Evaluation of latent hemoptysis in Sulfur Mustard injured patients

Article *in* Environmental Toxicology and Pharmacology · September 2006

DOI: 10.1016/j.etap.2005.12.009 · Source: PubMed

CITATIONS
8

READS
56

4 authors, including:

Mostafa Ghanei
Baqiyatallah University of Medical Sciences
388 PUBLICATIONS **5,518** CITATIONS
SEE PROFILE

Ahmadreza Djalali
Center for Research and Education in Emergency and Disaster Medicine, Novara, I…
46 PUBLICATIONS **543** CITATIONS
SEE PROFILE

Jafar Aslani
Baqiyatallah University of Medical Sciences
71 PUBLICATIONS **1,486** CITATIONS
SEE PROFILE

Available online at www.sciencedirect.com
SCIENCE DIRECT
Environmental Toxicology and Pharmacology 22 (2006) 128–130
ENVIRONMENTAL TOXICOLOGY AND PHARMACOLOGY ETAP
www.elsevier.com/locate/etap

Evaluation of latent hemoptysis in Sulfur Mustard injured patients

Mostafa Ghanei *, Mehdi Eshraghi, Ahmad Reza Jalali, Jafar Aslani

Baqiyatallah Medical Sciences University, Research Center of Chemical Injuries, Mollasadra Street, Tehran, Postal Code 14359151371, Islamic Republic of Iran

Received 17 July 2005; accepted 29 December 2005
Available online 29 March 2006

Abstract

Introduction: Hemoptysis is one of the mustard exposed patients' symptoms. Data from one study on survivors of Sulfur Mustard attacks during World War I had revealed an increased rate of lung cancer among them. Aim of this study was to determine lung HRCT and fluorescence bronchoscopy findings in mustard exposed patients with hemoptysis.
Materials and methods: In this cross-sectional study we evaluated 98 patients with protracted hemoptysis in association with history of single exposure to SM. For this mean we used different lung cancer screening tools including HRCT, bronchoscopy (WLB and fluorescence) and pathology (bronchial lavage cytology and biopsy).
Results: Mean time of exposure to SM among cases was 15.5 ± 4.3 (mean $\pm$ S.D.) years ago. Mean age of studied patients was 48.3 ± 8.2 years. No finding had been found supporting the malignancy in any of cases via imaging and pathological evaluations. Cytological investigation of bronchial lavage for TB (staining and culture) and/or malignancy in all cases was negative. Pathology findings of specimens were: 9% normal, 83% chronic inflammation and 8% squamous metaplasia.
Conclusion: Though our findings are in accordance to other studies which are conducted by other Iranian researchers so far, we cannot overlook the risk of lung cancer among SM patients in future. In conclusion, hemoptysis per se in acutely exposed SM patients could not be considered as a valuable evidence of lung malignancy and it is more likely due to other pathologies of respiratory system in SM patients and close monitoring of these patients for early detection of any kind of malignancy is suggested.

Keywords: Chemical warfare; Mustard gas; Lung cancer; Iran; Chest HRCT; Fluorescence bronchoscopy

1. Introduction

Sulfur Mustard (SM), a well-known chemical weapon, has been widely used by Iraqi ex-regime against Iranian troops and civilians between 1980 and 1988 (Security Council of the United Nations Document, 1986). Besides the vast acute casualties, frequent use of this agent resulted in chronic illnesses and disabilities among survivors (Khateri et al., 2003). It is shown that respiratory involvement is the main long consequence of exposure to SM (Ghanei et al., 2003). Common clinical manifestations of lung involvement in SM patients include cough, shortness of breath and sputum (Emad et al., 1995).

In addition to these three pulmonary symptoms, hemoptysis has also been reported in SM injured patients (Bijani et al., 2002). Since previous studies have shown an increase rate of malignancy in SM patients (Easton et al., 1988; Beebe, 1960; Case and Lea, 1955), this symptom is usually distressing and raises both physicians and patients concern about possible underlying malignancies in these cases (Hirshberg et al., 1997).

Indeed SM has definite mutagenic and carcinogenic effects; it has been reported as a risk factor for occupational lung cancers (Weiss and Weiss, 1975; Easton et al., 1988; Wadaa et al., 1968). So tumor screening in SM patients especially if they have warning symptoms like hemoptysis is very important. In this regard, we examined the application of the latest screening tools for lung cancer; "*fluorescence bronchoscopy*" and "*Chest HRCT*", in Iraq–Iran war's SM injured cases complaining of protracted hemoptysis.

2. Methods and materials

Based on a descriptive study, from 2000 to 2003 (on average 15 years after chemical attacks), 98 patients with documented exposure to SM and history of hemoptysis were evaluated for early evidences of lung cancer.

* Corresponding author. Tel.: +98 21 8053770; fax: +98 21 8040106.
E-mail addresses: m.ghanei@bmsu.ac.ir, mghanei@excite.com (M. Ghanei).

1382-6689/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.etap.2005.12.009

2.1. Inclusion criteria

(a) Documented chemical exposure by military health services. Exposure in this study was defined as a single, high-dose exposure to a chemical agent that causes permanent respiratory disability in exposed people.
(b) Association of patient's medical records (e.g. patient hospitalization after exposure).

2.2. Exclusion criteria

All previous diagnosed patients with lung cancer, suspected cases of pneumonia or acute infective bronchitis, diagnosed patients with bleeding disorders and patients with unstable angina or uncontrolled hypertension.

2.3. HRCT

Each HRCT examination consisted of five 1.0-mm collimation images obtained during both deep inspiration and full expiration, respectively, with the patient lying in a supine position. Non-contrast images were obtained. The HRCT scans were reviewed by two radiologists and two pulmonologists. The only data available to the HRCT reviewers were patient's age, sex and history of exposure to SM. The inspiratory images were assessed for the presence of bronchiectasis and the expiratory images were also assessed for the presence and lobar distribution of air trapping. To determine the overall frequency of each lesion and prevalent lobar involvement, we analyzed HRCT findings based on the lesion type in total number of lobes in all patients.

2.4. Bronchoscopy and biopsy

Performance of fluorescence bronchoscopy was started by inhalation of 200 mg of 5-ALA diluted in 5 ml NaCl 0.9% by a conventional jet nebulizer for a homogenous deposition with a dose of 60 mg in 2.5 ml NaCl 0.9%. The patients underwent fluorescence bronchoscopy 90–120 min after inhalation of ALA. All procedures were performed by one bronchoscopist assisted by an experienced nurse. After applying topical anesthesia (Lidocaine, aerosolized) to the patient's nasopharynx and larynx. Approximately 5 ml of 1% lignocaine jelly was instilled into each nostril and then the patient was sedated with small incremental doses of IV midazolam until judged to be lightly asleep. During the procedure, patients were given supplemental oxygen at a rate of 3 l/min through nasal prongs directed into the mouth and monitored for oxygen saturation, pulse rate and possible arrhythmias. Alarms were set to go off if the saturation fell below 90% or if the pulse was below 55 or above 130. Supplemental oxygen was continued until the patient was awake following the procedure.

The flexible fiberoptic bronchoscopy (FFB) was performed using the transnasal route. Routine administration of sedatives or anxiolytics was avoided, but IV midazolam was administered during FFB if deemed necessary by the bronchoscopist to improve patient comfort and tolerance of the procedure. In our institution, most bronchoscopies are performed without premedication other than topical anesthesia.

At first, white light bronchoscopy (WLB) was used to investigate the tracheobronchial tree. In this phase, normal and abnormal regions were defined. Erythematouse mucosa, inflammation, granulma tissues and hyperplasia were considered as non-specific abnormalities, while regions with irregularity or thickness in bronchial mucosa were considered as suspicious neoplastic regions (dyspalsia/carcinoma in situ) (Haubinger et al., 1999).

During fluorescence bronchoscopy, regions with green light reflects were considered as "Normal Mucosa" while light brown to dark reddish brown reflection lights were considered as "Suspicious Mucosa" (Lam and McLean, 1990), and biopsies were took from these areas. In addition, bronchial lavage was done before taking biopsies. All specimens were sent to an expert pulmonary pathologist in one hospital center.

3. Results

The mean age of the investigated patients was 38 ± 9 years (23–81 years). 97 patients were male and 1 was female. Mean time of exposure to SM among cases was 15 ± 1.4 years ago (13–19 years). Most of cases (93.9%) had only once exposure to SM, only 4.4 and 1.7% of cases reported twice and thrice exposure, respectively. Seventy-nine percent of patients had the history of skin blisters, 26% of eye lesions and visual disorders and 92% of patients were hospitalized due to SM exposure just after accident. In radiological evaluation (CX-ray and Chest HRCT) no finding had been found supporting the malignancy in any of the cases. Chest HRCT findings are indicated in Table 1. The results of WLB and FB are shown in Tables 2 and 3. Cytological investigation of bronchial lavage for TB (staining and culture) and/or malignancy in all cases was negative. Pathology findings of specimens were: 9% normal, 83% chronic inflammation and 8% squamous metaplasia.

Table 1
Chest HRCT findings in 50 patients 15 years after documented exposure to SM

Finding	Frequency (%)
Air trapping	76
Bronchiectasis	74
Mosaic parenchymal attenuation (expiratory)	72
Dilated irregular trachea and major airways	66
Bronchial wall thickening	90
Interlobular septal thickening	26

Table 2
White light bronchoscopy results

Finding	Frequency (%)
Normal mucosa	4.1
Erythema and inflammation	65
Granulma	4
Local bleeding	10
Mucosal vascular congestion	11
Mucosal thickness	12
Suspicious neoplastic mucosa	No case

Table 3
Fluorescence bronchoscopy results

Finding	Frequency (%)
Normal mucosa	68.1
Suspicious mucosa	31.9

Table 4 shows comparison between FB findings and pathology results; color alteration was observed in 25% of normal tissues, 32% of inflammatory mucosa and 60% of squamous metaplasia that means probability of reddish brown light reflec-

Table 4
Comparison between FB and pathology findings

FB findings	Pathology findings (%)			Total (%)
	Normal	Chronic inflammation	Squamous metaplasia	
Normal mucosa	6	57.5	3	66.5
Suspicious mucosa	1.5	27.5	4.5	33.5
Total	7.5	58	7.5	100

tion is three times more in squamous metaplasia than other conditions ($p < 0.05$).

4. Discussion

As our findings confirm, the dominant pulmonary pathology in SM patients with latent hemoptysis is a chronic inflammatory process, and after 15 years of exposure to SM no finding has been found in favor of malignancy in them. Our findings are in accordance with other recent large scale studies on Iranian SM injured cases which could not show an increase risk of malignancy in them so far (Ghanei et al., 2003). However, there is one report of increased risk of lung cancer in acutely mustard exposed veterans of World War I (Norman, 1975). This study was published nearly 60 years after exposure of veterans to SM. And maybe, like any kind of cancer, represents the important role of time needed to evolve detectable malignancy.

Nearly all other studies, which have shown increased lung cancer in human due to SM exposure, have mainly focused on chronically SM exposed individuals (e.g., Japanese factory workers). Those patients certainly had received a remarkable dose of SM at work.

We are not aware about the mustard dose received by our patients or WWI veterans. Most of our patients had only one exposure to SM, however as Zarchi and Holakouie Naieni (2004) have described in their reports; frequency of gas exposure is not associated with a significant rise in the risk of lung injury and this may be explained by ambient gas concentrations and duration of exposure and temperature. However, skin symptoms, after exposure in our patients, shows that they had received pathological level of mustard. Whether this was not enough to switch on carcinogenesis process in them or anti-tumor mechanisms could overwhelm cancerous changes; it is hard to answer this question at the moment.

As it was mentioned earlier we found out that the pathology behind hemoptysis in SM patients is a chronic inflammatory process within airways. Moreover, our radiological findings (bronchiectasis, air trapping in expiration and inspiratory mosaic parenchymal attenuation) are pointing us to the diagnosis of *Bronchiolitis Obliterans* (Skeens et al., 1989). So far two researchers have reported occurrence of BO after acute exposure to SM (Thomason et al., 2003; Dompeling et al., 2004). These findings are in accordance with the belief that the main scenario after irritant gas inhalation is BO (*Bronchiolitis Obliterans*) or BOOP, though the exact nature of the disease is not fully understood (Shusterman, 1999). So, we think that it is reasonable to correlate the hemoptysis in our patients to existence of BO (Mroz et al., 1997).

Finally, we conclude that hemoptysis in acutely exposed SM patients could not be considered as a valuable evidence of lung malignancy, however we cannot deny the need for tumor detection in SM patients with hemoptysis.

References

Beebe, G.W., 1960. Lung cancer in World War I veterans: possible relation to mustard gas injury and 1918 influenza epidemic. J. Natl. Cancer Inst. 25, 1231–1251.

Bijani, K.h., Moghadamnia, A.A., 2002. Long-term effects of chemical weapons on respiratory tract in Iraq–Iran war victims living in Babol (North of Iran). Ecotoxicol. Environ. Saf. 53, 422–424.

Case, R.A., Lea, A.J., 1955. Mustard gas poisoning, chronic bronchitis, and lung cancer. Br. Med. J. 9, 62–72.

Dompeling, E., Jobsis, Q., Vandevijve, r.N.M., Wesseling, G., Hendriks, H., 2004. Chronic bronchiolitis in a 5-yr-old child after exposure to sulphur mustard gas. Eur. Respir. J. 23 (2), 343–346.

Easton, D.F., Peto, J., Doll, R., 1988. Cancers of the respiratory tract in mustard gas workers. Br. J. Ind. Med. 45, 625–659.

Emad, A.F., Rezaian, G., Hoseini, K., Ghayyoomi, S.M.A., 1995. Chronic Pulmonary Sequelae of Sulfur Mustard Gas Exposure in Man: A Report of 36 Cases, vol. 182, pp. 1–5.

Ghanei, M., Aslani, J., Khateri, S., Hamadanizadeh, K., 2003. Public health status of the civil population of Sardasht 15 years following large-scale wartime exposure to sulfur mustard. J. Burns Surg. Wound Care 2 (1), 7 [serial online].

Haubinger, K., Stanzel, F., Huber, R.M., 1999. Auto fluorescence detection of bronchial tumors with the D-light/AF. Diag. Therap. End. 5, 105–112.

Hirshberg, B., Biran, I., Glazer, M., Kramer, M.R., 1997. Hemoptysis: etiology, evaluation, and outcome in a tertiary referral hospital. Chest, Chicago 112 (2), 440–445.

Khateri, S., Ghanei, M., Keshavarz, S., Soroush, M., Haines, D., 2003. Incidence of lung, eye, and skin lesions as late complications in 34,000 Iranians with wartime exposure to mustard agent. J. Occup. Environ. Med. 45 (11), 1136–1143.

Lam, S., McLean, D., 1990. Detection of early lung cancer using low dose photofrin II. Chest 97 (2), 333–337.

Mroz, B.J., Sexauer, W.P., Meade, A., Balsara, G., 1997. Hemoptysis as the presenting symptom in bronchiolitis obliterans organizing pneumonia. Chest 111 (6).

Norman, J.E., 1975. Lung cancer mortality in World War I veterans with mustard-gas injury: 1919–1965. J. Natl. Cancer Inst. 54, 311–317.

Security Council of the United Nations Document, 1986. Reports of Specialists Appointed by the Secretary General to Investigate Allegations by the Islamic Republic of Iran Concerning the Use of Chemical Weapons, New York, S/16433.

Skeens, J.I., Fuhrman, C.R., Yousem, S.A., 1989. Bronchiolitis obliterans in heart–lung transplantation patients: radiologic findings in 11 patients. Am. J. Roentgenol. 153, 253–256.

Shusterman, D., 1999. Upper and lower airway sequel of irritant inhalations. Clin. Pulm. Med. 6 (1), 18–31.

Thomason, J.W., Rice, T.W., Milstone, A.P., 2003. Bronchiolitis obliterans in a survivor of a chemical weapons attack. JAMA 290 (5), 598–599.

Wadaa, S., Miyanishi, M., Nishimoto, Y., Kambe, S., Miller, R.W., 1968. Mustard gas as a cause of respiratory neoplasia in man. Lancet 1 (7553), 1161–1163.

Weiss, A., Weiss, B., 1975. In: Thieme, G. (Ed.), Karzinogenese Durch Lost-Exposition Beim Menschen, Ein Wichtiger Hinweis fur die Alkylantien-Therapie. Deutsche Medizinische Wochenschrift, Stuttgart, pp. 919–923.

Zarchi, A., Holakouie Naieni, K., 2004. Long-term pulmonary complications in combatants exposed to mustard gas: a historical cohort study. Int. J. Epidemiol. (advance access published May 26, 2004).