Original Article

Pathologic Lesions of Liver, Kidney and Lung in the Autopsy of 100 Mustard Gas-Exposed Iranian War Veterans

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ABSTRACT

Background & Objectives: **Respiratory, central nervous system, and skin complications of mustard gas toxicity have previously been studied; however, the liver and kidney side effects due to this intoxication have not been fully noted. We aimed to evaluate the frequency of liver, kidney and lung lesions in mustard gas-exposed Iranian veterans who had been exposed to the toxin almost 2 decades before.**

Methods: **A total of 100 veteran bodies underwent autopsy by at least two forensic medicine specialists. The liver, kidney and lung specimens were sent for pathological examination and their lesions, severity of the lesions, and the relation between the type/severity of the lesions and the time elapsed since their appearance were studied.**

Results: **A total of 83%, 63%, and 62% of the veterans had lung, liver, and kidney pathologies. The most common pathologies included liver steatosis, interstitial fibrosis of the kidney, and lung atelectasis.**

Conclusion: **Liver and kidney pathologies are far more common than what is considered in the mustard gas-exposed veterans. These pathologies are often accompanied by very severe lung complications.**

Keywords: **Sulfur Mustard, Autopsy, Lung, Liver, Kidney, Pathology**

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Introduction

The war between Iraq and Iran (1980-1988) compelled lots of expense and human loss to both countries. Iran was attacked by chemical weapons many times during the period of this war for more successive killings (1).

Mustard is an oily liquid with poor characteristic of water dissolution with its color ranging between yellow and dark brown depending on its impurity. Manufacturing the mustard weapons is easy and the nomenclature comes from its odd odor of garlic (1-4). It is generally absorbed from the skin, lungs (inhalational), and the eye mucosa.

It is an alkylating agent causing long- and short-term effects on the skin, eyes, and respiratory system. The absorption can cause a widespread spectrum of hematologic, gastrointestinal, and ocular abnormalities. Inhalation of mustard gas can result in hoarseness and respiratory failure.

Even decades after the exposure, the long-term and severe side effects of its inhalation can cause chronic obstructive pulmonary disease (COPD), lung fibrosis, recurrent ulcers of the cornea, chronic conjunctivitis, abnormal skin pigmentation, and different types of cancers.

The most common cancers induced by mustard gas are lung adenocarcinoma, squamous cell carcinoma, and small cell carcinoma (2, 3).

Although the respiratory, central nervous system, and skin complications of mustard gas toxicity have previously been studied, the liver and kidney side effects due to this intoxication have not been fully noted. On the other hand, previous studies have mainly evaluated the clinical manifestations of the intoxicated patients while autopsy results can better determine the nature of the induced pathologies. We aimed to determine the frequency, type, and severity of pathologic abnormalities of the liver, kidney, and lungs in the chemical war veterans of Iran-Iraq war who had been referred to Forensic and Legal Organization after death and had undergone autopsy.

Materials and Methods

This retrospective cross-sectional study was performed in Forensic and Legal Organization of Tehran, Iran between 2009 and 2012. All files of the deceased veterans who had been referred to this organization after death and had undergone autopsy were reviewed. Information including age at death, the time elapsed between exposure and death, type of the gas being exposed to, and autopsy results were recorded. The data were analyzed using statistical package for social sciences (SPSS) version 15, and Chi-square, ANOVA, and Pearson's tests. A *P* value less than 0.05 was considered to be statistically significant.

Results

All cases had been exposed to mustard gas. Mean age of death was 54.54±9.28 years (range; 41 to 79 years). Mean time elapsed between exposure and death was 24.60±1.32 (range; 21 to 28 years). Lung, liver, and kidney biopsies were normal in 13%, 37%, and 38% of the patients, respectively. In those with liver pathologies, chronic hepatitis and steatosis were the most common pathologies (17% and 15%, respectively; Table 1). The most common kidney abnormalities were interstitial nephritis (22%), glomerulosclerosis (18%), and nephrosclerosis (9%). These were atelectasis (31%), hemorrhagic edema (25%), interstitial fibrosis (23%), and alveolar was fibrosis (18%) in the deceased veterans with lung abnormalities.

Table 1- Frequency of Pathological Complications in the Autopsy of the 100 Deceased Veterans

Organ	Pathological findings	Severity of the complications		
		Mild	Moderate	Severe
Lung	Athelectasis	0	20	11
	Hemorrhagic edema	1	10	14
	Pulmonary edema	0	5	4
	Interstitial fibrosis	1	5	17
	Alveolar wall fibrosis	1	4	10
	Emphysema	1	10	2
	Tuberculosis bronchopneumonia	0	0	1
	Squamous cell carcinoma	0	0	1
Liver	Congestion	0	1	6
	Submassive necrosis	0	0	8
	Portal fibrosis	0	5	2
	Steatosis	1	5	9
	Steatohepatitis	1	1	1
	Chronic hepatitis	0	12	5
	Adenocarcinoma	1	0	0
	Cirrhosis	0	0	4
Kidney	Hemorrhagic necrosis	0	0	4
	Glomerulosclerosis	1	11	6
	Chronic pyelonephritis	0	5	2
	Chronic interstitial nephritis	1	14	7
	Acute tubular necrosis	0	0	5
	Nephrosclerosis	1	3	6
	Tubular atrophy	1	1	1

Most of the cases with lung, liver, or kidney pathologies were between 45 and 55 years of age. Mean age was significantly higher in those with lung pathologies (55.97±9.98 versus 52.03±7.37 years; P=0.039). Such a significant higher age was not detected in the deceased patients with liver or kidney pathologies (P=0.47 and 0.41, respectively). Mean time elapsed between exposure and death was not significantly different between those with and without lung (P=0.69), liver (P=0.19), and kidney abnormalities (P=0.29). No significant relation was found between the mean age of the patients or the time elapsed between exposure and death on one side and severity of the pathology on the other side in none of the above-mentioned pathologies. The total frequency of all lung, liver and kidney pathologies is summarized in Table 2.

Table 2- Frequency of the Liver, Lung, and Kidney Pathologies in Different Age Groups of the Deceased Veterans

Age group (yr)	Total frequency	Liver pathologies	Kidney Pathologies	Lung pathologies
<45	10	8	7	11
45-49	29	18	18	25
50-54	24	15	18	25
55-59	13	13	10	17
60-64	9	5	5	16
65-69	2	2	2	12
≥70	13	6	4	11

Discussion

Few studies have evaluated the pathologic features of mustard gas-exposed patients to date. This number is definitely less with the studies evaluating its frequency in the autopsy results. Since the respiratory system is the first part of the body being attacked by the chemical gases, the first signs and symptoms that develop are those of the skin followed by the respiratory system (5, 6).

During the eight-year war between Iraq and Iran, Iran was attacked by chemical weapons more than 260 times and almost 5000 army soldiers were exposed to these chemicals especially the mustard gas (2). Iran, therefore, has the highest rate of affection by these chemicals. Since the clinical signs and symptoms imply the possible inflammatory and immunologic mechanisms (7-11), molecular patterns should also be concerned in these patients, as well. Psychiatric parameters, life style, and socioeconomic circumstances are of the factors being affected by these clinical complications.

Many previously performed studies have evaluated the lung complications of these patients; however, our study is one of the limited ones performed on the kidney and liver complications of them.

Some studies (1, 2, 11, 12) have shown that the frequency of lung complications in mustard gas-intoxicated patients is about 100%. This is while our results showed that lung complications consisted almost 88% of the complications of these patients and even 13% of the veterans had died without any confirmed lung, kidney, or liver pathologic complications. It therefore seems that death has been due to other reasons. Since the time elapsed between exposure and death was more than 20 years in all of these veterans, our results showed that even after passing of two decades, lung complications may still be missing in some of these patients. This may be due to the less sample size of the previous studies in comparison to ours.

Another superiority of our study is that all pathologies were confirmed in autopsy. This is while in the most previous studies, the complications of the chemical weapons were evaluated during the patients' lives and autopsy would definitely better show the pathologies in comparison with the laboratory tests in life time.

Our results showed that the age of the patients at the time of death as well as the time elapsed since exposure did not statistically relate with the type and severity of the pathology and organ of involvement. This is in accordance with the previous studies (5, 6). Ghanei *et al.* showed that the severity of involvement was significantly correlated with the time elapsed since exposure (12); this was not confirmed by our results.

On the other hand, some studies showed that the inflammatory complications (in eyes, skin, respiratory system, and sometimes in the GI system) are the earliest signs and symptoms of the exposure (5). However, the accurate time of occurrence of the liver and kidney is

missing. According to the previous studies, lung complications are of the latest signs and symptoms (5, 6, 12). In our study, the evaluation was performed after death and therefore, the time of the occurrence of the complications was not discussed.

It should be mentioned that the kidney complications might follow other complications including diabetes mellitus. The background diseases might have an impact on the exacerbation of the patients' complications. It was therefore better if the medical charts of these patients would have been reviewed.

Liver and kidney complications have less been evaluated in the human studies. In the animal models, rats and mice have been more evaluated in this regard. It has been shown that the mice show destructive liver changes almost two hours after exposure to chemical gases (4). These changes begin to develop two hours after the exposure in molecular levels and cause liver enzyme abnormalities with inducing abnormalities in the protein description and preventing mRNA formation. The same changes are seen in kidney enzymes.

New medications have been proposed for the treatment of the most common lung complications of the mustard gas (13). New prospective studies are warranted to evaluate these medications as well as drugs for the management of the liver and kidney complications of these patients to improve their life expectancy and quality.

Conclusion

Many studies have evaluated the pathologies developing after exposure to chemical gases. However, few studies have concentrated on the complications and pathologies of the liver and kidney in these patients. Our results show that despite what is generally assumed, severe and fatal pathologies of the liver and kidney are common in these patients.

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References

1. Evison D, Hinsley D, Rice P. Chemical weapons. BMJ 2002; 324(7333):332-5.

2. Bullman T, Kang H. A fifty year mortality follow-up study of veterans exposed to low level chemical warfare agent, mustard Gas. Ann Epidemiol 2000; 10:333-8.

3. Momeni AZ, Enshaeih S, Meghdadi M, Amindjavaheri M. Skin manifestations of mustard gas. A clinical study of 535 patients exposed to mustard gas. Arch Dermatol 1992;128:775-80.

4. Balali-Mood M, Hefazi M. The pharmacology, toxicology, and medical treatment of sulphur mustard poisoning. Fundam Clin Pharmacol 2005;19:297-315.

5. Balali-Mood M, Hefazi M. Comparison of early and late toxic effects of sulfur mustard in Iranian veterans. Basic Clin Pharmacol Toxicol 2006;99:273-82.

6. Namazi S, Niknahad H, Razmkhah H. Long-term complications of sulphur mustard poisoning in intoxicated Iranian veterans. J Med Toxicol 2009;5:191-5.

7. Emad A, Rezaian GR. Immunoglobulins and cellular constituents of the BAL fluid of patients with sulfur mustard gas-induced pulmonary fibrosis. Chest 1999;115:1346-51.

8. Emad A, Rezaian GR. Characteristics of bronchoalveolar lavage fluid in patients with sulfur mustard gas-induced asthma or chronic bronchitis. Am J Med 1999;106:625-8.

9. Emad A, Emad V. Elevated levels of MCP-1, MIP-alpha and MIP-1 beta in the bronchoalveolar lavage (BAL) fluid of patients with mustard gas-induced pulmonary fibrosis. Toxicology 2007;240:60-9.

10. Emad A, Emad Y. Increased granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) levels in BAL fluid from patients with sulfur mustard gas-induced pulmonary fibrosis. J Aerosol Med 2007;20:352-60.

11. Mahmoudi M, Hefazi M, Rastin M, Balali-Mood

M. Long-term hematological and immunological complications of sulfur mustard poisoning in Iranian veterans. Int Immunopharmacol 2005;5:1479-85.

12. Ghanei M, Naderi M, Kosar AM, Harandi AA, Hopkinson NS, Poursaleh Z. Long-term pulmonary complications of chemical warfare agent exposure in Iraqi Kurdish civilians. Inhal Toxicol 2010;22:719-24.

13. Zamani N. Pirfenidone; can it be a new horizon for the treatment of pulmonary fibrosis in mustard gas-intoxicated patients? Daru 2013;21(1):13.