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Pulmonary Complications of Chemical Warfare 15 Years after Exposure

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ABSTRACT

Introduction: Chemical weapons, (mainly mustard gas-MG) were heavily used by Iraq against Iranian soldiers between 1984-1986. It has acute effects on respiratory tract in the form of tracheobronchitis and ARDS, whereas chronic respiratory complications include chronic bronchitis, bronchiectasis, asthma and pulmonary fibrosis. There are few reports about human victims. Some of them describe acute effects while our purpose is to define chronic sequelae and their microbiologic, radiologic and physiologic behavior.

Materials and Methods: Fourty four chemical weapon injured patients with moderate to severe disability were selected by AMA criteria (1). All of them underwent history taking and physical examination, ABG, spirometry, CXR, HRCT, bronchoscopy and BAL for cytology and quantitative culture.

Results: Of forty four patients; 29(66%) had diagnosis of chronic bronchitis by ATS criteria (2), 8 (18%) and 7 (16%) had diagnosis of bronchiectasis and asthma respectively. The most common HRCT finding was ground glass appearance. In one-fourth of patients BAL culture was positive and revealed unusual organisms (*S.aureus*, *S.coagulase negative*, *E.coli*), BAL neutrophils were increased in bronchiectatic group (258 ± 136 hpf) vs. (96 ± 49 hpf), (148 ± 133 hpf) ($p<0.01$ p). Bronchiectatic patients were younger than the other groups (35.5 ± 6.1 yr) vs. (43.5 ± 5.2 yr), and (42.3 ± 5.2 yr) ($p<0.01$).

Conclusion: The most common respiratory complication of MG is chronic bronchitis. Unusual microorganisms should be considered in the treatment of pulmonary infections. Persons who are exposed to mustard gas at younger age maybe more prone to development of bronchiectasis. (*Tanaffos* 2003; 2(6): 45-50)

Key Words: Chemical weapon, Lung injury, Mustard gas

INTRODUCTION

Chemical weapons, mainly "Mustard Gas" (MG) were heavily used by Iraq between 1984-1986 against Iranian soldiers (3,4,5). Although MG mortality is about 2%, (6) its acute and chronic morbidity is much more.

After MG exposure, respiratory system, skin, and eyes are affected (3,4,5,6,14). The respiratory system complications are irreversible (6) and include chronic bronchitis, asthma, bronchiectasis and pulmonary fibrosis (3-7).

Our study was carried out in order to evaluate the late sequelae and microbiologic study of respiratory

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system in 44 moderate to severe, chemically injured patients.

MATERIALS AND METHODS

The study group consisted of 44 moderate to severely injured male patients (based on American Medical Association grading) (1) fifteen years after MG exposure.

It was carried out between Nov/1999 and Jan-2000; inclusion criterion was at least one heavy exposure to chemical weapon (MG) as documented by relevant records in "Bonyad Janbazan Registry of Khorasan province. The patients with history of smoking, mining, farming, milling and previous lung disease were excluded from the study. After taking a medical history and physical examination, arterial blood analysis, CXR, spirometry (Fukoda ST-90 Tokyo, Japan) and HRCT were done. Bronchovideoscopy (Olympus BF type I-T 200) with premedication including local lidocaine was performed by transnasal route in all patients. One hundred ml aliquots of saline were used to irrigate by wedging FOB in the most inflamed bronchi of upper and lower lobes on each side up to total of four hundred ml. The BAL fluid was sent for cytology, and quantitative culture. Positive BAL culture was defined as more than 10000 colony count of a single organism. Culture media were agar, blood agar & McConkey.

If there was narrowing or vegetation, a bronchial biopsy was taken. According to clinical and paraclinical data, the patients were categorized in to three main groups: 1-asthmatics (increase in FEV1 > 15% of base line by β_2 agonist, wheezing and nocturnal symptoms), 2-Chronic bronchitis (as defined by ATS-(2). 3- Bronchiectasis (based on excessive mucus production and HRCT finding having cystic, numerous cylindrical, lesions, signet sign). A minor subgroup of patients had asthmatic bronchitis (defined by at least 15% increase in FEV1 following β_2 agonist inhalation in chronic bronchitis

patients). Data were analyzed by Mantel-Haenzel tests for linear association, Fisher exact and Pearson test.

RESULTS

All of the patients were male. The age range of patients was 29-85 years (41.7 ± 12.4). The average time after exposure was 16.6 years, number of MG contacts were 1-3 times. 29(66%) out of 44 patients had chronic bronchitis, 8 (18%) and 7(16%) patients had bronchiectasis and asthma respectively. The most common symptom and sign were productive cough (88%) and wheezing (95%). Increased bronchovascular marking and crowding of bronchi were the most common CXR findings (60%). The most common HRCT findings were ground glass appearance (53%), interstitial and septal thickening (35%), collapse-consolidation (32%), air trapping (30%), bronchiectasis (26%), honey comb (20%). Lingula (38%) and right lobe (35%) were the most common involved lobes. Spirometric findings showed FEV1/FVC of $63.6\% \pm 14\%$, FEV 1.7 ± 0.63 lit and FVC of 2.43 ± 0.67 lit. PaO₂ range was 45-97 mmHg (64.9 ± 9.5) while PaCO₂ was 25 ± 46 (38.2 ± 4.4). The frequency of chemical attacks was 1-3 (1.2 ± 0.5).

There was no correlation between age, 0-1 PaO₂, frequency of attacks and FEV1 and frequency of attacks and PaO₂.

There was also no significant correlation between frequency of attacks and FEV1/FVC.

The most common bronchoscopic finding was inflammation (91%). Twenty-five percent of patients had positive culture, which consisted of five patients with *S.aureus*, three patients with *S.coagulase* negative and three patients with *E.coli*. Only one of four biopsies showed dysplastic changes. Individuals of bronchiectatic group were significantly younger than two other groups ($p < 0.01$) (table 1)

Table 1. Mean age of groups and number of patients

Diagnosis	No of patients	Mean age (Year)	p-value
Chronic bronchitis	29	42.3±5.2	NS*
Bronchiectasis	8	35.5±6.1	P<0.01 **
Asthma	7	43.5±5.2	NS *

* Values of comparison between asthma and chronic bronchitis groups

** Values of comparison between bronchiectasis group and asthma, bronchiectasis group and chronic bronchitis.

Neutrophil content of BAL of the bronchiectatic group was significantly higher than the others whereas their macrophage content was lower (p<0.01) (table 2)

Table 2. Cellular components of BAL fluid

No. of cell /hpf	Asthma (4)	Chronic bronchitis (24)	Bronchiectasis (4)
Total	325±75	306±110	325±83
Neutrophil	96±49 *	148±133	258±136 **
Macrophage	202±148	140±95	24±15***

* Value of comparison between asthma and chronic bronchitis. (p<0.01)

** Value of comparison between bronchiectasis and chronic bronchitis. (p<0.01)

*** Value of comparison between bronchiectasis, asthma and chronic bronchitis separately

Spirometric ABG data are presented in table 3.

Table 3. Spirometric and ABG finding

	Mean	Std. Deviation
FEV ₁ *	1.72±6.3 lit	(p=0.77)
FEV ₁ percent ± ***	63.6%± 14.6%	(p=0.12)
FVC	2.4±6.7 lit	
Po ₂	64.9±9.5mmHg	
PCo ₂	38.2±4.4mmHg	(p=0.49)
Age	41.8±12.6 yr	
Frequency of attacks	1.2±0.5	

* Correlation between FEV₁ and frequency

** Correlation between PCo₂ and frequency

*** Correlation between FEV₁ percent and frequency

DISCUSSION

MG is capable to penetrate cell walls of different tissues (3,5,6). Since MG has intermediate solubility, both upper and lower respiratory tracts are involved. It may cause altered ciliary activity, epithelial damage, scarring and hypocomplementemia (3,5,14). These damages predispose patients to repeated infections and thence bronchiectasis (3).

Recently Calvet et al. showed decreased activity of neutral endopeptidase in MG injured experimental animals as a main mechanism of asthma (8). In 1988 Sohrabpour and Masjedi showed air flow obstruction in 50% of their MG injured patients. They showed decreased number of macrophages and increased number of neutrophils in BAL fluid of their patients (6). They concluded that respiratory complications are quite resistance to therapy (6). In 1991, Freitag et al. showed *S.aureas*, *H. influenza* and *P. aeruginosa* in BAL fluid culture of Iranian injured soldiers (4). In 1997, Emad and Rezaian showed that chronic bronchitis as the most common complication and more severe forms of asthma in older patients (3).

They showed no case of bronchogenic carcinoma. They had done TBLB for all of their patients and demonstrated pulmonary fibrosis in 12.18% of 197 patients (3).

They mentioned some common features between IPF and MG induced pulmonary fibrosis in cellular component of BAL and pathology (3). Our study showed chronic bronchitis as the most common clinical diagnosis (66%). In accordance to Masjedi and Sohrabpour study, we showed persistent diseases, although some of them are reversible by β₂ agonist. (19 out of 44 asthma and asthmatic bronchitis group).

In contrast to Emad's study, 37% of chronic bronchitis group had a reversible component (asthmatic bronchitis). They do not recall this sub group of patients in their study. In another study, which had a very close rate of reversibility to our

study, Hosseini et al. showed reversibility in 37.7% of their 45 COPDs after MG exposure and labeled them as asthmatic bronchitis. This may be due to atopy or hyperresponsiveness induced by MG (15). Although our results of reversibility were very close to Hosseini's study, he recalled that the rate may be an underestimation because of concomitant use of inhaled corticosteroids by some patients.

Induction of airway hyperresponsiveness by MG has been demonstrated in animal models by intratracheal instillation of MG (8). Two weeks after exposure, guinea pigs showed hyperresponsiveness to substance P and histamine (8).

BAL neutrophil count of bronchiectatic group was higher than two other groups ($p < 0.011$) It may be due to more infectious process in bronchi.

Twenty five percent of patients had positive culture including *S.aureus*, *S.coagulase* negative and *E.coli*. It is worthy to know that positive cultures were present in three groups. Culture results had more resemblance to Freitag's study than the usual microorganisms in COPD (9). Individuals of bronchiectasis group were younger than other groups ($p < 0.01$). This finding reemphasizes the results of Emad's study. He showed that chronic bronchitis and moderate to severe asthmatic patients were older (3). This may be due to increased hyperresponsiveness in older patients and vulnerability of bronchi to destruction in younger patients.

Our study did not show any case of bronchogenic carcinoma by cytology or biopsy, probably because it needs at least twenty two years of latent period (10-13). Although some evidences such as mixed pattern on spirometry and HRCT findings strongly suggest pulmonary fibrosis, we did not consider it as a distinct diagnosis. Whether open lung biopsy is required for diagnosis of pulmonary fibrosis in MG injured patients or transbronchial lung biopsy suffices, needs further studies. We conclude that persons who were exposed to MG at a younger age

may be more prone to the development of bronchiectasis. Unusual microorganisms should be considered in the treatment of pulmonary infections. Our study does not show any case of bronchogenic carcinoma.

Abbreviations: AMA= American Medical Association, ARDS= Acute Respiratory Distress Syndrome, ATS=American Thoracic Society, BAL= Broncho-Alveolar Lavage COPD= Chronic Obstructive Pulmonary Disease, CXR = Chest X-Ray, HRCT= High Resolution Computed Tomography, IPF= Idiopathic Pulmonary Fibrosis, MG= Mustard Gas, OLB= Open lung Biopsy, TBLB= Trans-Bronchial Lung Biopsy.

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