine kinase-MB fraction, troponin T or I), OR new onset of depressed LV function by imaging, OR abnormal imaging consistent with myocarditis (MRI with gadolinium, gallium-67 scanning, anti-myosin antibody scanning)
Confirmed myocarditis	1) Histopathologic evidence of myocarditis by endomyocardial biopsy or on autopsy
Suspected pericarditis	1) Typical chest pain (made worse by supine position, improved with leaning forward, pleuritic, constant) 2) No evidence for alternative cause of such pain
Probable pericarditis	1) Meets criteria for suspected pericarditis 2) Has one or more of the following: pericardial rub on auscultation OR ECG with diffuse ST-segment elevations or PR-segment depressions not previously documented OR echocardiogram revealing an abnormal pericardial effusion
Confirmed pericarditis	1) Histopathologic evidence of pericardial inflammation in pericardial tissue from surgery or autopsy

*Summary, adapted from the CDC website, MMWR weekly, May 30, 2003.
  CDC = Centers for Disease Control and Prevention; ECG = electrocardiogram; LV = left ventricle; MRI = magnetic resonance imaging.

In the same time period up to 1970, the European literature reported at least seven non-fatal pediatric cases of post-vaccinial myopericarditis (26–29) and two fatal pediatric cases (30,31), both with inflammatory infiltrate (but no mention of eosinophils) of the myocardium on autopsy. Review of the Australian literature produced reports of 11 non-fatal (32–34) and 1 fatal (35) adult cases of post-vaccinial myopericarditis, the last with a mixed cardiac infiltrate on autopsy.

Conversely, cardiac complications were rarely described during that time period in the U.S. The American literature discusses only two non-fatal adult cases (36,37) and two fatal adult cases (38,39). Multiple reports exist discussing other complications, but none were cardiac (40–43). It was thought that this was due to the use of a different strain of vaccinia in the U.S., the New York City Board of Health strain (Dryvax, Wyeth Laboratories, Marietta, Pennsylvania) than was used in Europe or Australia. Given the current experiences using the New York City Board of Health vaccine strain in the last year, we must now question the validity of this assumption and wonder if the difference was actually due to variations in monitoring and reporting.

With the benefit of a more structured reporting system set up by the DoD, we have extensive data on the 468,000 personnel who have been vaccinated. Personnel have been monitored for evidence of multiple adverse events, including pericarditis and myocarditis. For purposes of data collection and reporting, the two have been combined into a single entity "myopericarditis" indicating signs and symptoms of one or both. As the program evolved and an increasing number of cases were reviewed, the DoD and CDC smallpox vaccination working groups developed case definitions for epidemiologic surveillance purposes of myoperi-

carditis (either pericarditis, myocarditis, or both) with the level of evidence to support the diagnosis being ranked as suspected, probable, or confirmed (Table 1). As of June 15, 2003, DoD has identified over 50 cases of suspected, probable, or confirmed myopericarditis occurring within 30 days of vaccination in these personnel, based upon clinical evaluation of symptoms, ECG, cardiac enzyme assays, echocardiography, and the exclusion of ischemic coronary artery disease.

DIAGNOSIS AND REPORTING

History and symptoms. Patients with myopericarditis may be asymptomatic or may report a range of symptoms, including chest pain, fatigue, shortness of breath, palpitations, decreased exercise tolerance, orthopnea, paroxysmal nocturnal dyspnea, increasing edema, and lightheadedness. The chest pain is classically a burning or a pressure that is pleuritic and may be relieved by sitting forward. It is often constant and without any relationship to exertion. As the Finnish studies have shown, asymptomatic ECG abnormalities (non-specific ST-T abnormalities that return to normal within 6 months) occur in up to 2% to 3% of smallpox vaccinees, the exact meaning of which is uncertain (14,20). Unfortunately, no studies to date have used cardiac biomarkers in a similar population to investigate these ECG abnormalities. Thus, the clinical significance of asymptomatic ECG changes post-vaccination remains unclear.

Finding a causal relationship between smallpox vaccination and myopericarditis relies heavily on a temporal link between the timing of vaccination and the onset of symptoms and/or ECG changes. Because tests for viremia are only rarely positive (16,21,44,45), and viral antibody titers

would normally go up after a successful vaccination, these two tests are useful for ruling out rare instances of active viral infection but not helpful in finding a cause in the majority of cases. Therefore, we must rely on a temporal relationship, and accept that there may be the rare coincidental case not due to smallpox vaccination but occurring soon after it.

ECG. Classically, ECG has been the primary diagnostic tool in the diagnosis of myopericarditis. Nearly all of the case reports from 1980 or before rely on symptoms alone or symptoms with ECG changes. These changes are predominantly ST- or T-wave abnormalities ranging from mild, non-specific T-wave flattening and inversion to dramatic ST-segment elevations that evolve into T-wave inversions but not Q waves. The presence of ECG abnormalities in the appropriate clinical setting is highly suggestive, but not diagnostic, of myopericarditis.

Cardiac catheterization. It has been well shown that myopericarditis often mimics acute myocardial infarction (13,46–48). Cardiac catheterization is primarily used in this acute setting to distinguish ischemic from inflammatory cell death. Although it is not diagnostic of myopericarditis, it plays a key role by diagnosing or excluding ischemic heart disease. In some cases in which suspicion of myopericarditis is high and coronary artery disease risk is low, it may be more appropriate to non-invasively rule out ischemic heart disease with a stress imaging test such as a stress echocardiogram or a nuclear stress perfusion scan. Right heart catheterization may be indicated in cases involving compromised hemodynamic function and suspected tamponade.

Endomyocardial biopsy. Although it is the gold standard for the diagnosis of myocarditis, biopsy is of limited utility, especially in acute myocarditis, because of the often patchy nature of active inflammation. In a large series of over 2,000 patients with clinically suspected myocarditis, endomyocardial biopsy was positive in only 10% (49–51). Wu et al. (52) provide a concise review of the indications for endomyocardial biopsy in the management of dilated cardiomyopathy and myocarditis. Given the risks of biopsy and the limited benefit, its use should be limited to the patient with left ventricular dysfunction and symptoms not responsive to conventional medical management.

Cardiac enzymes and markers of inflammation. Earlier studies of post-vaccinial myopericarditis sporadically evaluated non-specific cardiac enzymes. More recent studies have shown both troponin T and I to be fairly specific for myocarditis when used in conjunction with clinical suspicion (53,54). Although they are significantly more sensitive than creatine kinase-MB fraction in detecting myocardial injury, both will be normal in 44% to 66% of subjects with immunohistologic evidence of myocarditis (53). Although a negative troponin assay may be of limited utility, when matched to the clinical suspicion of myocarditis, an elevation of troponin is over 90% predictive of myocarditis (53,54). Troponin T and troponin I are useful adjuncts in the workup of potential myopericarditis, and positive values

should significantly raise suspicion of myocarditis but normal values alone should not rule it out.

Markers of inflammation in the serum, namely the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), have not been thoroughly reviewed as diagnostic tools in myopericarditis. They are general markers of inflammation that are more sensitive than specific, as they do not differentiate between causes of inflammation. Given their low cost, both ESR and CRP are fundamental laboratory assays in working up possible myopericarditis, as they will help to show if a general inflammatory state is in effect, and in theory are likely predictive of benefit from anti-inflammatory treatment.

Echocardiogram. The echocardiogram is extremely useful for localizing wall motion abnormalities, evaluating left ventricular function, identifying a pericardial effusion, and demonstrating tamponade. Although not helpful in the definitive diagnosis of myopericarditis, the echocardiogram may greatly affect treatment and medical management.

Magnetic resonance imaging (MRI). Although the studies looking at MRI in the diagnosis of myocarditis have been small, they are promising. When MRI images are examined for post-gadolinium enhancement of the myocardium, almost 100% of patients show focal or diffuse enhancement not seen in normal control subjects. Two studies have shown 100% sensitivity and specificity for myocarditis detection by MRI (55,56), and an editorial encourages its use to detect myocarditis (57). Magnetic resonance imaging will initially show a focal enhancement in acute myocarditis, but within a week this becomes diffuse (55,58). The MRI abnormalities may persist at least one month after onset of symptoms (55). Magnetic resonance imaging is a useful and likely underutilized tool in the diagnosis of myopericarditis and should be considered in any case that is not made completely clear by less expensive tests and clinical history and presentation.

Indium-111 antimyosin antibody scintigraphy. This study uses radiolabelled antibodies to cardiac myosin (MyoScint, Centocor) to localize areas of cardiac cell death. It has been shown to be approximately 66% sensitive and 71% specific in the detection of myocarditis in patients clinically suspected of myocarditis (59). It may be especially helpful in conjunction with resting thallium images in working up patients with suspected acute myocardial infarction who have normal cardiac catheterizations. By showing areas of inflammation with the antimyosin antibody scan that correspond to areas of normal perfusion by thallium scan, Sarda et al. (60) showed that 78% of patients with suspected acute myocardial infarction but normal cardiac catheterization had likely myocarditis. Given the limited availability of this scan and the lower sensitivity and specificity than that seen with MRI, cardiac MRI appears to be the study of choice.

Gallium-67 scan of the heart. Gallium-67 scanning makes use of the fact that gallium-67 binds to white blood cells and reveals areas of inflammation. In a 1984 study comparing gallium scan to the gold standard of biopsy in
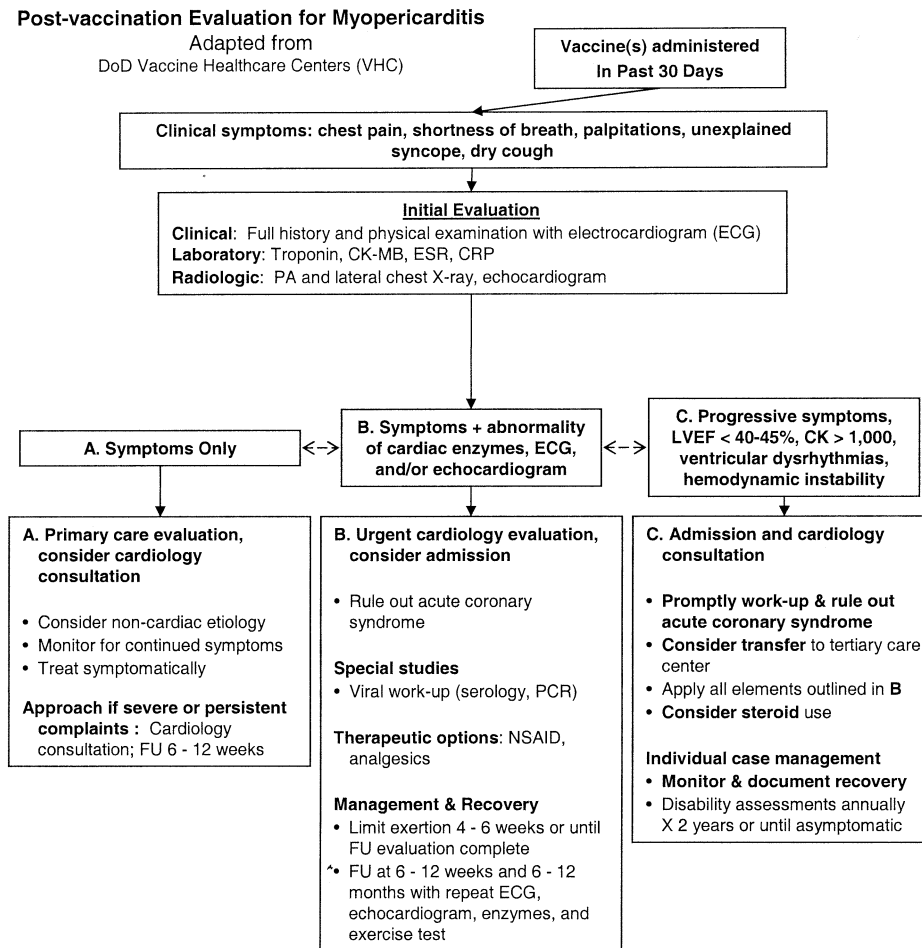
Post-vaccination Evaluation for Myopericarditis
Adapted from
DoD Vaccine Healthcare Centers (VHC)

Vaccine(s) administered
In Past 30 Days

Clinical symptoms: chest pain, shortness of breath, palpitations, unexplained syncope, dry cough

Initial Evaluation
Clinical: Full history and physical examination with electrocardiogram (ECG)
Laboratory: Troponin, CK-MB, ESR, CRP
Radiologic: PA and lateral chest X-ray, echocardiogram

A. Symptoms Only

B. Symptoms + abnormality of cardiac enzymes, ECG, and/or echocardiogram

C. Progressive symptoms, LVEF < 40-45%, CK > 1,000, ventricular dysrhythmias, hemodynamic instability

A. Primary care evaluation, consider cardiology consultation

- Consider non-cardiac etiology
- Monitor for continued symptoms
- Treat symptomatically

Approach if severe or persistent complaints : Cardiology consultation; FU 6 - 12 weeks

B. Urgent cardiology evaluation, consider admission

- Rule out acute coronary syndrome

Special studies
- Viral work-up (serology, PCR)

Therapeutic options: NSAID, analgesics

Management & Recovery
- Limit exertion 4 - 6 weeks or until FU evaluation complete
- FU at 6 - 12 weeks and 6 - 12 months with repeat ECG, echocardiogram, enzymes, and exercise test

C. Admission and cardiology consultation

- **Promptly work-up & rule out acute coronary syndrome**
- **Consider transfer** to tertiary care center
- Apply all elements outlined in **B**
- **Consider steroid** use

Individual case management
- **Monitor & document recovery**
- Disability assessments annually X 2 years or until asymptomatic

Figure 1. Adapted from the clinical guideline algorithm used by the Department of Defense Vaccine Healthcare Center. CK = creatine kinase; CRP = C-reactive protein; ECG = electrocardiogram; ESR = erythrocyte sedimentation rate; FU = follow-up; LVEF = left ventricular ejection fraction; NSAID = non-steroidal anti-inflammatory drug; PA = posteroanterior; PCR = polymerase chain reaction.

patients with dilated cardiomyopathy, gallium scanning demonstrated 87% sensitivity and 86% specificity for myocarditis (61).

Viremia. Historically, viremia was detected in only one case of fatal myopericarditis (39) by electron microscopy. In the DoD's case series, two cases were biopsied, neither of which revealed vaccinia virus by polymerase chain reaction or viral culture. A study of Coxsackie myocarditis revealed that in 41 patients with myocarditis and antibodies to coxsackie, virus was isolated from only three patients (44). In part, this may be due to difficulty in accurately identifying the virus, but most likely it means that most cases of post-viral myocarditis take place after completion of active viral infection. This both points to an autoimmune mechanism, perhaps virally triggered, and it means that viral cultures and searching for active infection may be of limited value in patients with myopericarditis.

Based on the above information and expert consensus, the DoD Vaccine Healthcare Center Network in collaboration with the Smallpox Vaccination Cardiac Working Group has developed a clinical guideline algorithm to standardize the evaluation and follow-up of individuals presenting with

possible myopericarditis. The attached algorithm delineates the current approach (Fig. 1).

REVIEW OF TREATMENT OPTIONS

Immunosuppressive therapy. Baldini and Bani (26) reported three cases in Italy of post-vaccinial myopericarditis, each managed with corticosteroids, and all three recovering. Matthews and Griffiths (24) reported a 25-year-old patient in the United Kingdom with post-vaccinial myopericarditis and congestive heart failure symptoms who showed dramatic recovery with steroid therapy (intravenous hydrocortisone initially and then oral prednisone). A pediatric patient in Greece became severely ill with myocarditis and congestive heart failure after smallpox vaccination, and also had a dramatic recovery after receiving cortisone and vaccinia immune globulin (VIG) (29). This latter case is especially intriguing, as the two treatments VIG and steroids work in nearly opposite ways: VIG neutralizes active viral infection, whereas steroids break an autoimmune inflammatory cycle. Giving steroids during an active viral infection could in theory cause the patient to worsen by

inducing an immunosuppressed state. Thus the efficacy of immunosuppression in post-vaccinial myopericarditis depends upon there being a post-infectious autoimmune inflammatory process as the cause, in which active viral infection does not play a role.

A series of studies address the role of immunosuppression in myocarditis unrelated to smallpox vaccination. Mason et al. (51) conducted a randomized trial of immunosuppressive therapy in patients with a left ventricular ejection fraction <45% and histopathologic diagnosis of myocarditis (lymphocytic infiltrate on cardiac biopsy) and showed no significant difference in change in ejection fraction or in mortality between the immunosuppressed group or the control group. Conversely, Camargo et al. (62) reported a benefit to prednisone with azathioprine or cyclosporine, over prednisone alone or just conventional treatment, in children with dilated cardiomyopathy and biopsy-proven active myocarditis. Likewise, Frustaci et al. (63) showed that patients with active lymphocytic myocarditis, circulating cardiac autoantibodies, and no viral genome in the myocardium respond favorably (by left ventricular function evaluation) to immunosuppression with prednisone and azathioprine. These models of myocarditis not associated with vaccinia may or may not have relevance to the vaccinia-associated disease presentation.

Thus far there have been only two cases reported of post-vaccinial myopericarditis treated with immunosuppressives. Murphy et al. (64) recently described a 29-year-old man who developed symptomatic heart failure three weeks after smallpox vaccination. The patient was treated with standard heart failure medications as well as high-dose corticosteroids. Within 10 days the patient had resolution of heart failure, a return of normal ventricular function, and resolution of serum inflammatory markers. A second case with post-immunization epicarditis, which was complicated by a fatal alveolitis, also did not demonstrate evidence of viral tissue infection.

Both cases, the first with endomyocardial biopsy and the second from autopsy examination, demonstrated a mixed lymphocytic infiltrate with eosinophil degranulation in areas of myocardial necrosis, suggesting an immune inflammatory mechanism of myocardial injury. These observations suggest that vaccinia-associated myopericarditis is due to an immune inflammatory response rather than a viral infection of the myocardium or pericardium.

Non-steroidal anti-inflammatory drugs (NSAIDs). The mainstays of treatment for the symptoms of pericarditis and myopericarditis are NSAIDs, with additional analgesics as needed, although there are no controlled clinical trials, and NSAIDs are not recommended in the first two weeks of pure myocarditis. Ibuprofen may be the preferred agent, as it has been found to be less gastrointestinally toxic than others in its class. In theory, any NSAID may be effective. Recommended doses of ibuprofen vary from 300 to 800 mg every 8 h as needed for symptom relief, and duration of treatment may be as little as a few days or may be for weeks

(65). There is one recent case report of myocarditis after smallpox vaccination treated successfully with NSAIDs (66).

VIG. Vaccinia immune globulin has been shown to be useful in the treatment of certain non-cardiac complications of the smallpox vaccine, to include progressive vaccinia, eczema vaccinatum, and ocular vaccinia, all of which are linked with uncontrolled vaccinia replication. Although it is helpful in these situations, only one publication reports its use in myocarditis after smallpox vaccination, in a six-year-old boy who recovered after treatment with both VIG and steroids (29). Given the absence of any proof of active viral infection in our experience with the DoD vaccinees, and the lack of historical proof in the literature, it is more likely that post-vaccinial myopericarditis is a non-infectious process that will not benefit from the anti-viral effect of VIG, or for that matter any other specific antiviral therapy.

Rest. Recommendations for rest after acute myocarditis are based on animal studies showing a large increase in mortality in mice that are made to exercise strenuously after infection with Coxsackie virus (67–69). A study reviewing sudden cardiac death in U.S. Air Force recruits found 17 of 19 cases to be associated with strenuous exertion, and of these 5 were associated with myocarditis, 1 post-vaccinial (39). Patients who have myocarditis and undergo exercise stress tests are more likely to show ectopic activity, and in fact older series have used this as a criterion for myopericarditis (20). Even at rest, patients with myopericarditis show more ectopy (19,44,70). These limited data suggest that avoidance of high-level exertion during the recovery and healing phase of myopericarditis (four to six weeks) is advisable.

Conventional heart failure treatment. Post-vaccinial myopericarditis that leads to left ventricular dysfunction should be treated no differently than other cases of cardiomyopathy with regard to management of the heart failure. Beta-blockers such as carvedilol or long-acting metoprolol as well as the angiotensin-converting enzyme inhibitors have been shown to be beneficial and should be used unless not tolerated by the patient. Diuretics, nitrates, and digoxin should be used as needed for symptom control. If needed, positive inotropes and left ventricular assist devices may be employed.

Treatment summary. Historically, most cases of post-vaccinial myopericarditis were self-limited and resolved completely in time (1,13–25). Unfortunately, a few did not (11,13,35,38,39). Therapeutic approaches to myopericarditis after vaccinia immunization are based on limited data, and there is a clear need for improved evidence regarding the efficacy of different approaches. In the absence of other etiologies and no evidence of active vaccinia systemic infection, non-steroidal anti-inflammatory therapy in most patients followed by corticosteroids in those with a more severe clinical presentation (reduced left ventricular function, evidence of congestive heart failure) appears to be a reasonable approach, in combination with conventional heart failure medications and

avoidance of high-level exertion. The role of VIG remains unclear, particularly in the absence of evidence suggesting an active viral infection. At the current time, the state of knowledge does not support a definitive evidence-based guideline, and continued outcomes data collection on patients affected with this problem is needed.

FUTURE DIRECTIONS

Future research is needed to better quantify the risk of myopericarditis after smallpox vaccination. A prospective trial following participants with serial ECGs and physical examinations, with confirmatory studies, as needed, is being planned. Further investigation should attempt to better elucidate whether post-vaccinial myopericarditis is a non-infectious immune reaction that is uniquely responsive to steroids. Also, more experience with diagnostic modalities is needed. Whether MRI, nuclear studies, laboratory evaluation, or something else entirely will become the confirmatory test of choice needs to be explored further. Myocarditis itself remains a poorly understood entity, and may be a final result of a process that can have multiple pathways (e.g., ischemic, infectious, post-infectious, autoimmune, toxic). Finally, we need to continue to follow patients diagnosed with post-vaccinial myopericarditis to establish whether long-term sequelae exist.

SUMMARY

Cardiac complications of smallpox vaccination, originally thought to be rare, have in the last 10 months of experience proven to be more common. Chest pain or heart failure symptoms after smallpox vaccination should be taken seriously and addressed with a diagnostic workup, treated appropriately, and reported to the CDC or the Vaccine Adverse Events Reporting System. Recently, the overall rate of symptomatic myopericarditis in DoD personnel after smallpox vaccination has approached approximately 1 in 10,000, a rate similar to that reported in some European studies from the 1960s. These cases have been detected via careful monitoring of vaccinees by the DoD using clinical screening for symptoms, and when indicated ECG, laboratory assay for myocardial injury, and echocardiogram. Further tests have been utilized as clinically indicated to rule out ischemic disease and other causes of cardiac inflammation. Only two cases have been histologically confirmed, but in neither of these cases nor in serum from 32 other affected patients has there been any evidence of vaccinia. Histology has shown a mixed lymphocytic infiltrate with eosinophil degranulation in areas of myocardial necrosis. These findings support a non-infectious pathogenesis of inflammation, similar to hypersensitivity myocarditis, which might be especially responsive to immunosuppression, a hypothesis that has held true in at least one case.

Although there is limited information regarding the risk to individuals with a history of congestive heart failure or coronary artery disease, such individuals should be excluded from smallpox vaccinations on the theoretical premise that increased inflammation could exacerbate a chronic problem. Likewise, there is little known on the potential additional risk portended by a previous episode of myopericarditis. Until further investigation can answer this question, we support a conservative approach not vaccinating individuals with a history of myopericarditis of any etiology.

The total number affected remains relatively small given the limited scope of smallpox vaccinations since December 2002. However, in the event of more widespread vaccine administration, in a population that could be less healthy than the U.S. military population, there is the potential for thousands of related myopericarditis cases. Fortunately, most of the recent cases, which receive ongoing review, have recovered promptly and completely, with follow-up assessments of their symptomatology, ejection fraction, and exercise capacity. Long-term follow-up to document stability of recovery is under way.

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REFERENCES

1. Grabenstein JD, Winkenwerder W Jr. U.S. military smallpox vaccination program experience. JAMA 2003;289:3278–82.
2. Halsell JS, Riddle JR, Atwood JE, et al. Myopericarditis following smallpox vaccination among vaccinia-naive U.S. military personnel. JAMA 2003;289:3283–9.
3. Barquet N, Domingo P. Smallpox: the triumph over the most terrible of the ministers of death. Ann Intern Med 1997;127:635–42.
4. Breman JG, Henderson DA. Diagnosis and management of smallpox. N Engl J Med 2002;346:1300–8.
5. Martin DB. The cause of death in smallpox: an examination of the pathology record. Mil Med 2002;167:546–51.
6. Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi D. Smallpox and its Eradication. Geneva: World Health Organization, 1988:1–68.
7. McClain J. Smallpox. In: Sidell FR, Takafuji ET, Franz DR, editors. Medical Aspects of Chemical and Biological Warfare. Washington, DC: Office of the Surgeon General, United States, 2003:540–59.
8. Friedman M, Friedland GW. Medicine's 10 Greatest Discoveries. New Haven, CT: Yale University Press, 1998:65.
9. World Health Organization. The global eradication of smallpox: Final report of the global commission for the certification of smallpox eradication. History of International Public Health, No. 4. Geneva: World Health Organization, 1980.
10. Centers for Disease Control and Prevention. Update: cardiac and other adverse events following civilian smallpox vaccination—United States, 2003. MMWR 2003;52:639–42.
11. Dalgaard J. Fatal myocarditis following smallpox vaccination. Am Heart J 1957;54:156–7.
12. Mant K. Mort subite due à une myocardite focale suivant une vaccination contre la variole. Ann Med Leg 1963;443:49–52.
13. Mathieu L. Vaccination antivariolique et thomboses coronarienne aigue. Arch Mal Coeur Vaiss 1953;48:802–6.
14. Ahlborg B, Linroth K, Nordgren B. ECG-changes without subjective symptoms after smallpox vaccination of military personnel. Acta Med Scand 1966;464 Suppl:127–34.
15. Bengtsson E, Holmgren A, Nystrom B. Smallpox outbreak and vaccination problems in Stockholm, Sweden 1963. Circulatory studies in patients with abnormal ECG in the course of postvaccinal complications. Acta Med Scand 1966;464 Suppl:113–26.
16. Bengtsson E, Lundstrom R. Postvaccinial myocarditis. Cardiologia 2003;30:1–8.

17. Bergstrom K, Erikson U, Nordbring F, Nordgren B, Parrow A. Acute non-rheumatic myopericarditis: a follow-up study. Scand J Infect Dis 1970;2:7–16.
18. Donadon W, Pagnan A, Dal Palu C. [Case of acute benign myocarditis caused by smallpox vaccination]. Minerva Cardioangiol 1974;22:642–5.
19. Gerzen P, Granath A, Holmgren B, Zetterquist S. Acute myocarditis: a follow-up study. Br Heart J 1972;34:575–83.
20. Helle EP, Koskenvuo K, Heikkila J, Pikkarainen J, Weckstrom P. Myocardial complications of immunizations. Ann Clin Res 1978;10:280–7.
21. 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.
22. Karjalainen J, Heikkila J. Incidence of three presentations of acute myocarditis in young men in military service: a 20-year experience. Eur Heart J 1999;20:1120–5.
23. MacAdam D, Whitaker W. Cardiac complications after vaccination for smallpox. Br Med J 1962;2:1099–100.
24. Matthews AW, Griffiths ID. Post-vaccinial pericarditis and myocarditis. Br Heart J 1974;36:1043–5.
25. Mead J. Serum transaminase and electrocardiographic findings after smallpox vaccination: case report. J Am Geriatr Soc 1966;14:754–6.
26. Baldini G, Bani E. [Cardiac Complications in Jennerian vaccination (clinical and electrocardiographic studies)]. Min Ped 1979;31:35–9.
27. Bessard G, Marchal A, Avezou F, Pont J, Rambaud P. [A new case of myocarditis following smallpox vaccination]. Pediatrie 1974;29:179–84.
28. Caldera R, Sarrut S, Mallet R, Rossier A. Existe-T-Il des complications cardiaques de la vaccine. Ann De Pediatric 1961;21:1281–4.
29. Moschos A, Papaioannou AC, Nicolopoulos D, Anagnostakis D. Cardiac complications after vaccination for smallpox. Helv Paediat Acta 1976;31:257–60.
30. Gatta A, Pieroni P. Miocardite acuta mortale dopo vaccinazione antivariolosa. Min Ped 1976;28:1691–6.
31. Larbre F, Thivolet J, Hermier M, Cotton JB, Gaudin-Richoux G. [Fatal acute myocarditis after smallpox vaccination]. Pediatrie 1966;21:345–50.
32. Feery BJ. Adverse reactions after smallpox vaccination. Med J Aust 1977;2:180–3.
33. Hallett P. A survey of complications to smallpox vaccination. Med J Aust 1969;1:898–901.
34. Price MA, Alpers JH. Acute pericarditis following smallpox vaccination. P N G Med J 1968;11:30–3.
35. Finlay-Jones LR. Fatal myocarditis after vaccination against smallpox: report of a case. N Engl J Med 1964;270:41–3.
36. Cangemi VF. Acute pericarditis after smallpox vaccination. N Engl J Med 1958;258:1257–9.
37. Lane JM, Ruben FL, Neff JM, Millar JD. Complications of smallpox vaccination, 1968. N Engl J Med 1969;281:1201–8.
38. Dolgopol V, Greenberg M, Aronoff R. Encephalitis following smallpox vaccination. AMA Archives of Neurology and Psychiatry 1955;73:216–23.
39. Phillips M, Robinowitz M, Higgins JR, Boran KJ, Reed T, Virmani R. Sudden cardiac death in Air Force recruits. A 20-year review. JAMA 1986;256:2696–9.
40. Griffin HE. Reactions to influenza vaccine. Ann Allergy 1959;17:179–87.
41. Kempe CH. Studies on smallpox and complications of smallpox vaccination. Pediatrics 1960;August:176–89.
42. 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.
43. Lane JM, Ruben FL, Abrutyn E, Millar JD. Deaths attributable to smallpox vaccination, 1959 to 1966, and 1968. JAMA 1970;212:441–4.
44. Smith WG. Coxsackie B myopericarditis in adults. Am Heart J 1970;80:34–46.
45. Tang WHW, Young JB. Myocarditis. Available at: www.emedicine.com. Updated October 8, 2002.
46. 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.
47. Klein RM, Schwartzkopff B, Strauer BE. Evidence of endothelial dysfunction of epicardial coronary arteries in patients with immunohistochemically proven myocarditis. Am Heart J 1998;136:389–97.
48. Miklozek CL, Crumpacker CS, Royal HD, Come PC, Sullivan JL, Abelmann WH. Myocarditis presenting as acute myocardial infarction. Am Heart J 1988;115:768–76.
49. Aretz HT, Billingham ME, Edwars WD, et al. Myocarditis. A histopathologic definition and classification. Am J Cardiovasc Pathol 1987;1:3–14.
50. Davies MJ, Ward DE. How can myocarditis be diagnosed and should it be treated? Br Heart J 1992;68:346–7.
51. Mason JW, O'Connell JB, Herskowitz A, et al. A clinical trial of immunosuppressive therapy for myocarditis. The Myocarditis Treatment Trial Investigators. N Engl J Med 1995;333:269–75.
52. Wu LA, Lapeyre AC III, Cooper LT. Current role of endomyocardial biopsy in the management of dilated cardiomyopathy and myocarditis. Mayo Clin Proc 2001;76:1030–8.
53. Lauer B, Niederau C, Kuhl U, et al. Cardiac troponin T in patients with clinically suspected myocarditis. J Am Coll Cardiol 1997;30:1354–9.
54. Smith SC, Ladenson JH, Mason JW, Jaffe AS. Elevations of cardiac troponin I associated with myocarditis: experimental and clinical correlates. Circulation 1997;95:163–8.
55. Friedrich MG, Strohm O, Schulz-Menger J, Marciniak H, Luft FC, Dietz R. Contrast media-enhanced magnetic resonance imaging visualizes myocardial changes in the course of viral myocarditis. Circulation 1998;97:1802–9.
56. Roditi GH, Hartnell GG, Cohen MC. MRI changes in myocarditis—evaluation with spin echo, cine MR angiography and contrast enhanced spin echo imaging. Clin Radiol 2000;55:752–8.
57. Gagliardi MG, Polletta B, Di Renzi P. MRI for the diagnosis and follow-up of myocarditis. Circulation 1999;99:458–9.
58. Laissy JP, Messin B, Varenne O, et al. MRI of acute myocarditis: a comprehensive approach based on various imaging sequences. Chest 2002;122:1638–48.
59. Kuhl U, Lauer B, Souvatzoglu M, Vosberg H, Schultheiss HP. Antimyosin scintigraphy and immunohistologic analysis of endomyocardial biopsy in patients with clinically suspected myocarditis—evidence of myocardial cell damage and inflammation in the absence of histologic signs of myocarditis. J Am Coll Cardiol 1998;32:1371–6.
60. Sarda L, Colin P, Boccara F, et al. Myocarditis in patients with clinical presentation of myocardial infarction and normal coronary angiograms. J Am Coll Cardiol 2001;37:786–92.
61. O'Connell JB, Henkin RE, Robinson JA, Subramanian R, Scanlon PJ, Gunnar RM. Gallium-67 imaging in patients with dilated cardiomyopathy and biopsy-proven myocarditis. Circulation 1984;70:58–62.
62. Camargo PR, Snitcowsky R, da Luz PL, et al. Favorable effects of immunosuppressive therapy in children with dilated cardiomyopathy and active myocarditis. Pediatr Cardiol 1995;16:61–8.
63. 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.
64. Murphy JG, Wright RS, Bruce GK, et al. Eosinophilic-lymphocytic myocarditis following immunization for smallpox in a previously healthy 29-year-old man. Lancet 2003;362:1378–80.
65. Braunwald E, Zipes DP, Libby P. Heart Disease: A Textbook of Cardiovascular Medicine. 6th edition. Philadelphia, PA: W.B. Saunders Company, 2001:1783–838.
66. Saurina G, Shirazi S, Lane JM, Daniel B, DiEugenia L. Myocarditis after smallpox vaccination: a case report. Clin Infect Dis 2003;37:145–6.
67. Cabinian AE, Kiel RJ, Smith F, Ho KL, Khatib R, Reyes MP. Modification of exercise-aggravated coxsackievirus B3 murine myocarditis by T lymphocyte suppression in an inbred model. J Lab Clin Med 1990;115:454–62.
68. Ilback NG, Fohlman J, Friman G. Exercise in coxsackie B3 myocarditis: effects on heart lymphocyte subpopulations and the inflammatory reaction. Am Heart J 1989;117:1298–302.
69. Kiel RJ, Smith FE, Chason J, Khatib R, Reyes MP. Coxsackievirus B3 myocarditis in C3H/HeJ mice: description of an inbred model and the effect of exercise on virulence. Eur J Epidemiol 2003;5:348–50.
70. Heikkila J, Karjalainen J. Evaluation of mild acute infectious myocarditis. Br Heart J 1982;47:381–91.