Comparison of Clinical Presentation of Acute Myocarditis Following Smallpox Vaccination to Acute Coronary Syndromes in Patients <40 Years of Age*

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Smallpox vaccine–associated myopericarditis may have a similar presentation to acute coronary syndrome (ACS). The clinical records of 78 young patients (<40 years of age) presenting with ACS (n = 16) or myocarditis after smallpox vaccination (n = 62) were reviewed. Comparisons were made among clinical presentation, cardiac enzymes, echocardiographic findings, and electrocardiographic changes. The presence of cardiac risk factors or focal wall motion abnormalities on echocardiography were associated with a diagnosis of ACS. There was a trend toward earlier elevation of troponin-I and creatine kinase in patients with myocarditis compared with ACS.

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Chest pain is a frequent complaint in young patients seeking medical attention. Even after initial evaluation with histories and physical and laboratory studies, there is considerable clinical overlap between young patients with acute coronary syndrome (ACS) and those presenting with myocarditis.[1–4] Recent reports have described the greater than expected incidence of myopericarditis after smallpox vaccination in United States military personnel,[5–7] and all these patients were identified after presentation for chest symptoms. However, little information exists to differentiate these patients from those with premature atherosclerosis causing ACS. The purpose of this

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TABLE 1 Patient Characteristics and Initial Findings Comparing Those With Subsequent Diagnoses of ACS and Postvaccinial Myocarditis

Characteristic	ACS (n = 16)	Myocarditis (n = 62)
Age (yrs)*	34.4 ± 5.7	26.7 ± 5.3
Men/women*	11/5	61/1
Diabetes mellitus*	3 (18.8%)	0 (0.0%)
Hypertension*†	7 (43.8%)	0 (0.0%)
Dyslipidemia*‡	6 (37.5%)	0 (0.0%)
Smoker*	8 (50.0%)	12 (19.4%)
Family history of premature atherosclerosis	3 (18.8%)	8 (12.9%)
On presentation		
Heart rate (beats/min)	64 ± 15	74 ± 17
Systolic blood pressure* (mm Hg)	139 ± 31	114 ± 11
Diastolic blood pressure (mm Hg)	80 ± 17	73 ± 8
Left ventricular ejection fraction (%)	51 ± 10	55 ± 8
Focal left ventricular wall motion abnormality*	11/13 (84.6%)	6/57 (10.5%)

*p <0.01; †hypertension defined as systolic blood pressure >140 mm Hg or taking any antihypertensive medication; ‡dyslipidemia defined as total cholesterol >200 mg/dl, low-density lipoprotein cholesterol >140 mg/dl, or high-density lipoprotein cholesterol <35 mg/dl.

TABLE 2 Comparison of Cardiac Enzymes for Patients With ACS and Postvaccinial Myocarditis

Variable	ACS (n = 16)	Myocarditis (n = 62)
Troponin-I (ng/ml)		
Initial	19 ± 33	12 ± 24
<12 h	28 ± 35	10 ± 16
≥12 to <24 h	27 ± 28	11 ± 13
≥24 to <48 h	17 ± 16	10 ± 19
≥48 h	6 ± 9	4 ± 4
Peak value*	40 ± 42	16 ± 26
Time to peak, mean (h)‡	10 ± 9	9 ± 13
Time to peak, median (h)‡	9	3
Creatinine kinase (IU/L)		
Initial	846 ± 1,305	493 ± 339
<12 h	1,408 ± 1,784	420 ± 282
≥12 to <24 h	1,062 ± 1,208	422 ± 361
≥24 to <48 h	691 ± 765	287 ± 328
≥48 h	177 ± 235	161 ± 172
Peak value†	1,352 ± 1,678	477 ± 371
Time to peak, mean (h)‡	7 ± 8	9 ± 13
Time to peak, median (h)‡		2

Data are presented as numbers or mean ± SD.
*p = 0.012; †p = 0.001; ‡"time to peak" defined as time from initial specimen collection.

study was to contrast patients with postvaccinial myocarditis with those with ACS.

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We retrospectively reviewed the consecutive clinical records of all patients <40 years old presenting with ACS from 1998 to 2003 (n = 16) and the records of military personnel who had myopericarditis after their smallpox vaccinations (n = 62). ACS was defined as chest pain consistent with a cardiac origin associated with elevated levels of cardiac-specific enzymes (troponin-I or creatine kinase-MB) and/or electrocardiographic changes. The definition of myocarditis after smallpox vaccination has been previously described.[8] Only those patients with complete historical, laboratory, and testing data were included in the evaluation. Demographic, historical, cardiac enzyme, electrocardiographic, echocardiographic, and cardiac catheterization data were collected.

Cardiac enzymes were reviewed and directly compared. They were then normalized to initial presentations and peak values. Statistical analysis was performed using JMP Professional version 5.0.1 (SAS Institute Inc., Cary, North Carolina). Student's *t* test was used for the comparison of normally distributed continuous variables. Yates' corrected chi-square and Fisher's exact tests were used for categorical variables. Analysis of variance with repeated measures over time was used for the comparison of indexed data. A p value <0.05 was considered statistically significant. This study was approved by our hospital's institutional review board.

There were 16 cases of ACS from 1997 to 1998 in patients <40 years old at our institution, and extensive records for 62 cases of postvaccinial myocarditis that occurred worldwide were available for review. All patients were without known preexisting cardiac disease, and all survived to hospital discharge. Chest pain was the dominant presenting symptom in every patient. Patients' demographic, clinical, and echocardiographic characteristics are presented in Table 1. Patients with ACS were older and had more cardiac risk factors than those presenting with smallpox vaccine–associated myocarditis. Echocardiography during the index hospital admissions demonstrated similar left ventricular ejection fractions; however, regional wall motion abnormalities were present in 85% of patients with ACS compared with 11% of those with myocarditis (likelihood ratio chi-square 14.0, p <0.001). Of the 62 electrocardiograms (14 of 16 for ACS, 52 of 62 for myocarditis) available for review, 31 showed ST-segment changes. The 2 groups had high incidences of pathologic electrocardiographic findings (86% for ACS and 58% for myocarditis, p = 0.06).

Cardiac enzyme data from all subjects appear in Table 2. There was a statistically significant difference in the peak cardiac enzyme values in patients with ACS compared with those with myocarditis (troponin-I, p = 0.012; creatine kinase, p = 0.001). Figure 1 reveals enzymes for patients with ACS normalized to the presenting cardiac enzyme level and demonstrates a typical increase and decrease associated with myocardial infarction in patients with ACS. However, patients with myocarditis presented at their peak measured creatinine kinase levels and near their peak troponin levels. Also, these cardiac enzymes had a more blunted increase and decrease, compared with those in patients with ACS. Figure 2 demonstrates the changes in cardiac enzymes normalized to the peak

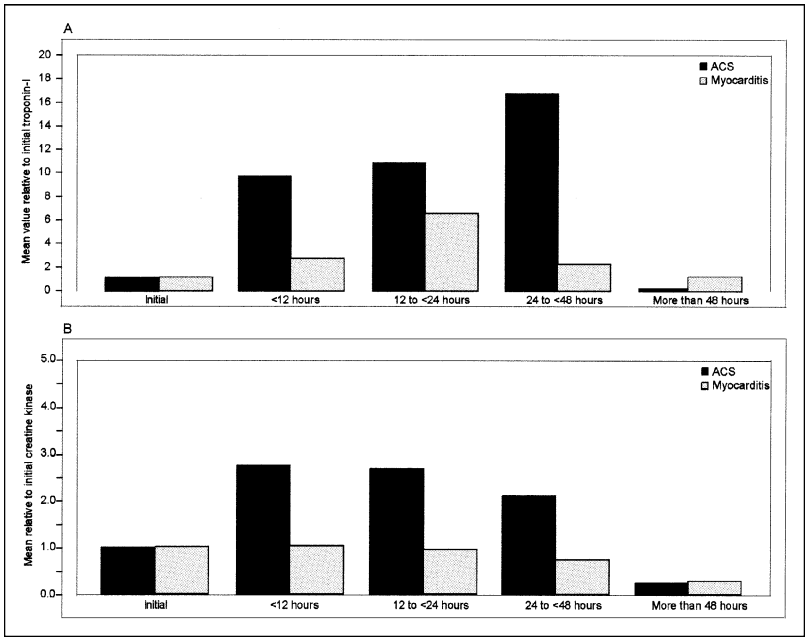

FIGURE 1. Increase and decrease of cardiac isoenzymes relative to initial values during hospitalization for ACS compared with myocarditis. It is apparent that for both troponin-I *(A)* and creatine kinase *(B)*, the increase and decrease of cardiac enzymes is more pronounced and dynamic in ACS than in myocarditis. Troponin-I was noted to increase to its highest level relative to initial sampling within 24 hours, and creatine kinase remained relatively unchanged from initial values in myocarditis.

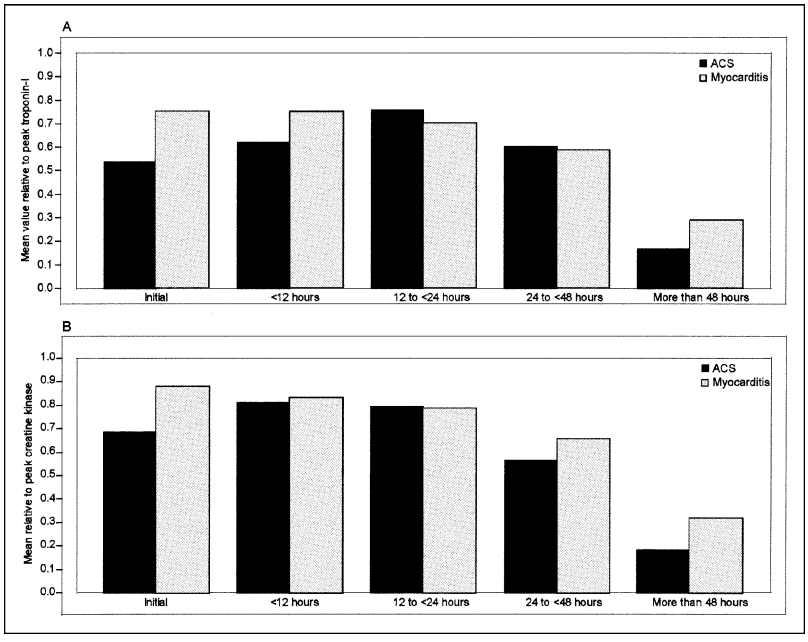

FIGURE 2. *(A)* Increase and decrease of troponin-I relative to peak values during hospitalization for ACS compared with myocarditis. With ACS, the mean value most approximated the peak value obtained at 12 to <24 hours, whereas the mean value most approximated the peak value on initial presentation in myocarditis. *(B)* A similar trend was noted for creatine kinase, with a mean value approximating the peak value on initial presentation in myocarditis.

values and shows the increase and decrease characteristic of ACS. In contrast, there was a more continuous release of cardiac enzymes in patients with myocarditis. It should be noted that even in myocarditis, the enzymes decreased to <30% of their initial values after 48 hours (Table 2).

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Myocarditis mimicking acute myocardial infarction has been previously reported. One study followed 34 patients with initial presentations consistent with acute myocardial infarction but normal coronary angiographic results.[1] Eleven of the 34 patients had biopsy-proved myocarditis, of whom 8 had ST-segment changes and 6 had abnormal echocardiographic results. A similar study of 10 patients (initially considered to have myocardial infarction but subsequently diagnosed with myocarditis) found abnormal echocardiographic results in 8.[2]

Previous studies of viral myocarditis mimicking myocardial infarction have focused on enteroviruses, adenoviruses, and parvoviruses and have been unrelated to vaccinations.[2–4] It is unknown whether the presentations of those patients would be substantially different from the ones described in this study. In our experience with postvaccinial myocarditis, regional wall motion abnormalities were less common than previously reported.[1,2]

In contrasting the presentations and ancillary testing of young patients with ACS and smallpox vaccine–related myocarditis within our cohort, several differences were noted. The patients with ACS were older, but admittedly, this is unlikely to be of clinical utility for diagnosing individual cases. Importantly, the patients with ACS did have more identified risk factors, specifically hypertension, dyslipidemia, and tobacco use. Therefore, in a young patient without these risk factors, myocarditis should be considered more strongly. In contrast, the presence of a focal wall motion abnormality on echocardiography would more strongly suggest ACS.

The patients with myocarditis tended to achieve peak enzyme concentrations earlier, relative to their presentation. Possibly, this is related to delayed presentation for care in those patients with myocarditis related to smallpox vaccination. Many of the patients with myocarditis in our series were either deployed overseas or in the process of military deployment. The ability to assay cardiac enzymes is

often more difficult in these scenarios. Although cardiac enzymes were elevated for a slightly longer time period after presentation in patients with myocarditis, enzymatic markers of active myonecrosis had resolved in most patients in the 2 groups <48 hours afterward, suggesting a transient nature of myonecrosis and lack of ongoing damage in this group.

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