Pulmonary Complications of Mustard Gas Exposure: A Study on Cadavers

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Abstract- Sulfur mustard gas is one of the chemical warfare gases that roughly about 45000 soldiers continue to suffer long-lasting consequences of exposure during the Iran–Iraq war between 1980 and 1988. According to the common pulmonary lesions due to this gas exposure, we studied gross and microscopic pulmonary lesions in cadavers and also assessed the main causes of mortality caused by mustard gas exposure. A case-series study was performed on hospital record files of 100 cadavers that were exposed with documented sulfur mustard gas during the Iran–Iraq war from 1979 to 1988 and autopsied in legal medicine organization In Tehran between 2005 and 2007 and gross and microscopic pathological findings of autopsied organs such as hematological, pulmonary, hepatic, and renal changes were evaluated. All cases were male with the mean age of 43 years. The time interval between the gas exposure and death was almost 20years. The most frequent pulmonary complication was chronic bronchitis in 81% of autopsied cadavers. Other pulmonary findings were progressive pulmonary fibrosis (9%), pulmonary infections and tuberculosis (29%), malignant cellular infiltration (4%), and aspergilloma (1%). According to the chronic progressive lesions caused by mustard gas exposure such as pulmonary lesions and also its high mortality rate, suitable programming for protection of the gas exposed persons and prohibiting chemical warfare are recommended.

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Introduction

Mustard gas, or sulfur mustard, is a vesicating agent that had been made in 1821 and used on troops fighting in the First World War (1). Sulfur mustard gas is one of the chemical warfare gases that has been known as a vesicant or blistering agent (2). This gas has been used during the Iran–Iraq war between 1980 and 1988 with over 100,000 poorly protected soldiers suffering severe and debilitating injuries as a result so that roughly about 45000 soldiers continue to suffer long-lasting consequences of exposure (3,4).

Mustard gas is a chemical alkylating compound agent that can be frequently absorbed through skin, respiratory system, genital tract, and ocular system. The first acute manifestations of mustard gas exposure are occurred in ocular system with threshold symptoms of tearing and irritation, respiratory tract with the damage to the terminal airways, and skin as erythematic or necrotic lesions (5). Also, respiratory problems are the greatest cause of long-term disability among these patients that are manifested as asthma, bronchiectasis, large airway narrowing, and pulmonary fibrosis (6). This gas has been also known as a DNA alkylating agent and categorized in carcinogenic group agents (7).

Several previous studies have considered the clinical manifestations and prognosis of patients who exposed to mustard gas, however, few studies have been done to assess pathological changes of the lungs in these patients. Therefore, to our knowledge, gross and microscopic pulmonary lesions were studied pathologically in cadavers and also assessed the main causes of mortality caused by mustard gas exposure.

Materials and Methods

A case-series study was performed on hospital record files of 100 cadavers that were exposed with documented sulfur mustard gas during the Iran–Iraq from 1979 to 1988 and autopsied in legal medicine organization in Tehran between 2005 and 2007. Exposure was confirmed by the written reports of the field hospitals, based on acute presentation by eye, skin and pulmonary symptoms of the exposure. In all patients, respiratory symptoms were began immediately after exposure to sulfur mustard gas and continued with

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no symptom free period. Patients with the history of smoking, lung disease before exposure to mustard gas, exposure to other chemical agents, any occupational history of toxic fume exposure or occupational risk factors that could lead to lung disease, any associated chronic disease (such as heart failure or connective tissue disease) with potential pulmonary involvement, or history of treatment with drugs that may cause acute pneumonitis or lung disease as a side effect were excluded. Demographic characteristics, underlying etiology of mortality, and pathological findings of autopsied organs such as hematological, pulmonary, hepatic, and renal changes were evaluated.

Results

All cadavers were male and about one-third of them were in the range of 30 to 40 years old (Figure 1). Eighty four percent of deaths were related to the complications of the lesions progression due to the gas exposure such as cardiopulmonary arrest, sepsis, and cancers (Table 1). Other common etiologies of deaths were accidents (11%) and suicide (2%).

The most common pathological findings in different organs were summarized in Table 2. Acute and chronic myelocytic leukemia were found in 5% and 3% of cases, respectively. In respiratory system, chronic bronchitis with Goblet cells hyperplasia, inflammation and the increase of Reid criteria, bronchopneumonia, tuberculosis, and pulmonary fibrosis in the end lung stage as honey combing feature were the most frequent pulmonary changes.

Table 1. Causes of death in patients who exposed to mustard gas

Etiology of death	Percent
Underlying disease:	
Pulmonary	34
Cardiac	22
Cancer	15
Sepsis	6
Cerebral	3
Epilepsy	2
Renal	1
Hepatic	1
Others:	
Accident	11
Suicide	3
Drug abuse	2

Also four cases of malignant cellular infiltrations from neck skin squamous cell carcinoma, acute myelocytic leukemia, and adenocarcinoma with unknown origin were observed in two lungs.

The most common pathological changes in the liver were steatosis (39%) and congestion (11%). The most frequent changes in kidneys were simple cysts and MPGN. Also, gliosis and abscess were common findings in cadavers' brains. The most frequent pathological findings in the cardiovascular system were atherosclerosis, acute myocardial infarction, and pericardial fibrosis.

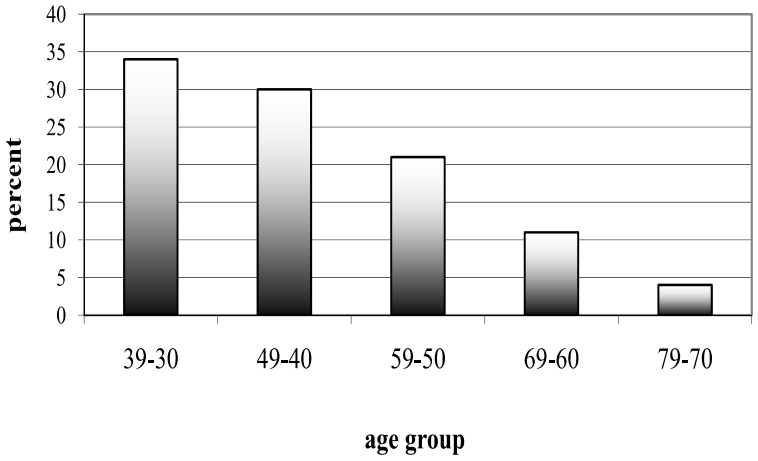

Figure 1. Age distribution of cases exposed to mustard gas

Table 2. The most common pathological findings in different organs in cadavers that exposed to mustard gas

Pathological findings	Percent
Pulmonary:	
Chronic bronchitis	81
Pneumonia	27
ARDS	11
Pulmonary fibrosis	9
Others	9
Hepatic:	
Steatosis	39
Congestion	11
Malignant infiltration	3
Others	8
Hematological:	
Acute myelocytic leukemia	5
Chronic myelocytic leukemia	3
Multiple myeloma	1
Aplastic anemia	1
Renal:	
Simple cyst	4
MPGN	2
Acute pyelonephritis	1
Chronic renal failure	1
Neural:	
Gliosis	7
Abscess	5
Tumor	3
Others	2
Cardiac:	
Atherosclerosis	44
Acute myocardial infarction	11
Old myocardial infarction	9
Others	8

Discussion

The present study has been comparable to other surveys, however in our survey; the complications of mustard gas exposure have been studied pathologically on cadavers.

The mean age of studied patients in our study was 43 years old and the time interval between the gas exposure and death was almost 20 years indicated that the age of the Iranian soldiers in Iran-Iraq war ranging 20 to 30 years.

Regarding to the most common etiologies of death, etiology in 84% of cases was different organs disorders such as pulmonary diseases that were directly a main cause of death in 34% of cases. This result indicated that pulmonary lesions can be one of the main causes of death even several years after exposure. This gas can destroy individual cells by reaction with cellular proteins especially in the lungs resulted in acute and chronic pulmonary complications such as pulmonary fibrosis. Also, chronic bronchitis is a well-known late complication of sulfur mustard gas inhalation in humans with an incidence of almost 50%, it was the most common pulmonary complication in some studies (8). In a study by Khateri *et al.*, it was found that among all patients who exposed to mustard gas, 42.5% exhibited lung lesions, with 37% classed as mild, 4.5% moderate, and 1.0% severe. Also, in their study, the patients exhibited an ongoing local inflammatory process of the lower respiratory tract (9). In another study, it has been indicated that the CD8 T cells in BAL fluid were significantly elevated in patients with pulmonary fibrosis, whereas CD4/CD8 ratio was decreased (10). Also, in Hefazi *et al.* study, main respiratory complications were diagnosed as chronic obstructive pulmonary disease (COPD) (35%), bronchiectasis (32.5%), asthma (25%), large airway narrowing (15%), pulmonary fibrosis (7.5%), and simple chronic bronchitis (5%) (11). Furthermore, increased airway responsiveness to salbutamol in most subjects exposed to chemical warfare can demonstrate the important role for asthmatic protocol treatment in gas exposed patients (12). Another study also showed that air trapping and tracheobronchomalacia are correlated, both as long-term sequelae in mustard gas–exposed cases (13). The results also provided strong evidence that exposure to mustard gas can cause cancers of the upper respiratory tract and some evidence that it can cause lung cancer and non-malignant respiratory disease (14).

In our study, the most common finding in pathological study of lungs was chronic bronchitis as goblet cell hyperplasia, severe inflammation in cutaneous and subcutaneous layers, and increase of Reid factor. High prevalence of this finding in our study in comparison to other studies can related to this fact that the lung lesions were considered on the basis of pathological gross and microscopic protocols, whereas other surveys were frequently had been based on bronchoscopic or lavage managements.

We also found a case of pulmonary aspergilloma as a dark mass in a patient who suffered from chronic myelocytic leukemia. It seems that this pathological finding might relate to the immune system suppression due to chemotherapy in that case. Also, pulmonary infections were found in 29 cases as infectious bronchopneumonia and tuberculosis.

According to the chronic progressive lesions caused by mustard gas exposure such as pulmonary lesions and also its high mortality rate, suitable programming for protection of the gas exposed persons in chemical factories is necessary. Also, all government should step towards prohibiting chemical warfare.

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