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Inspiratory and Expiratory High-Resolution CT Findings and Chronic Pulmonary Effects of Mustard Gas Exposure

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Abstract: The aim of this study, was to assess the pulmonary lesions in patients with sulfur mustard gas exposure and their relationship with age, gender, exposure frequency and pulmonary symptoms and compare with non-exposed ones as control group. A case-control study was performed on 125 patients with documented sulfur mustard gas exposure during the Iran-Iraq war in 1983-1988, referred to a medical imaging center in Tehran, Iran in 2007, for High Resolution Computed Tomography scan (HRCT). The age-matched control subjects (n = 26) had not history of mustard gas exposure and had minimal clinical manifestations as indication for HRCT. Dyspnea (97.6%), cough (84.8%) and purulent sputum (77.6%) were seen more in patients with sulfur mustard gas exposure than control group. In exposed group, the most common HRCT findings were patchy (61.6%) and diffuse (13.6%) air trapping, emphysema (8%) and mild and focal fibrosis (4.8%). In control group, among all findings, only patchy air trapping was detected that was less frequent than exposed group (3.8 vs 61.6%, $p<0.001$). The most common pulmonary effects of sulfur mustard gas in HRCT are patchy and diffuse air trapping, emphysema and mild and focal fibrosis and the severity of these changes are associated with patient's age.

Key words: Chemical warfare, high resolution computed tomography scan, mustard gas, pulmonary disease

INTRODUCTION

Mustard gas, or sulfur mustard, is a vesicating agent that was used on troops fighting in the First World War and recently during the Iran-Iraq war between 1980 and 1988 (Bagheri *et al*., 2003). Mustard gas was used again by Iraqi forces against Iranian forces, with over 100,000 poorly protected soldiers suffering from severe debilitating injuries as a result. However, roughly ⅓ of these soldiers continue to suffer long-lasting consequences of exposure (Cox, 2007; Kehe and Szinicz, 2005). Mustard gas is frequently absorbed by inhalation and is capable of inducing acute, chronic and in some cases, progressive airway and pulmonary parenchymal damages (Bagheri *et al*., 2003; Calvet *et al*., 1994).

Respiratory problems are the greatest cause of long-term disability among patients with combat exposure to mustard gas and can be presented with productive severe cough, purulent sputum, dyspnea, chest tightness, chest pain, nocturnal dyspnea and possibly alveolar hemorrhage (Willems, 1989) that has been found to be present in >80% of Iranian veterans after their initial exposure. Main objective clinical findings in these patients are also generalized wheezing, crackles, decreased lung sounds, clubbing and cyanosis (Balali *et al*., 1986). In addition, the clinical picture of adult respiratory distress syndrome may be present, as seen in Iranian victims who suffered multi-system organ failure (Balali-Mood and Hefazi, 2006).

However, few studies have been done with regard to chronic respiratory effects of mustard gas and yet there is controversy about their results. The purpose of this study, was to investigate the long term pulmonary effects of mustard gas exposure and their relationship with age, gender, exposure frequency and pulmonary symptoms.

MATERIALS AND METHODS

This case-control study was conducted on 125 patients with documented exposure to sulfur mustard gas during the Iran-Iraq war in 1983-1988, referred to a referral medical imaging center in Tehran, Iran in 2007 for High Resolution Computed Tomography scan (HRCT) with the complains of dyspnea, cough, purulent sputum, or hemoptysis. Exposure was confirmed by the written reports of the field hospitals, based on acute

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presentations including eye, skin and pulmonary symptoms at the exposure time. Patients with the history of smoking, lung disease before exposure to mustard gas, any occupational history of toxic fume exposure or occupational risk factors that could lead to lung disease, any associated chronic disease (such as heart failure or connective tissue disease) with potential pulmonary involvement, or history of treatment with drugs that may cause acute pneumonitis or lung disease as a side effect were excluded.

Also, 26 age-matched, nonsmoking, nonatopic patients without the history of mustard gas exposure and with minimal clinical manifestations that had indication for HRCT were selected as control group. All participants signed an informed consent form before their enrollment. All subjects had a complete history. No subjects had a history of exposure to organic or inorganic dusts. The study protocol was approved by ethics committee of Tehran University of Medical Sciences.

HRCT was done by a scanner (Siemens Somatom plus 4). Each examination consisted of one mm collimation images with 20 mm interval from lung apex to the dome of the diaphragm, obtained in both deep inspiration and full expiration, with the patient in supine position.

All images were restructured using a high spatial resolution algorithm and were shown at standard HRCT lung window setting for viewing the lung parenchyma (level about 700 HU center, 1500 HU width). HRCT images were reviewed by a single pulmonary radiologist and findings were recorded. No intravenous contrast was administrated.

Normal morphologic changes can be seen on expiratory CT that includes an anterior bowing of the posterior tracheal and major bronchial membrane. We used this sign to determine the proper expiration and excluded those patients with inappropriate level of expiration. The inspiratory images were reviewed before the expiratory images and were assessed for the presence of bronchiectasis, emphysema, fibrotic changes and other CT findings. The expiratory images were also assessed for the presence of air trapping and its lobar distribution. Lack of homogeneous increase in lung attenuation and persistent areas of decreased attenuation were considered to show patchy air trapping. In normal subjects, relatively lucent areas in expiration in anterior portions of the lungs and superior segments of the lower lobes could be seen, which are not categorized as abnormal air trapping in our study. We also, used Houns field Unit (HU) number for the diagnosis of air trapping. An abnormal pattern was defined as areas of heterogeneous lung attenuation determined by the assessment of HU in heterogeneous areas using the monitor of the system. A difference of >100 HU in adjacent segments was considered as abnormal. Considering that limited air trapping has been reported in normal individuals the presence of air trapping was considered as abnormal only if it exceeded 25% of the cross-sectional area of an affected lung on at least one scan level. In some patients, the lung attenuation was homogeneous in expiration but appeared to be almost similar to the corresponding inspiration images. In these patients, the HU of lung parenchyma was measured both in the inspiratory and expiratory corresponding cuts and compared. If the lung attenuation was not increased as much as 100 HU in expiration, it was considered as diffuse air trapping.

The presence or absence of reticular pattern, honey combing, focal fibrosis, sacular brochiectasis, tubular brochiectasis, bronchial wall thickening, patchy or diffuse air trapping, ground glass opacity, mosaic pattern, consolidation with air bronchogram, septal thickening, nodularity, tracheal and major bronchus abnormality and emphysema were recorded and compared between the 2 groups.

Results were expressed as the mean±SD for quantitative variables and percentages for categorical variables. Categorical variables between the groups were compared using chi-square test or Fisher's exact test if required; continuous variables were compared by independent samples t-test for variables with normal distributions and Mann-Whitney U test for variables with non-normal distributions. The $p = 0.05$ or less were considered statistically significant. All statistical analyses were performed using SPSS version 13 for Windows.

RESULTS

The mean age of patients in the two groups was similar (38.5±9.8 vs 39.7±10.6, $p = 0.578$). Male to female ratio in exposed patients was more than control groups (Table 1). The mean interval between the time of exposure and examination in case group was about 20 years.

Dyspnea, cough and purulent sputum were more frequent among patients with sulfur mustard gas exposure than control group. However, hemoptysis was not observed in the exposed group. The frequency of exposure was 1 time in 64%, 2 times in 30.4% and 3 times in 3.2%. Also, 2.4% of patients exposed to mustards gas >3 times.

The HRCT findings in exposed group were summarized in Table 2. The most common findings were patchy (61.6%) and diffuse (13.6%) air trapping. Emphysema was detected in 8% of patients. HRCT revealed mild and focal fibrosis in 4.8 and 4.8% of patients, respectively. In control group, among all

Table 1: Demographic characteristics and clinical manifestations in patients exposed with sulfur mustard gas and control group

Characteristics	Gas exposed group (n = 125)	None exposed group (n = 26)	p-value
Male gender (%)	99.2	88.5	0.002
Age (years)	38.5±9.8	39.7±10.6	0.578
Dyspnea at rest (%)	87.2	0.0	<0.001
Exertional dyspnea (%)	97.6	57.7	<0.001
Cough (%)	84.8	30.8	<0.001
Purulent sputum (%)	77.6	3.8	<0.001
Hemoptysis (%)	0.0	7.7	0.029

All results were indicated as mean±SD or percentage, p<0.05 was significant

Table 2: HRCT findings in patients with mustard gas exposure

Findings	Frequency (%)
Mild fibrosis (reticular pattern)	4.8
Severe fibrosis (honey combing)	1.6
Focal fibrosis	4.8
Sacular bronchiectasis	1.6
Tubular bronchiectasis	2.4
Patchy air trapping	61.6
Diffuse air trapping	13.6
Ground glass opacity	0.8
Mosaic pattern	0.8
Consolidation with air bronchogram	0.0
Septal thickening	2.4
Nodularity	1.6
Emphysema	8.0

findings, only patchy air trapping was detected that was less frequent than the exposed group (3.8 vs 61.6%, p<0.001).

Severe fibrosis and secular bronchiectasis were frequently detected in left and right upper lobes of 2 lungs in both inspiratory and expiratory positions in exposed patients, whereas tubular bronchiectasis was observed in left lung in the 2 positions. Ninety four patients (75.2%) in exposed group had abnormal expiratory HRCT and 24 cases (19.2%) had abnormality both in inspiratory and expiratory HRCT. None of the controls had abnormal inspiratory or expiratory HRCT.

There was no relationships between the respiratory changes related to mustard gas exposure and gender (p = 0.343), clinical manifestations (p = 0.544) and exposure frequency (p = 0.676). However, patients with respiratory changes were older than the others (39.6±9.9 vs 34.1±8.0 years old, p = 0.005).

DISCUSSION

Respiratory problems are the greatest cause of long-term disability among patients with exposure to sulfur mustard gas during wars that influence and worsen the quality of life of these patients. Thus, the clinical assessment of these patients and the study of long term consequences of this agent are necessary for the improvement of life quality (Attaran *et al*., 2006).

In the present survey and on the basis of inspiratory and expiratory HRCT, we studied both demographic characteristics and clinical manifestations related to mustard gas exposure and considered the role of these criteria on pulmonary changes in these patients. We found that dyspnea, cough and purulent sputum were the most common manifestations in gas exposed group. Similar results were found in our previous study (Bakhtavar *et al*., 2008). In a study by Beheshti *et al*. (2006) all studied patients were symptomatic with cough, dyspnea and/or felt tight in the chest. In Bijani and Moghadamnia (2002) study, although nearly all the victims complained of cough, dyspnea, respiratory distress with use of accessory muscles and hemoptysis, physical examination revealed no abnormal finding in ⅓ of them. In another similar study, a triad of cough, expectoration and dyspnea has been found to be present in >80% of Iranian veterans 3 years after initial exposure. The clinical manifestations of mustard gas exposure result from multiple mechanisms and depend upon dose and duration of exposure and include DNA damage, particularly to the tissues with rapidly dividing cells, such as the respiratory system. Long-term exposure to sulphur mustard gas have been associated with an increased incidence of cutaneous and respiratory complications and even malignancies (Saladi *et al*., 2006). Under extreme circumstances, necrosis of the skin and mucous membranes of the respiratory system, bronchitis and bronchopneumonia occur. It has been clear that mustard gas readily combines with various components of the cell such as amino acids, amines and proteins (Dacre and Goldman, 1996).

In our study, the most common HRCT findings were patchy and diffuse air trapping, emphysema and fibrosis, however, bronchial wall thickening, consolidation with air bronchogram and tracheal and major bronchus abnormalities were not found. In Bagheri study, HRCT abnormality was detected in 100% of studied patients who exposed with mustard gas and the most common HRCT findings were bronchial wall thickening, suggestive of interstitial lung disease, bronchiectasis and emphysema (Bagheri *et al*., 2003). In Beheshti *et al*. (2006) survey, all patients had significant air trapping in HRCT. Other similar studies revealed a series of delayed destructive pulmonary squeal such as chronic bronchitis, asthma, bronchiectasis, large airway narrowing and pulmonary fibrosis (Emad and Rezaian, 1997; Hefazi *et al*., 2005). Lung fibrosis was the most conflicting issue in mustard gas exposed patients. Initially some studies addressed the association of this gas exposure with lung fibrosis (Dacre and Goldman, 1996). However, HRCT and histopathological findings in these reports had some conflicts and hence recent investigations did not support them. The understanding of the various patterns of

diffuse lung disease that might result in fibrosis has evolved over the last 50 years (Costabel and King, 2001). It is believed that long-term survival of these patients is not consistent with expected prognosis of patients with idiopathic pulmonary fibrosis, which is a generally fatal disorder with a reported median survival of 3-5 years (Bjoraker *et al*., 1998). Furthermore, the association of some cell-mediated mechanisms related to the presence of neutrophils, eosinophils and higher concentrations of interleukin-8, G-CSF and GM-CSF in BAL fluid with the development of fibrosis in sulfur mustard was demonstrated (Emad and Emad, 2007).

Bronchiectasis in our study was found in only 4% of patients. Several studies have identified bronchiectasis as a persistent problem in mustard gas-exposed patients. Pathological evidence on the direct effects of mustard gas on bronchial wall mucosa was reported and more importantly, recurrent respiratory infections following gas inhalation were known to be responsible for the development of bronchiectasis (Dompeling *et al*., 2004; Freitag *et al*., 1991).

In the present study, emphysema was detected in 8% of patients even after removal of confounding factors like smoking. Although, in some studies, while emphysema has been reported to be associated with mustard gas exposure, after removal of confounding factors, evidence did not support the correlation between emphysema and exposure to mustard gas and radiological studies did not show any evidence of emphysema (Ghanei *et al*., 2004a, b). However, this relationship needs to be clarified in future studies.

In our study, only high age was related to the severity of pulmonary changes related to mustard gas exposure. Similarly, in Zarchi *et al*. (2004) study, the estimated risk of pulmonary complications from war exposure to mustard gas increased with age. Also, in Emad and Rezaian (1997) study, there was a significant correlation between the age and the severity of asthma. However, in their study, there was no significant correlation between the patient's age and the severity of bronchitis and fibrosis.

As it was shown in our previous study (Bakhtavar *et al*., 2008), the most common pulmonary changes in HRCT of exposed patients are patchy and diffuse air trapping, emphysema and mild and focal fibrosis.

CONCLUSION

It is concluded that the respiratory clinical manifestations are more prevalent among patients with mustard gas exposure than non-exposed ones and the severity of the pulmonary changes (in HRCT) increases with the patient's age.

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