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Long Term Cardiac Abnormality after Single High Dose Exposure to Sulfur Mustard?

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INTRODUCTION

Sulfur mustard (SM) [bis (2-chloroethyl) sulphide); CASRN: 505-60-2] is a potent alkylating agent.[1] During the Iran- Iraq war (1980–1988), it was used widely against the Iranian soldiers by Iraqi forces. More than 45,000 victims are now suffering from their long-term health effects.[2] Mustard can cause severe systemic intoxication besides their pronounced local damaging capacity. It can diffuse rapidly via lung capillary bed to blood circulation. This quick distribution is with a long terminal half life ($t1/2\alpha = 5.56$ minutes; $t1/2\beta = 3.59$ hours).[3] Heart is the next organ which encounters its pass. In terminally ill patients suffering from cancer, radioactivity of the injected 14C-labeled SM nearly disappears from the blood after several minutes and is excreted mainly in the urine within 24 hours.[4]

Cardiac abnormalities have recently been reported to occur years after treatment with chemotherapeutic drugs. One of the most commonly used classes of chemotherapeutic agents is alkylators. Cardiac events associated with chemotherapy vary from mild transient blood pressure and/or electrocardiographic (ECG) changes to more serious arrhythmias, myocarditis, pericarditis, myocardial infarction and cardiomyopathy, which may end in left ventricular (LV) dysfunction or congestive heart failure (CHF).[5,6]

Although cough and dyspnea are the major chief complaints and the most investigated symptoms in mustard-exposed patients, in addition to lung other underlying sources should be considered. Cardiotoxic effects of other alkylating agents are well recognized; however, for the first time we hypothesize that single high dose exposure to SM can induce late cardiac effects. Knowledge about its cardiac effects can provide us with new information in order to avoid mustard-induced cardiotoxic effects, which can be detected even in asymptomatic persons by means of various methods. We sought to determine whether or not a single dose exposure to SM gas can induce cardiac abnormalities.

METHODS

Between the years 2004 and 2006, 58 patients who met the eligibility criteria agreed to participate in the study and underwent cardiologic evaluations adequate to meet the requirements of the study. They were referred to our center with a history of a single high dose exposure to SM gas approximately 18 years back. The levels of mustard gas (MG) exposures experienced by veterans, which were sufficient to cause skin reactions (erythema, vesicles, and ulceration) were defined as high dose. Patients with prior history of mediastinal or spinal radiation, chemotherapy (that are known to be associated with chronic or late cardiotoxic effects) and history of rheumatic or congenital heart disease were excluded. Patients with major risk factors of epicardial coronary artery disease (CAD) such as hyperlipidemia, diabetes, heavy smoking and family history of CAD were also excluded. No patient had known hypothyroidism at the time of the echocardiographic evaluation. Written informed consent (approved by the appropriate Institutional Board Review) was obtained from each patient prior to enrollment. The echocardiographic study consisted of a two-dimensional echocardiogram and Doppler evaluation with stress-velocity analysis, which were obtained through parasternal long- and short-axes, apical four-chamber, and subcostal four-chamber views. During echocardiography, the pericardium, valvular anatomy and function, left- and right-sided chamber size, and cardiac function were also assessed.[7] We determined age-specific normal ranges for fractional shortening and contractility (measured as the velocity index). Impaired relaxation of LV was defined as an increase of the late atrial filling phase so that (E wave)/(A wave) ratios on the mitral Doppler pattern decline; $E/A < 1$ (delayed relaxation pattern), increased isovolumic relaxation time and also increased E wave deceleration time. Pulmonary vein velocity pattern resulting from atrial contraction was also compatible

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Table 1. Cardiac findings in the study group

Evaluation	Total	Type of finding	No	Description [ref]
Echocardiography	58	*Normal*	35	
		MVP	8	Marked superior systolic displacement of mitral leaflets ⩾2 mm above annulus [9]
		LV systolic dysfunction	1	Left ventricular systolic dysfunction <55% apical four chamber view in left lateral position with Simpson's method.[10]
		LVdiastolic abnormality	14	Increase in diastolic filling pressure which maybe responsible for occurrence of dyspnea that reveals in Doppler echocardiography of mitral valve flow with decrease E wave (early left ventricular filling velocity) and increased A wave (velocity of LV filling contributed by axial contraction).[11–13]
		Pericardial effusion	1	Pericardial effusion appears as a lucent separation between parietal and visceral pericardium.
		Increased PAP	1	PAP = 28 mmHg according to tricuspid regurgitation (TR), jet flow and Bernoulli's equation method.[14,15]
Stress myocardial perfusion imaging	29	*Positive*	7	Decreased tracer uptake in a surface large enough to be considered significant by the experts. Abnormal segments were defined as reversible (partial or total normalization on redistribution imaging) or fixed.
		Negative	22	
Coronary angiography	7	*Normal*	3	No obstructive plaque in epicardial coronary artery
		Single vessel disease	1	Significant coronary artery obstruction: Luminal diameter stenosis > 60%.[16]
		Two vessels disease	–	
		Three vessels disease	–	
		Non obstructive CAD	1	Non obstructive coronary artery disease: Luminal diameter stenosis < 50%
		Myocardial bridge	2	Systolic narrowing of epicardial coronary artery.[17]
Exercise stress test	32	*Negative*	29	
		Positive	–	
		Incomplete	3	
		Inconclusive	–	
Exercise tolerance test	32	*Negative*	29	
		Positive	–	
		Inconclusive	–	
		Incomplete	3	
Electrocardiogram	60	*Normal*	54	
		Hemi block	3	
		Bundle branch block (BBB)	–	
		ST depression	2	
		ST elevation	1	

with diastolic abnormalities, i.e., increased reverse Pva wave and decreased Pvd wave.

Furthermore, physical examination, electrocardiogram, exercise stress test and/or optimal low-dose dobutamine test gated with 10 mercury (99m) Tc-sestamibi single-photon emission computed tomography (SPECT) were performed. Patients performed an exercise treadmill test (ETT) using Bruce protocol.[8] A semi-quantitative treadmill score was derived, with ETT being considered as 1) positive: horizontal or downsloping ST segment depression of 1 to 2 mm measured 0.08 second after the J point, occurring for a workload >75 W, with or without chest pain; 2) strongly positive: ST segment depression >2 mm at any workload, or >1 mm for a workload ⩽75 W, post-exercise ST depression for a duration >6 minutes; 3) negative: when ST segment remained isoelectric and heart rate ⩾85% of the maximum age-predicted heart rate was achieved; and 4) nondiagnostic in all other cases. Patients who did not achieve 85% of age-related work load were defined as incomplete EET. Stress/rest 99mTc-MIBI

cardiac perfusion study was performed according to a standard protocol. Patients were asked to discontinue anti-ischemic drugs at least 48 hours before the tests. Patients with incomplete exercise stress tests due to dyspnea or other abnormalities underwent perfusion imaging scans. Coronary angiography was performed while some evidence of ischemia was detected in perfusion imaging scans.

RESULTS

The study group comprised of 58 males within the age 45.6 ± 6.2 years (range 28-50). They were exposed to high dose SM at least 18 years back. Their mean weight was 67.2 ± 8.3 kilogram.

In 56 subjects (96.5%), no significant coronary artery disease was found. LV diastolic abnormality (relaxation impairment) was detected in 23% of subjects. There were no considerable valvular or conductive abnormalities. Table 1 shows all cardiac findings and their related descriptions in details

DISCUSSION

It is worthy noting that we did not find any significant ischemic heart disease in most patients established by ETT, stress/rest 99mTc-MIBI and coronary angiography. The results of 99mTc-MIBI scan showed 22 normal patients, while 7 subjects showed some evidence of ischemia in at least one region of LV zones, which was contrary to Gholamrezanezhad *et al.* (2006). In a study on myocardial perfusion scans of 22 SM-intoxicated patients (21 male and 1 female, all <44 years) using a 1-day stress and rest protocol with (99m)Tc-MIBI, found a high rate of non-homogenous uptake, left and right ventricular enlargement and ischemia.[18]

Shortness of breath during exercise (exertional dyspnea) (NYHA class II or III) has been increased in our patients in recent years. Also, chest pain has been added to the previous symptoms. In a 24 months cohort study (n = 247) in patients with exposure to MG, Iyriboz did not report chest pain in his series.[19] In the current study, chest pain would worsen by exercise and/or cough. It would also occur after long standing periods.

LV diastolic abnormality (relaxation impairment) is another major finding which was observed in 23% (14/60) of patients. Although there are many known etiologies for diastolic dysfunction, so far it is the first report in which LV relaxation impairment has been reported in this setting. However, diastolic function has been found to play an important role in cardiac morbidity and mortality and has influence on both preload and afterload. Diastolic function is influenced by ventricular structure and composition such as myocardial relaxation, ventricular filling, and the ventricle's passive elastic properties.[12] One of the major determinants is heart rate, which determines how much time is available for ventricular filling. In our series, the heart rate was in the range of 70–90 beats per minute. Moreover, there was no pericardial thickness or left ventricular hypertrophy. However, pericardial thickness was not evaluated by CT scan, and also we did not assess intrapericardial pressure.

There were no important long-term abnormalities in cardiac conductive system. . Study of Iyriboz on the initial cases (n = 77) had shown ECG conduction defects in 30% of patients in the first week.[19] However this acute phase evaluation was not performed with the same aim as our study.

There were no considerable valvular abnormalities in our patients. However, mitral valve prolapse (MVP) and mild mitral regurgitation were found in 8 subjects (13.8%). Endomyocardial biopsy could probably define chronic cardiotoxicity and recognition of diastolic pathology. Our results probably reflect the fact that in some patients in our series diastolic abnormality would lead to diastolic or systolic dysfunction in future. We recommend a more comprehensive evaluation and annual follow-ups for recognition of diastolic abnormality progression to higher stages.

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