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LATE COMPLICATIONS OF SULFUR MUSTARD IN RESPIRATORY SYSTEM

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ABSTRACT

In the last few years many chemically injured patients have been visited throughout the country in order to investigate the late respiratory complications of sulfur mustard. 35 patients who were previously admitted for mustard poisoning underwent complete clinical examination as well as spirometry, fiberoptic bronchoscopy (FOB), Bronchoalveolar lavage (BAL), and transbronchial lung biopsy (TBLB).

The results of this study reveal a high incidence of air flow obstruction in these patients (50%). BAL shows decreased numbers of macrophages and increased numbers of lymphocytes and neutrophils, and the presence of eosinophils (between 1 to 5%). Certain pathologic features have been encountered. We conclude that late respiratory complications of sulfur mustard are major causes of morbidity and are quite resistant to therapy.

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INTRODUCTION

Mustard was discovered in 1917 and used in the First World War. This agent is classified among vesicants or blister agents and from the chemical view point is 2,2-dichloroethyl sulfide or S - $(CH_2\text{-}CH_2\text{-}Cl)_2$. This substance is know as "LOST" in Germany and «HD» in the United States. It was understood in 1935 that if sulfur is replaced with nitrogen, the blistering properties of the substance is reserved so nitrogen mustard was synthesized. This substance had different types and from the military view point 2,2,2 trichloroethyl amine or HN_2 has gained more attention and its blistering properties resembles those of HD.

Physical properties

Mustards are able to penetrate cell walls of different tissues as well as many other materials such as wood, leather, paint, etc. They are quite resistant to cold and temperate climate and less resistant in warm climate. If mustard is dissolved in water, it hydrolyzes promptly (almost 60% in 24 hours) and forms alcohol and hydrochloric acid.

Toxicology

HD and HN_3 are the most devestating mustards firstly because they are very resistant, and secondly they are absorbed by the skin, eyes, and respiratory epithelium, and lastly there is no effective treatment after binding with cell proteins.

Liquid mustard in a dose of 50 mg/cm^2 causes erythema and in 250 to 500 mg/cm^2 causes blisters.[2]

If swallowed, only a few milligrams cause nausea and vomiting. In the case of HN_3, only 2 to 6 mg could result in systemic intoxication. Development of hypersensitivity reactions is quite common.

From the biochemical view mustards have cytostatic, mutagenic, and cytotoxic effects. Although cell wall and intracellular enzymes may be affected by mustard, however the present evidence shows that DNA is the most sensitive target.[2] Clinical manifestations of mustard gas poisoning have been described.[1,3] Despite the fact that the mortality rate of mustard is said to be between 1 to 2%,[4] the morbidity rate seems to be much higher, and in this regard the respiratory system (specially when protective masks have not been used) plays a major role. In order to investigate the pathophysiologic nature of the respiratory symptoms

we conducted this study on a group of patients who survived mustard gas poisoning.

MATERIALS AND METHODS

35 combatants who were suffering from respiratory symptoms and were between 18 to 59 years of age (mean, 28± 10.4) were studied. The interval between chemical exposure injury and beginning the study was between 6 weeks to one year. All subjects had a complete history and physical examination. Work up included a standard PA chest roentgenogram and simple spirometry using vitalograph and measurment of FEV_1, FEV_1/FVC and FEF 0.25-0.75.

Bronchoscopy was performed under local anesthesia with an Olympus BF3 bronchofiberoscope using either transoral or transnasal technique.

Bronchoalveolar lavage fluid was collected after wedging the bronchoscope in right middle lobe and washing with 200-300 cc saline. Specimens were processed by Pasteur Institute of Tehran. Transbronchial lung biopsy (TBLB) was performed in all cases and tissue samples were examined in Sina Hospital.

RESULTS

Frequency of symptoms is shown in Table I. Cough, expectoration, and dyspnea are the most freqent complaints.

Spirometric studies in 29 cases whose tests were acceptable show an obstructive pattern in 16 cases (55%) manifested with low FEV_1 and FEV_1 /FVC as well as a significant decrease in FEF 0.25-0.75.

A restrictive pattern was noticed in seven cases (24%), small airway disease in four cases (13.8%), and only two cases (6%) had normal spirograms.

Bronchoalveolar lavage was performed in 27 of 35 cases and the following results were obtained:

Significant decrease in macrophages-18 cases (66%).

Increased number of lymphocytes-15 cases (55%).

Increased number of neutrophils (5-35%)-21 cases (78%).

Presence of eosinophils (1-5%)-13 cases (48%).

Pathologicfindings: four groups of lesions were noticed as follows:

1- Nonspecific bronchitis or pneumonitis with desquamation and inflammation of bronchial mucosa and submucosal edema, lymphoid reaction with eosinophilia.

2- Acute destruction of alveoli with or without hyaline membrane, necrosis of alveolar cells with capillary injury causing intraalveolar hemorrhage, and filling of some of the alveoli with a fibrin-like material.

3- D.S.P. like reaction, infiltration of mononuclear cells in the alveoli as well as interstitium which was PAS and iron positive, proliferation of type II alveolar cells with some interstitial fibrosis.

4. Interstitial fibrosis was diagnosed in four cases which was associated with squamous metaplasia and sloughing of bronchial epithelium. Alveolar spaces

Table I. Frequency of Symptoms

Symptoms	Cough	Expectoration	Hemoptysis	Dysphonia	Wheezing	Dyspnea
No.of Patients	32	27	5	29	26	13
% Total	91%1	77%	14%	83%	74%	37%

CXR findings are summarized in Table II.

Table II. Frequency of CXR Findings

CXR Finding	Normal	Vascular marking	Reticulonodular Pattern
No.of patients	10	18	7
% Total	20%	51%	20%

were irregular and alveolar walls were thick. Some of the capillaries were obstructed.

Epithelial revision and honey combing were not present. There was subepithelial fibrosis in bronchioles along with infiltration of inflammatory cells.

DISCUSSION

The destructive effects of mustard on cells of living organisms are well known.[1] This substance can penetrate through skin, eyes, and respiratory system and can cause local as well as systemic reactions.[3] Some of its complications such as ophthalmologic complications have a benign course and full recovery takes place in a week. However, in rare cases corneal ulcers may need corneal transplant. Respiratory complications are more serious and not only are considered among the important causes of mortality, but also are the main cause of morbidity in most of the victims.

The mortality of sulfur mustard is said to be between 1-2%, but morbidity is much higher and considering the simple technique which is involved in production of this substance, it is named the "atomic bomb of the poor"![4]

The present study shows that a high percentage of victims suffer from respiratory symptoms even several months after exposure. In addition, these patients are more prone to respiratory infections and bronchiectasis may eventually ensue in some cases.[1] We have seen patients who have been admitted four to five times a year because of respiratory infections. An interesting phenomenon is discrepancy between clinical symptoms and roentgenographic findings and despite severe dyspnea, cough, and sometimes hemoptysis, chest roentgenogram is normal in many instances. In this regard spirometric studies are much more informative in diagnosis and prognosis of the patients. As mentioned, 94% of our patients had abnormal spirograms in the form of obstructive, restrictive, combined, or small airway disease pattern. Unfortunately, some of the chemically injured patients smoked or used to smoke before, the number of whom is not known in our study. This may have a role in abnormal lung function of patients, but usually in the this age group (28 ± 10.4) even despite smoking, only a low percentage of patients may have abnormal lung function in the form of small airway obstruction.

Thus, the results of spirometric studies could be truly attributed to the effect of mustard. On the other hand restrictive pattern may become a predominant pattern when fibrosis takes place.

Another interesting finding is extrathoracic mechanical obstructions at the level of the larynx due to granulation tissue especially after intubation, and can be easily diagnosed by bronchoscopy.

Results of BAL compared with normal figures[8] reveals decreased number of macrophages and increased lymphocytes and neutrophils.

Presence of eosinophils is certainly abnormal. Recent investigations on idiopathic pulmonary fibrosis reveal the important role of eosinophils through liberation of oxygen radicals in the pathogenesis of the disease.[5-7]

Presence of eosinophils in BAL could be interpreted in two ways:

a) These cells are due to severe injuries of the tissue,

b) Presence of these cells may herald fibrosis and more serious complications.

The nature of pathologic changes reveals a progressive process which in the case of infection may progress even faster. As squamous metaplasia is reported in some cases and considering some reports which prove the higher incidence of bronchogenic carcinoma in these victims,[9] it seems logical to perform a periodic bronchoscopy and alveolar lavage in mustard victims in order to detect cancer cases as early as possible.

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