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ORIGINAL PAPER

Late respiratory effects of sulfur mustard: how is the early symptoms severity involved?

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The association between severity of exposure to sulfur mustard (SM) and late respiratory complications is not clear. The aim of this study was to determine the presence of late pulmonary complications in patients with mild, moderate, and severe initial symptoms of sulfur mustard exposure. This was a retrospective cohort study on patients with mild, moderate, and severe initial symptoms of sulfur mustard exposure (during 1983–1988) in Baqyatallah University of medical sciences (2004–2005). The 'mild' group ($n = 115$) had no early symptom at the time of exposure. The 'moderate' group ($n = 273$) had early symptoms after exposure and were not hospitalized for that reason. The 'severe' group ($n = 215$) had early symptoms and had been hospitalized accordingly. Pulmonary function tests and high-resolution computed tomography of the chest were performed. The chi-square test was used for data analysis. The severe and moderate groups had a similar frequency of obstructive pattern (21%), whereas only one patient in the mild group showed this pattern. Air trapping did not significantly differ between groups. In the mild group, 74.8% ($n = 86$) showed significant air trapping, whereas it was 62.3% ($n = 170$) in moderate and 67.0% ($n = 144$) in severe groups ($P = 0.057$). Moderate and severe exposure to sulfur mustard causes an equal risk of late pulmonary complications, while mild exposure has lesser risk. Bronchiolitis obliterans is the main underlying respiratory consequence of sulfur mustard exposures and may relate to host factors rather than to severity of early symptoms. *Chronic Respiratory Disease* 2008; **5**: 95–100

Key words: mustard gas; late complications; symptons severity; respiratory

Introduction

Sulfur mustard (SM) is an alkylating chemical warfare agent that was widely used during World War I and in Iran–Iraq war between 1983 and 1988.[1] The eye, skin, and the respiratory system are the three major targets for the early and late toxic effects of SM.[2,3] Respiratory complications are the most common delayed problem, whereas cutaneous and ocular lesions tend to alleviate or remain constant as time passes.[2–4]

The effect of SM exposure can be altered by many factors. Severity of exposure, which is usually reflected by patients' symptoms at the time of exposure, is supposed to be important. Some environmental and host susceptibility factors may also alter the effects.[2,5–7]

Verifying the relationship of early symptom severity with the occurrence of late complications requires a comparison of the later effects with the history of mild and severe initial exposures. The exposure dose and severity could not be defined exactly in warfare situations, especially when the gas spreads through an indefinite area. Few studies provide useful information about the impact of mild exposure, whereas almost all reports thoroughly document long-term pulmonary effects after severe exposure to SM.[8,9] Thus, there is not enough evidence to support the idea that severity of exposure and early symptoms may accurately predict late respiratory complications. The aim of this study was to determine the relationship between SM early symptom severity and late respiratory complications.

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Methods and materials

Patients and settings

A retrospective cohort study on individuals with three different degrees of early symptoms of exposure to SM was conducted in Baqyatallah University of medical sciences (2004–2005). All patients' exposure to SM during Iran–Iraq war (1983–1988) was documented by Janbazan Medical and Engineering Research Center, which is the official center responsible for war-disabled victims' welfare. We defined the contaminated areas as regions that was attacked by chemical missiles or bombardment and documented based on the army documentations. All patients were military personnel with a single exposure to SM due to a known presence in the contaminated area during the Iran–Iraq war, certified by veteran's affairs (Janbazan) and army documentations.

The 'mild' group (115 patients) included exposed individuals who had no early symptoms at the time of exposure. The 'moderate' group (273 patients) included those who had experienced early symptoms after exposure but were not hospitalized. These patients were judged to have moderate exposure. The 'severe' group (215 patients) included individuals who experienced early symptoms immediately after the exposure and were hospitalized accordingly.[7]

A pulmonologist visited all patients with late respiratory symptoms. Early respiratory symptoms were obtained according to the patients' self reports. All patients underwent high-resolution computed tomography (HRCT) and pulmonary function tests (PFT).

High-resolution computed tomography

HRCT examinations were obtained on one scanner (HiSpeed Advantage; General Electric Medical Systems, Milwaukee). Each HRCT examination consisted of five 1.0-mm collimation images obtained during both deep inspiration and full expirationy, with the patient lying in a supine position. Images were obtained at the levels of the aortic arch, midway between the aortic arch and tracheal carina, tracheal carina, midway between the tracheal carina and the right hemidiaphragm, and 1 cm above the right hemidiaphragm. No IV contrast was administered. All images were reconstructed using a high–spatial resolution algorithm and displayed at standard (level, −700; width; 1500) and narrow (level, −700; width, 1000) lung window settings.

Inspiratory images were read before expiratory ones, and images displayed at standard windows before narrow window settings. The inspiratory images were assessed for the presence of bronchiectasis according to the previously established computed tomography criteria.[10–12] The mosaic parenchymal pattern was defined as areas of heterogeneous lung attenuation in a lobular or multilobular distribution in expiratory phase.[13] The expiratory images were also assessed for the presence of air trapping. The criteria used to diagnose air trapping were alteration of normal anterioposterior lobar attenuation gradients and/or lack of homogeneous increase in lung attenuation resulting in persistent areas of decreased attenuation.[14] The extent of air trapping was quantified and categorized using the same system as defined for hyperlucent regions on inspiratory images. As limited air trapping has been reported in normal individuals,[14] the presence of air trapping was noted, scored, and considered indicative of bronchilitis obliterans (BO) in study patients only when it exceeded 25% (significant air trapping) of the cross-sectional area of an affected lung on at least one scan level. Expiratory images displayed at standard and narrow window settings were directly compared to determine differences in the conspicuity of significant air trapping.

Pulmonary function test

Spirometry was performed according to American Thoracic Society criteria.[15] Forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) were recorded using spirometer (Jaeger, Hochberg, Germany). All measurements were analyzed as percent of predicted values (FEV1%, FVC%).[16] Subjects were seated with a nose clip in place and were asked to perform at least three forced expiratory maneuvers. Both the patients and the technician received visual feedback from a monitor during the test, which was repeated until three technically satisfactory curves with reproducible contour were obtained. All the indices used for the analysis were derived from the same maneuver, which was the one with the largest FVC. Reference values for predicted measures were derived from Iranian criteria.[16]

According to the Global Initiative for Chronic Obstructive Lung Disease criteria,[17] the obstructive pattern was determined using FEV1/FVC < 70% as cutoff point. In the nonobstructive patients, a

restrictive pattern was considered if FVC < 80% of the predicted value.

PFT results were reported as restrictive (FVC% <80% of predicted and FEV1/FVC >80%), obstructive (FEV1%/FVC% <70%), and normal.[17]

Statistical analysis

Relative frequency of symptoms, signs, PFT results, and HRCT findings was calculated. Chi-square test was applied to compare frequencies between groups. Median and mean (±SD) is reported where indicated. Kruskal–Wallis test and analysis of variance were performed to compare numerical data between groups. Fisher's exact test was applied for relationship between HRCT and PFT results. Analysis was performed by SPSS 12 software, and P values <0.05 were considered statistically significant. The study was approved by our local ethic committee at Baqyatallah University of medical sciences and has been conducted in accordance with the Declaration of Helsinki.

Results

The mean (±SD) age of patients did not significantly differ between mild (42.3 ± 7.4), moderate (43.1 ± 6.4), and severe (42.2 ± 6.9, $P = 0.24$) groups. In the severe group, 82.2% of patients (178 of 215) reported cough and 80.5% (173) reported dyspnea at the time of exposure. This was significantly higher than 19.4% in moderate group (53 of 273, $P < 0.001$). Cigarette smoking status was not significantly different between groups (Table 1).

PFT results

Thirty-three patients (28.7%) in mild group had normal PFT compared with 44% in other groups (120 in moderate, 96 in severe, $P = 0.009$). Severe and moderate groups had similar frequency of obstructive pattern (21%), whereas only one patient in mild group showed this pattern. The presence of a restrictive pattern did not significantly differ between groups because one patient (of 115) in mild group, 10 (of 273) in moderate, and two (of 215) in severe group showed this pattern ($P = 0.06$). FEV1/FVC could not be differentiated between groups. The mean (±SD) was 79.9 ± 12.3 in mild group, 80.4 ± 7.1 in moderate group, and 77.5 ± 12.3 in severe group ($P = 0.4$). Groups were not different in the terms of FEV1%. It was equal to 98.1 ± 12.7 in mild, 88.5 ± 18.7 in moderate, and 80.9 ± 22.2 in severe group ($P = 0.07$).

HRCT results

Abnormal HRCT findings were similar between groups. Twenty percent of patients in mild group (23 of 115), 26.7% in moderate (73 of 273), and 25.1% in severe (54 of 215) group had normal HRCT results ($P = 0.37$). Air trapping and emphysema were insignificantly different between groups (Table 2). The mean (±SD) score of air trapping was

Table 1 Cigarette smoking status in each group

	Mild	*Moderate*	*Severe*	P *value*
Previous smokers (*N*)	17.3% (19)	16.6% (42)	17.6% (35)	0.9
Cessation period (years)[a]	7.13 ± 5.5	7.33 ± 5.4	9.92 ± 6.9	0.4
Current smoking rate (pack/year)[b]	6.2	1.5	2.5	0.1
Current smokers	7.0% (8)	4.8% (13)	%9 (4.2)	0.5

[a]Data are presented as mean ± SD.
[b]Data are presented as median, pack/year is calculated as: cigarettes/day/20 × years.

Table 2 Prevalence (*N*) of abnormal HRCT findings in each group

	Mild	*Moderate*	*Severe*	P *value*
Significant air trapping	74.8% (86)	62.3% (170)	67.0% (144)	0.057
Mosaic perfusion	0.9% (1)	1.5% (4)	1.4% (3)	0.89
Emphysema	4.3% (5)	12.5% (34)	7.9% (17)	0.29
Tree in bud	0.9% (1)	1.1% (3)	2.3% (5)	0.44
Tracheomalacia	1.7% (2)	2.2% (6)	2.3% (5)	0.9

Table 3 Comparison of different signs and symptoms between different groups

	Mild	*Moderate*	*Severe*	P *value*
Rale (*N*)	2.6% (3)	3.3% (9)	4.2% (9)	0.7
Crackle (*N*)	1.7% (2)	2.9% (8)	4.2% (9)	0.4
Wheezing (*N*)	9.6% (11)	18% (46)*	23% (51)[a]	0.004
Cough (*N*)	96.3% (104)	93.6% (248)	94.7% (195)	0.57
Dyspnea (*N*)	98.2% (110)	96.2% (254)	97.6% (200)	0.5
Hemoptysis (*N*)	75.8% (157)	70.2% (177)	75.7% (84)	0.3

[a]$P = 0.07$.

equal to 3.9 ± 2.3 in mild, 3.9 ± 2.2 in moderate, and 3.9 ± 2.9 in severe group ($P = 0.9$).

Wheezing had increased from mild to severe group, but crackles and rales did not show this difference (Table 3). Respiratory symptoms did not differ between groups (Table 3). The Fisher exact test did not show any significant relationship between PFT results and chest HRCT findings ($P = 0.5$, Table 4).

Discussion

Our results showed that the severity of SM early symptoms is related to the risk of late obstructive pulmonary disease. Patients with mild early symptoms had a lower risk for obstructive respiratory pattern than others with moderate or severe symptoms. The obstructive pattern accounted for the most common feature of pulmonary involvement after SM exposure,[18,19] which was not different in patients with moderate and severe early symptoms. Patients with mild early symptoms, who developed respiratory complications in long term, usually have normal lung function, followed by mild obstructive involvement.[20,21] It seems that if the exposure is severe enough to cause early symptoms and hospitalization, the risk of late pulmonary involvement will increase. But later, the variation from moderate to severe and different periods of hospitalization after the exposure did not alter the outcome. Hence, other factors such as individuals' susceptibility would be more important than early symptom severity or hospitalization.

Table 4 Comparison of chest HRCT and pulmonary function test (PFT) results ($n = 603$)

	Chest HRCT	
	Significant air trapping	*Normal*
Normal PFT	27.4% (165)	13.9% (84)
Abnormal PFT	39% (235)	19.7% (119)

The nature of an exposure effect in combat situations is not simple. A large variety of factors can greatly affect the soldier's response to SM exposure.[8] Temperature, humidity, skin moisture, exposed surfaces, fitness of personal protective equipment, wind and direction, activity level of the soldier (at rest or running), and host susceptibility factors may also alter the effects.[2,5,6] Receiving an effective exposure, which can be defined as an exposure capable of causing early symptoms, is necessary to develop late respiratory problems. But if the symptoms occur, the severity of early symptoms could not predict the severity of delayed complications.

Findings of chest HRCT as the imaging procedure of choice in SM-exposed patients[22] do not correlate with the severity of early symptoms. Our results showed that more severe early symptoms did not increase the incidence of significant air trapping or mosaic perfusion, which was reported to be the most frequent radiological findings in both symptomatic and asymptomatic SM-exposed patients.[23,24] Histopathological investigations and radiological evidence have already shown that bronchiolitis obliterans is the underlying cause of chest HRCT findings.[24,25] Significant air trapping is the most sensitive and accurate radiologic indicator of BO.[26]

Exposure to respiratory irritants is known to cause small airway disease and affect transfer capability. However, in the case of exposure to SM, bronchiolitis should be considered the major long-term sequel following SM exposure.[23–25,27] Findings of the study are not extensive enough to suggest a definitive mechanisms for the development of bronchiolitis. We can just suggest that BO may not be related to the symptom severity or the period of hospitalization after exposure and other factors involved in its pathogenesis should be noticed.

Fibroproliferation and tissue remodeling clearly play an important role in pathogenesis of BO.[28] Many growth factors may promote fibroblast replication and collagen accumulation,[28,29] whereas the

role of transforming growth factor-β (TGF-β) is the most crucial.[30–32] Overexpression of TGF-β in macrophages and mesenchymal and mesoendothelial cells can cause BO changes.[33–35] TGF-β target protein is substantially increased in bronchoalveolar lavage (BAL) aspirates and target tissues of SM-exposed patients.[36] Thus, host susceptibly such as immunologic factors may play an important role in developing delayed complications while severity early symptoms are not predictive.

Air trapping in mild group was not significantly less than in others. Patients in mild group might have had a better expiration during imaging, leading to diagnosis of less significant air trapping. In other two groups, unsatisfactory expiration may cause difficulties in diagnosis of significant air trapping. Thus, more frequently detected significant air trapping in mild group may not suggest more occurrences but more accuracy. Such conditions could affect our results of HRCT studies and should be considered a potential limitation.

We should not give weight to the period of hospitalization after early symptoms to predict late respiratory complications, and patients with moderate and severe symptoms should receive similar care. There was a gap of about 16 years between exposure and this study. This should be taken into account in generalizing our findings because we may have lost some severely affected patients. However, the trend of the disease may have differed between groups during these 16 years.

The first contact with SM is mostly painless and only a garlic or sulfur odor can be noticed.[37] Patients experience a symptom-free period for several hours. Mild exposures are associated with a longer symptom-free period. After that the patient may just have some transient itching or eye watering.[37] This transient irritation some days after exposure may be simply neglected in combat situation. This may be the case in the mild group.

In conclusion, a dose of SM exposure capable of causing early symptoms is necessary to result in developing late respiratory complications. The severity of such early symptoms and the period of consequent hospitalization would not alter the risk of future pulmonary disease. The nature of an SM exposure effect in combat situations cannot be explained by the exposure severity and the occurrence of early clinical complications. Host susceptibility and immune factors such as TGF-β may play a crucial role in developing late respiratory complications. Bronchiolitis obliterans, as the main underlying disease, seems to depend on host response rather than a dose–response pathophysiology.

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