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Long-Term Respiratory Disorders of Claimers with Subclinical Exposure to Chemical Warfare Agents

Mostafa Ghanei, Hosnieh Fathi, Mohammad Mir Mohammad, Jafar Aslani, Fariborz Nematizadeh

Baqiyatallah Medical Sciences University, Research Center for Chemical Injuries, Tehran, Iran

It is well documented that inhalation of sulfur mustard causes injury of the respiratory system. While all of the reports and surveys thoroughly document long-term pulmonary effects after significant exposure to mustard, there is no direct evidence that addresses the issue of long-term respiratory effects in individuals who were exposed to very low level of mustard and suffered no acute respiratory tract injury. Our subjects were selected among all those who were in chemically contaminated areas with chemical warfare agents (CWA) and had been registered for an annual checkup. Subclinical exposure's definition is the absence of any acute symptoms at the time of exposure. We used standard respiratory questionnaires, and chest HRCT examinations and a pulmonary function test were done. Based on exclusion criteria from total of 200 patients claiming respiratory problems, just 77 veterans entered the study. After performing HRCT for all our patients there were 13 (38.23%) veterans with no observable defect, 13 (38%) of them had just significant air trapping in their HRCTs. All the others had at least air trapping (AT), which added to other defects. Septal wall thickening was seen in five veterans (14.7%) and bronchiectasis was seen in three (8.8%) cases. This study suggest that exposure to CWA was responsible for the occurrence of the bronchiolitis obliterans syndrome observed in our patients. There are many civilian and military people who have been present in contaminated area without signs and symptoms at the time of exposure, and early detection of such a population could be lifesaving.

Modern chemical warfare emerged in 1915, when the German army used chlorine for the first time in a large-scale offensive against the Allies during World War I (WWI). The incident rapidly increased activities on both sides of the conflict toward development of protection against chemical attacks and more effective chemical weapons. As improved gas masks became more protective against inhaled poisons, researchers looked for one that would have damaging effects through absorption into skin and other mechanisms. In July 1917, in Belgium, the blister agent sulfur mustard, called mustard gas, because it had a mustard or garlic-like odor, was used for the first time. Its effectiveness has made it a chemical weapon of choice from 1917 to the present day, as evidenced by its use by Iraq against Iran in 1987 (Pechura & Rall, 1993).

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Address correspondence to Mostafa Ghanei, MD, Professor of Medicine–Pulmonologist, Baqiyatallah Medical Sciences University (BMSU), Research Center for Chemical Injuries, Mollasadra Street, PO Box 19945–546, Tehran, Iran. E-mail: m.ghanei@bmsu.ac.ir

Sulfur mustard (HD) is capable of producing severe chemical injuries in primarily three major organs: skin, eyes, and lungs. It is well documented that inhalation of sulfur mustard causes injury of the respiratory system, manifested by chest pain, cough, sore throat, and hoarseness. Lethal exposures result in death from respiratory failure, secondary pneumonia, and occasional hemorrhagic pulmonary edema. While all of the reports and surveys thoroughly document long-term pulmonary effects after significant exposure to mustard, there is no direct evidence that addresses the issue of long-term respiratory effects in individuals who were exposed to a very low level of mustard and suffered no acute respiratory-tract injury (Perrotta, 1996).

Thousands of Iranian soldiers with respiratory symptoms claim that their problems are related to their presence in a chemical warfare-contaminated area. Following a governmental invitation to all symptomatic patients who had documented presence in contaminated areas with chemical agents during the Iraq–Iran war to come for an annual checkup, we took the opportunity of running a case series based on their signs and symptoms.

METHODS

Patients

In December 2002, about 15 yr after exposure, a governmental association supporting veterans' affair asked all those who were in chemically contaminated areas with chemical warfare agents (CWA) to come for a complete check up. We defined contaminated area as regions witch was attacked by chemical misslies or bombardment and documented based on the army documentations.

Our subjects were selected among all those who had been registered for annual checkup, based on subclinical exposure's definition, which is absence of any acute symptoms at the time of exposure (Sartin, 2000). Cases who were present in attacked areas without any acute signs and symptoms at the time of attack were entered our study. Some of our cases mentioned that they saw other people injured near them with specific signs and symptoms of HD exposure. We excluded those who had even minor symptoms like lacrimation, cough, red eyes, or any other at the time of exposure. We excluded patients with the following concurrent, potentially confounding conditions: smoking (current and ex-smokers), having dusty jobs, reliability of the patient, and problems with lung involvement such as collagen vascular diseases, immunological disorders, heart diseases, organ transplantation, radiation therapy, chronic thyroidits, recurrent pulmonary infectious diseases, or even usage of drugs like phenytoin, bleomycin, methotrexate, or carbamazepin, which are known to have etiologies of drug-induced lung diseases (Epler, 2001).

Data Collection

To obtain a valid and standard questionnaire, we used standard respiratory questionnaires such as the British Medical Research Council (1996) questionnaire, and the American Thoracic Society's standardized respiratory symptoms questionnaire (Department of Health and Human Services, 1978). We put together all those items related to our survey, plus detailed questions on smoking habits, occupational exposure, and also battlefield questions based on the Organisation of Prohibition Against Chemical Weapons (OPCW) suggestions to help the witness of exposure recall his memories, which could help us to differentiate a real chemical agent exposure history from a suspicious one (OPCW, 2002).

Records on individual veterans, including respiratory questionnaires' information concerning the prevalence of cough, sputum, wheezing, sleep disturbance, breathlessness, and history of nocturnal awakening due to dyspnea and chest pain, as well as duration of presence in battlefield, disability percentile (all but respiratory), smoking habit, and occupational exposures, were received by a licensed physician.

Pulmonary Function Test

In addition, respiratory measurements were available on each veteran and included forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1). The tests were performed by experienced lung function technicians under the direction of licensed physicians using a standard spirometer (Jegger). All the patients were familiar with the equipment and very experienced in performing the maneuvers. While seated with a nose clip in place, subjects were asked to perform at least three forced expiratory maneuvers with verbal encouragement to blow maximally throughout until they felt there was no air to expel. Both the patients and the technician received visual feedback from a monitor screen 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. The data were transmitted weekly to a spirometery quality control center for rigorous review of data quality (Botto et al., 1997) and adherence to spirometery inclusion criteria.

Chest High-Resolution Computerized Tomography

Chest high-resolution computerized tomography (HRCT) examinations were obtained on one scanner (HiSpeed Advantage; General Electric Medical Systems). Each HRCT examination consisted of five 1.0-mm collimation images obtained during both deep inspiration and full expiration, 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 intravenous (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 previously established CT criteria. The mosaic parenchymal pattern was defined as areas of heterogeneous lung attenuation in a lobular or multilobular distribution in expiratory phase. The HRCT scans were reviewed by a radiologist and a pulmonologist. A quick-read form was developed by the group's consensus for ease of reporting. The only data available to the HRCT reviewers were patient's age, sex, and history of exposure to HD. The interobserver agreement for air trapping, bronchiectasis, and mosaic parenchymal attenuation was registered. The expiratory images were also assessed for the presence and lobar distribution of air trapping. The criteria used to diagnose the presence of air trapping were alteration of normal anterior posterior lobar attenuation gradients and/or lack of homogeneous increase in lung attenuation resulting in persistent areas of decreased attenuation. The extent of air trapping was quantified and classified using the same system as defined for hyperlucent regions on inspiratory images, considering that limited air trapping has been reported in normal individuals. Presence of air trapping was considered indicative of bronchiolitis obliterans (BO) only if it exceeded 25% 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 air trapping.

Data Analysis

Research data were gathered using Microsoft Access database (version 2002, Microsoft Corporation, Redmond, WA); then they were transferred to the SPSS analytic package (SPSS version 11.0 lead software) for analysis.

DEFINITIONS

Dusty job: Any job related to toxic fume inhalation, mineral, or industrial dust exposures (Murray et al., 2000).
Nonsmoker: Never smoked and quit for more than 10 yr.
Ex-smoker: Smoked previously and quit for at least 1 yr.
Current smoker: Continues to smoke more than one cigarettes or pipes daily at least for 1 yr.
Chronic sputum production: Phlegm in the morning or during the day or night for more than 3 mo/yr for 2 yr.
Chronic cough: Cough in the morning or during the day for more than 3 mo/y for 2 yr.
Chronic wheeze: Chest whistling or wheezing most days or nights.
Dyspnea: Shortness of breath on effort or which walking up a slight hill.
Abnormal physical examination: The presence of rales, clubbing, or cyanosis
Pulmonary function status was defined as follows (McDuffie et al., 1991):

1. Restrictive ($FVC < 80\%$ of predicted and $FEV_1/FVC > 80\%$).
2. Obstructive ($FEV_1/FVC < 70\%$).
3. Mixed ($FVC < 80\%$ of predicted, FEV_1/FVC ratio between 70% and 80%).
4. No dysfunction.

RESULTS

In total, 200 veterans claiming respiratory problems had been questioned, and based on exclusion criteria just 77 veterans entered the study. They had a mean age of 38.9 yr (±5.44 SD). There were a mean of 24.22 mo presence in the field. The longest period was 60 mo, while the shortest one was only 2 mo.

Our report here is based on 34 cases (44%) of those who met our criteria and were included in our study; 21 of them suffered other war injuries as well, so their disability percentile based on military code sheets reached a mean of 23.61%.

They had different episodes of presence in contaminated areas: 12 (40%) of the cases had been in a documented polluted field only once, while 14 (46.7%) of them were there twice. We had 8 veterans who met the place for more than 2 times. Respiratory complaints had started at least 2 yr before our interview, while in some cases it was about 14 yr, that they suffered from their condition (see Figure 1).

Complaints like cough, phlegm, wheeze, and dyspnea did not have a gross difference in 15 (44%) seasonally, but were worse in winter in 9 (26.5%) of them, while in 5 summer affected symptoms. We checked other long-term adverse effects of mustard as well; there were 20 (58%) with skin problems and 14 (41.2%) with ophtalmic symptoms. Posttraumatic stress disorder (PTSD) was seen in seven of them. Different symptoms are listed in Table 1.

Night sleep disturbance was seen just once in 6 (17.64%); interestingly enough, we had only 4 person with a snoring habit.

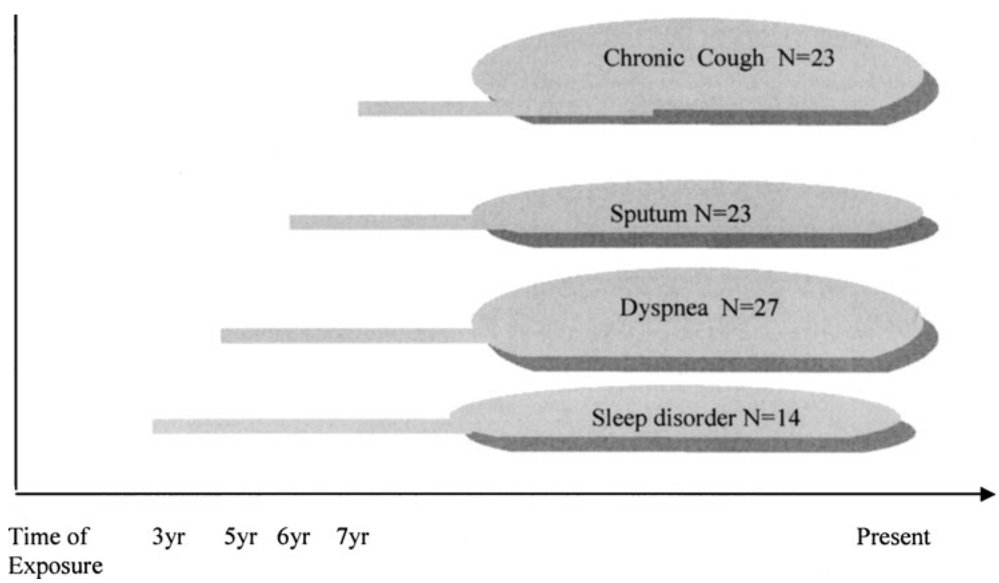

FIG. 1. Time of presenting of symptoms.

TABLE 1
Respiratory symptoms

Respiratory complaints	Number	Percent
Dyspnea	27	79.4
Cough	27	79
Phlegm	23	67.6
Chronic cough	23	67
Chest pain	16	47.1
Arousal Night sleep	14	41.2
Hemoptysis	11	32.3

We had six veterans who had experienced symptoms like an asthma attack, all in their own third decade, for the first time.

There was not any prominant problem in physical exams. All chest x-rays were normal. Pulmonary function results are indicated in Table 2.

After performing chest HRCT for all our patients there were 13 (38.23%) veterans with no observable defect; 13 (38%) of them had just significant air trapping in their HRCTs. All the other had at least air trapping (AT), which added to other defects. Septal wall thickening was seen in 5 veterans (14.7%) and bronchiectasis was seen in 3 (8.8%). Mosaic pattern defects were just seen in one patient.

DISCUSSION

Chest HRCT imaging of the lungs of our cases showed bronchiectasis, decreased size of the vessels, and air trapping on expiratory films. Previous study showed that these findings are most consistent with BO syndrome (BOS) (Muller & Miller, 1995). It also has been noted that air trapping, as detected on expiratory HRCT, was the most sensitive and accurate radiologic indicator of BOS (Kraft et al., 1993).

There are many etiologies for BOS, such as previous childhood infections (particularly measles, adenovirus, and *Mycoplasma*); toxic fume inhalation; graft-versus-host disease following bone-marrow transplantation; chronic rejection following lung or heart–lung transplantation; and autoimmune connective tissue disorders, such as rheumatoid arthritis treated with penicillamine therapy, and polymyositis (Skeens et al., 1989; King, 1989).

Several factors suggest that exposure to CWA was responsible for the occurrence of the BO syndrome observed in our patients. First of all, no other cause was identified. Because of the retrospective nature of this work, exhaustive data were not obtained for every patient, particularly concerning the search for infectious pathogens. However, when performed, the search for infectious pathogens (bacteria, fungi, mycobacterium, and viruses) was always negative. The second reason is that findings of this study did not fit with idiopathic (cryptogenic) bronchiolitis obliterans, because it is a rare disorder that occurs in patients (especially women) who have no obvious inciting agent or associated systemic disorder, yet who have airflow obstruction clinically, and constrictive bronchiolitis histologically (Hogg et al., 1968). Typical clinical findings of idiopathic bronchiolitis obliterans include several weeks or months of dyspnea and a nonproductive cough. Bilateral early inspiratory crackles are often heard. The vital capacity may be decreased. The FEV_1 or FEV_1/FVC may be severely decreased. Near normal spirometery and also normal physical exam and male gender of our patients are not features of this disease. Normal pulmonary function test data were detected in the presence of exertional dyspnea in most of our cases because the branching pattern of the bronchial tree results in an increasingly large number of small airways in peripheral generations, and these airways contribute little to total pulmonary resistance. So, a large proportion of small airways may be damaged or obliterated without impairing any of the conventional tests of pulmonary function (Wohl & Chernick, 1978). Previous study confirmed that bronchiolitis obliterans and, even more rarely, bronchilitis obliterans organizing pneumonia (BOOP) are rare complications of irritant inhalation injury. The agent most often implicated in such cases is nitrogen dioxide (e.g., in silo-filler's disease), but ammonia, fly ash, hydrogen bromide, sulfur dioxide, and zinc chloride smoke bombs have all been associated in case reports (Leung, 1998). The researchers explained that irritant-related bronchiolitis obliterans is characterized clinically by an acute exposure incident of moderate to high severity (with development of tracheobronchitis or chemical pneumonitis), a period of partial resolution, and then clinical deterioration 2 to 4 wk later. Patients typically present with fever, chills, and cough, and may have a normal chest radiograph or, if BOOP is present, diffuse alveolar opacities may be evident on chest radiograph (Bando et al., 1995). However, our findings suggested that it may be possible that exposure to very low dose of CWA could lead to BOS without significant clinical symptoms at time of exposure.

TABLE 2
Pulmonary function tests results

Condition	Number	Percent
Restrictive	2	5.88%
Obstructive	0	0
Mixed	3	8.82%
No dysfunction	29	85.29%

On the whole, the treatment of OB has been unsuccessful, but a study by Bando and colleagues (1995) has shown that resolution or stabilization with augmented immunosuppression occurs frequently if the diagnosis is made when patients are still in BOS stage 0. Thus, by allowing detection and treatment of OB in a preclinical stage, prospective measurements of ventilation distribution might prevent irreversible lumenal occlusion and scarring of the airways. This finding is very important for our country because sulfur mustard (HD) as a chemical weapon has been employed with devastating results against Iranian peoples both military and civilian targets by Iraqi forces (Security Council of the United Nations, 1986). There are many civilian and military people who have been present in contaminated area without signs and symptoms at time of exposure, and early detection of such a population could be lifesaving.

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