Clinical, High Resolution Computed Tomography and Pulmonary Function in Sulphur Mustard Victims

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Abstract- We aimed to evaluate clinical, high resolution computed tomography (HRCT) and pulmonary function test (PFT) findings after 18-23 years of exposure in veterans of sulphur mustard (SM) exposure. We performed a cross-sectional study of 106 patients. Inclusion criteria were 1: documented exposure to SM as confirmed by toxicological analysis of their urine and vesicular fluid after exposure 2: single exposure to SM that cause skin blisters and subsequent transient or permanent sequel. Cigarette smoking and pre-exposure lung diseases were of exclusion criteria. After taking history and thorough respiratory examination, patients underwent high resolution computed tomography and spirometry. Clinical diagnoses were made considering the findings. More than 85% of the patients were complaining of dyspnea and cough. Obstructive pattern (56.6%) was main finding in spirometry followed by restrictive and normal patterns. HRCT revealed air trapping (65.09%) and mosaic parenchymal attenuation patterns (58.49%) as most common results. Established diagnoses mainly were chronic obstructive pulmonary disease (COPD) (54.71%), bronchiolitis obliterans (27.35%) and asthmatic bronchitis (8.49%). There were not any significant association between the clinical findings and results of PFT and HRCT imaging and also between PFT and HRCT findings (P-values were more than 0.05). Considering debilitating and progressive nature of the respiratory complications of SM exposure, attempts are needed for appropriate diagnosis and treatment.

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Key words: Chemical victims; Long term; Mustard gas; Respiratory complication

Introduction

Mustard gas is the vesicant with the highest military significance. With technical impurity, it has dark oily appearance with typical odour of mustard or garlic (1,2). Mustard gas first use as chemical agent was in World War I. During 1981-1989 about 100,000 of Iranian military and civilian population suffered from mustard gas exposure (3).

Sulphur mustard (SM) is lipophilic and can penetrate epithelial tissue easily. The eye, respiratory tract and skin of unprotected victims would be the most damaged organs (4). At present, the widely accepted theory of mustard toxicity proposed alkylation of cell constituents, resulting in physiological, metabolic and genetic failures (5,6). Mustard toxicities in respiratory tract could be assessed in either acute or late phase after exposure (4).

To assess lung injuries of mustard gas, diverse paraclinical methods were used. Spirometry was widely applied for testing pulmonary function. Ordinary chest X ray can be normal in 20% of mustard exposed individuals (7), thus high resolution computed tomography (HRCT) was introduced as a powerful tool in detecting both bronchial and airway abnormalities (8,9). Over a decade after exposure, a study over Iranian victims showed that survivors are mainly suffering from respiratory (42.5%), ophthalmic (39.3%), and cutaneous (24.5%) sequel (10). Other studies of SM exposed population indicated bronchial wall thickening, interstitial lung disease, bronchiolitis obliterans, bronchiectasis and emphysema.
as major findings discovered by high HRCT and lung biopsy (11,12).

The aim of this study was to evaluate clinical signs and symptoms along with findings resulted from HRCT and pulmonary function test (PFT) after 18 to 23 years from exposure to SM in accidentally exposed victims.

Materials and Methods

Subjects
We performed a cross-sectional study on victims of mustard gas exposure from September 2005 to December 2006. Inclusion criteria were 1: documented exposure to SM as confirmed by toxicological analysis of their urine and vesicular fluid after exposure 2: single exposure to SM that cause skin blisters and subsequent transient or permanent sequel. We did not enrolled individuals with history of cigarette smoking (n=15) and pre-exposure respiratory conditions (n=3). They had regular follow-ups at an outpatient clinic established for chemical victims. One hundred and six male patients fulfilled the above criteria and were enrolled in the study. All subjects were examined thoroughly for clinical evidence of respiratory complications. HRCT and PFT were performed for all participants within two weeks. The study was approved by the ethical committee of Ahwaz University of Medical Sciences. Patients received written informed consent before participation.

High resolution computed tomography (HRCT) imaging technique
HRCT examination were obtained on one scanner (HiSpeed Advantage, General Electric Medical Systems, Milwaukee) with 1-mm collimation and 10-mm intervals from proximal trachea to diaphragm. Scans were performed in supine position during deep inspiration and prone position during full expiration. Pulmonologists and radiologists evaluated the scans. Lobar findings were classified as normal, mosaic pattern of lung attenuation, air trapping, hyperlucency, consolidation, bronchiectasis, reticular, and nodular abnormalities based on established criteria (8,13,14). The mosaic pattern of lung attenuation was defined as areas of heterogeneous parenchyma attenuation in a lobular or multilobular distribution in expiratory phase (14). The presence of air trapping was assessed in expiratory images and was described as changing of normal anterior posterior lobar attenuation gradients and/or lack of homogeneous increase in lung attenuation resulting in persistent areas of decreased attenuation (8). If air trapping was exceeded 25% of the cross-sectional area of a lung on at least one scan level it was considered indicative of bronchiolitis obliterans (8).

Pulmonary function test (PFT) technique
In order to evaluate lung function, pulmonary function variables were measured, using a flow sensing spirometer (FUDAC 50; FUKUDA Sangyo, Chiba, Japan). Spirometry was performed according to American Thoracic Society criteria (15). Each subject was trained to give his best effort. After 15 min resting, patients were asked to perform at least 3 forced expiratory manoeuvres at one minute intervals. All the parameters used for the analysis were derived from the same manoeuvre with the largest FVC. For patients who demonstrated obstructive pattern, PFT variables were repeated 5 min after two puffs of salbutamol (100µg/puff) in order to probe for reversibility of obstruction (asthmatic trait). These patients had been asked not to use short-acting inhaled drugs within 4 h of testing, long-acting β-agonist bronchodilators and oral therapy, 12 h prior to the test. PFT results was interpreted by a pulmonologist and categorized in normal, obstructive and restrictive patterns regarding published criteria (16,17). The severity grading of respiratory impairment was based on the values of forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC). Normal respiratory function was defined as (FVC≥80% and FEV1≥80%) of predicted. Mild respiratory impairment was defined as (60%≤FVC<80%) or (60%≤FEV1<80%) of predicted, moderate as (50%≤FVC<60% or 40%≤FEV1<60%) of predicted, and severe as (FVC<50% or FEV1<40%) of predicted (17).

Clinical diagnoses
Diagnosis of COPD was made according to the history of cough and sputum production along with PFT characteristics patterns (decreased FEV1 and FVC with decreased FEV1/FVC <70% predicted) in the absence of bronchiectasis. Patients with asthma trait were defined as presence of typical attacks of dyspnea, nocturnal cough and wheezing with >15% increase in the FEV1 after bronchodilator inhalation. Bronchiectasis and small airway conditions relied mainly on HRCT findings and for pulmonary interstitial diseases HRCT findings plus restrictive pattern of PFT (decreased FEV1 and FVC with FEV1/FVC normal or increased) was used (17).
Statistical analysis

Descriptive analyses results are presented with numbers and percentages. Chi-Square and Fisher’s exact test were used to compare the qualitative statistics of paraclinical findings with clinical symptoms. Data were analysed using SPSS software (version 17.0; SPSS Inc., Chicago, USA). \( P \)-values less than 0.05 were considered statistically significant.

Results

There were 106 male veterans aged from 32 to 56 (mean age of 41). Mean time passed from exposure was 20.5 ± 1.2 years. 94.34% (n=100) had respiratory symptoms. The frequency of symptoms were dyspnea in 95 cases (89.62%), chest pain in 74 cases (69.81%), productive cough in 70 cases (66.70%), hemoptysis in 34 cases (32.70%), and non-productive cough in 25 cases (23.80%). Pulmonary signs including wheeze in 50 cases (47.16%), ronchi in 23 cases (21.69%) and fine crackles (rales) in 18 cases (16.98%) were detected as the main complaints in 84% (n=91) of the studied population. In pulmonary function test, 86.79% (n=92) had dysfunction spirometry test. PFT revealed more obstructive pattern (56.60%, n=60) than restrictive pattern (30.18%, n=32, \( P<0.01 \)) (Figure 1).

![Figure 1. Spirometer test findings in sulphur mustard victims after 18 to 23 years of exposure.](image)

![Figure 2. Expiratory High Resonance Computed Tomography Scan from 3 cases; reveals air trapping, mosaic parenchymal attenuation and hyperlucency. A: a 55 years old male with complain of dyspnea and productive cough and ronchi in physical exam. B: a 46 years old male with dyspnea and non-productive cough and wheeze. C: a 50 years old female with dyspnea, chest pain, productive cough, ronchi and fine crackles.](image)
In this study, HRCT imaging results were air trapping in 69 cases (65.09%), mosaic parenchymal attenuation in 62 cases (58.49%), normal in 16 cases (15.9%), hyperlucency in 11 cases (10.37%), bronchiectasis in 8 cases (7.54%), nodular in 7 cases (6.6%), reticular in 5 cases (4.71%), and consolidation in 3 cases (2.83%) (Figure 2). They comprised of chronic obstructive pulmonary disease (COPD) in 58 cases (54.71%), bronchiolitis obliterans in 29 cases (27.35%), asthmatic bronchitis in 9 cases (8.49%), bronchiectasis in 8 cases (7.54%), and lung fibrosis in 1 case (0.94%) as noted in figure 3. There were no significant association between the clinical findings and results of PFT and HRCT imaging (P-values were more than 0.05). Spirometry findings also did not have significant correlation with HRCT findings (P>0.05).

Discussion

In this study veterans inhabitant to main target of chemical attack in Iran were evaluated for clinical and paraclinical consequences of respiratory system after an average of 20.5 ± 1.2 years after exposure. Our patients’ main clinical findings were dyspnea and cough, each observed in more than 85% of subjects after 18-23 years of exposure consistent with other surveys including previous studies performed over Iranian victims with a higher frequency that suggests the progression of complications by time passing. Other observed symptoms were chest pain and hemoptysis (mainly streaky) which were more seen in our study (4,10-12,18,19). In a study three years after initial exposure, common symptoms in veterans were described as triad of cough, expectoration and dyspnea (20). Studies assessing longer outcomes also confirmed persistence of these findings after 10 to 15 years (11,19,21). Wheeze was the most clinical sign among patients as found in another study (11). Our findings demonstrated that main pattern of respiratory complication in pulmonary function test was obstructive. This supports previous studies regarding the dominancy of obstructive over restrictive pattern (10,11,18-20,22,23). In our study, predominant abnormal findings of HRCT imaging were air trapping and mosaic parenchymal attenuation pattern. These findings confirm those from previous studies which were performed on the SM victims except in relatively lower rate of bronchiectasis (7,10-12,19,21-24). We demonstrated that COPD, bronchiolitis obliterans, asthmatic bronchitis and bronchiectasis were the most common diagnoses for the individuals. This was along with the studies performed over victims after 10 to 20 years after initial exposure to SM in which chronic obstructive pulmonary disease, bronchiolitis obliterans, bronchiectasis, and asthma were found to be dominant affecting conditions (10,11,21-25). We observed low rate of lung fibrosis (0.94%) in our
subjects. Applying histological methods such as lung biopsy may reveal possible changes that are not detectable by HRCT. A study reported 12% of the lung fibrosis using transbronchial lung biopsy (10) also in other studies there were 9% (24) and 7.7% lung fibrosis (26).

To explain our milder results comparing with others, it should be considered that we had excluded smokers. These could have resulted in decrement of deteriorating conditions among the victims enrolled in this study. Lack of information about duration, amount and droplet size of inhaled gas during exposure is a general problem among similar studies. As when delivered in smaller size, the agent may reach smaller bronchioles and results in more severe symptoms. This in turn can result in some discrepancies in different studies. Different applied instruments and diagnostic criteria are contributing factors that should not be neglected. The principal limitation of the present study is its cross sectional nature that preclude the determination of the direction of causality, however we took advantage of a relatively large sample size.

In conclusion, we have shown the importance of paying more attention as time passing to prevent adverse complications.

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