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Long-term Effects of Mustard Gas on Iranian Veterans.

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Abstract:

During the Iraq-Iran war of 1980 -1988, the most commonly used chemical warfare agents (CWA) were nerve agents and sulfur mustard gas (SM). SM was used frequently as a chemical weapon by Iraq during the war against Iran, and had deleterious effects on Iranian military troops and the unprotected inhabitants of Sardasht, Iran and Halabche, Iraq. In this report, we review the scientific literature to develop an understanding of the health consequences that victims from both countries experienced as a result of exposure to SM. Currently, 45 000 Iranians are suffering from the long-term effects of mustard gas, which includes cutaneous, respiratory, cardiovascular, neuromuscular and ocular complications. Because many of the health consequences associated with SM exposure have a late onset, and because these effects can drastically reduce quality of life, it may be necessary to instruct military experts to equip and train local chemical and biological response teams in order to establish strategies for inhibiting the production and use of chemical weapons. In addition, it is highly recommended that any remaining chemical weapons existing around the world are safely destroyed.

Keywords: Mustard Gas, Iran, Veterans

Introduction:

Historically, sulfur mustard has been one of the most common chemical warfare agents used in military combat, with large stockpiles still existing in several countries around the world. The clinical picture of poisoning is well known from the thousands of victims who were exposed during World War I and during the Iraq-Iran war. Sulfur mustard (SM) is a bifunctional alkylating substance, and is still regarded as a significant threat in chemical warfare and terrorism. Victims of World War I and the Iran-Iraq war have suffered from devastating chronic health impairments. Even decades after exposure, severe long-term effects such as chronic obstructive lung disease, lung fibrosis, recurrent corneal ulcer disease, chronic conjunctivitis, abnormal pigmentation of the skin and various forms of cancer have been diagnosed in these individuals.[1, 2] The cytotoxic effects are manifested in metabolic disturbances such as enzymatic deficiencies, vesicant action, abnormal mitotic activity and cell division, bone marrow disruption, disturbances in hematopoietic activity and systemic poisoning.[3] SM exposure affects many organs such as the skin, eyes and lungs, as well as the gastrointestinal, endocrine and hematopoietic systems.[4, 5, 6] In one study, the late onset of lung, eye and skin lesions among 34 000 Iranians with wartime exposure to SM was 42.5%, 39.3% and 24.5%, respectively.[7]

The aim of the present review is to discover the late complications caused by exposure to SM and to elucidate possible related pathways. It is hoped that our findings will help in the development of treatments for patients who suffer from the adverse effects of chemical warfare poisoning.

Methods:

Scientific reports on the effects of SM as a chemical agent in Iran and other countries were reviewed. Articles indexed in the PubMed database, Google and Iran Medex from 1956 to 2009 were searched by using the following key words: mustard, chemical agent, complications, Iran. Country-specific information was obtained by adding a country name to the search. The search was restricted to publications written in English and Persian.

Results:

Pulmonary effects

In a study by Ghassemi-Broumand, Aslani & Emadi [8], the late complications of SM in 600 patients were evaluated 19 years after exposure in the city of Sardasht, Iran. Primary ocular manifestations were present in 96.2% of these patients, respiratory manifestations were present in 80.7% of patients and cutaneous manifestations were present in 83.8% of the cases.[8]

SM exposure can lead to the development of chronic bronchitis, bronchiectasis and lung fibrosis.[9] Apart from chronic bronchitis, the main causative factors of chronic cough were identified in a previous study as being bronchospasm, postnasal drip syndrome and gastroesophageal reflux disease (GERD), which accounted for 66%, 46% and 44% of

chronic cough cases, respectively.[10] In another study using high-resolution computer tomography (HRCT) to examine the chests of 155 SM-exposed patients, the most frequent complications found were: air trapping (76%), bronchiectasis (74%), mosaic parenchymal attenuation (MPA) (72%), irregular and dilated major airways (66%), bronchial wall thickening (BWT) (90%) and interlobular septal wall thickening (SWT) (26%). These findings suggested the diagnosis of bronchiolitis obliterans (BO).

Fifteen years after exposure to SM as a chemical warfare agent (CWA), many patients were suffering from chronic and often disabling respiratory symptoms such as shortness of breath, cough and tightness of the chest. While most patients had normal chest roentgenograms, their chest HRCT findings were highly suggestive of BO.[11] Another important finding was the significant variation in tracheal and major airway diameter upon inspiration and exhalation, as well as the irregularity in wall thickness in two-thirds of patients examined that was not associated with BO. Direct toxic effects of SM can lead to tracheobronchial stenosis with different degrees of involvement ranging from diffuse tracheal stenosis of the isolated left main bronchus or glottis and subglottis stenosis.[12]

Exposure to SM causes pulmonary complications resulting in disability in affected patients; however, HRCT upon inspiration was normal in most of the patients examined. Expiratory HRCT showed patchy air trapping as the most common complication, which is suggestive of small air way diseases such as bronchiolitis obliterans. Therefore, it is recommended that HRCT is performed for both deep inspiration and full expiration in patients with a history of CWA exposure.[13] The diagnosis of chronic lung disease due to SM may be difficult. In these cases, a surgical lung biopsy may be helpful as constrictive (obliterative) bronchiolitis can be present in symptomatic patients with normal PFTs and chest HRCTs.[14]

An analysis of lung samples from 11 cases of subjects exposed to SM showed changes such as organizing pneumonia (OP) and bronchiolitis obliterans OP (BOOP). Inhalation of SM can lead to persistent and clinically significant lung disease many years after exposure.[15] The main respiratory complications reported in forty male subjects with confirmed SM poisoning were chronic obstructive pulmonary disease (COPD) (35%), bronchiectasis (32.5%), asthma (25%), large airway narrowing (15%), pulmonary fibrosis (7.5%) and simple chronic bronchitis (5%). Because arterial blood gas (ABG) and HRCT measures rely on objective markers, they could prove to be useful in the diagnosis of respiratory complications and for the evaluation of the severity of these conditions.[16] Neutrophils alveolitis, presence of eosinophils and higher concentrations of chemokines such as macrophage inflammatory protein-1(MCP-1) and monocyte chemoattractant protein-1 α and β (MIP-1 α, and MIP-1 β) in bronchoalveolar lavage (BAL) fluid were associated with the development of pulmonary fibrosis in SM victims.[17] Neutrophils alveolitis, the presence of eosinophils and higher concentrations of interleukin-8, granulocyte

colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) in BAL fluid were associated with the development of fibrosis in SM victims.[18] The increased levels of cytokines and growth factors in the BAL fluid suggest a possible causative mechanism in the lungs due to SM-induced PF by recruitment of neutrophils and eosinophils into the lung.[19] According to a previous study, re-establishment of the activation-inactivation or oxidant-antioxidant balance in favor of activation and antioxidation would be useful as a therapeutic strategy to suppress the pathological mechanisms underlying lung injuries.[20]

Gastrointestinal effects

In a study of 40 Iranian SM exposed subjects and 40 controls with symptoms of gastro-esophageal reflux disease, the frequency of endoscopic esophagitis in the chemically exposed group was significantly higher than is was in the control group. Chest HRCT evaluation demonstrated that half of the exposed group had more than 25% air trapping in expiratory films, which is indicative of bronchiolitis obliterans (BO). In addition, many patients were also suffering from asthma, chronic bronchitis and bronchiectasis.[21]

A study which examined 247 workers who were exposed to SM in the United States revealed that the healing of burns varied according to the natural pigmentation of skin, and in many cases, multiple chronic skin infections developed from the same burns. Months after exposure, bronchitis and posttraumatic stress disorder became highly prevalent among exposed patients, regardless of initial presentation. Any remaining symptoms that were reported did not lead to any organ pathology, with the exception of one case of Barrett's esophagus and one case of oral metaplasia.[22] Finally, a case of esophageal cancer with extension into the left first bronchus was reported in an individual who had been exposed to occupational mustard gas poisoning.[23]

These reports highlight the need for gastroesophageal surveillance in subjects with SM exposure and gastroesophageal reflux.

Cardiovascular effects

In a study by Gholamrezanezhad et al [24], the results of scintigraphic myocardial perfusion scans in 22 mustard intoxicated patients and in 14 controls revealed a pattern of myocardial perfusion that was significantly different from controls. According to the authors, these findings could be suggestive of either coronary artery disease or mild cardiomyopathic changes.[24]

Cutaneous effects

Skin complications were identifed in forty Iranian SM exposed patients. The skin complications identifed included: hyperpigmentation (55%), erythematous popular rash (42.5%), dry skin (39%), multiple cherry angiomas (37.5%), atrophic scarring (27.5%), hypopigmentation (25%), hair loss (10%) and hypertrophy (2.5%). Light microscopy revealed epidermal atrophy, hyperkeratosis, basal membrane hyperpigmentation and non-

specific dermal fibrosis. Electron microscopy showed increased melanocytes and melanosomes within the epidermis and increased collagen fibers and mononuclear inflammatory cells within the dermis. The signs were recorded in the order of hyperpigmentation, erythematous popular rash, dry skin, multiple cherry angiomas, atrophic scar, hypopigmentation, hair loss, eczema, lichenification and hypertrophy. Scars from second degree burns which were classified as hyper or hypopigmented, or as atrophied or hypertrophied were diagnosed in 70% of patients.[25] Of the approximately 34,000 Iranians who had sustained mustard agent exposure during the Iran-Iraq war, lesions of the skin were detected in 24.5% of cases. Within each subpopulation, patients were ranked according to the severity of their lesions.[26]

Ophthalmic effects

In one study, the symptoms identifed in 40 SM exposed patients were blurred vision (50%), itching (42.5%), burning sensation (37.5%), photophobia (30%), tearing (27.5%), reading difficulties (10%), red eye (10%), eye pain (2.5%) and foreign body sensation (2.5%). Abnormal findings in the limbus were recorded as peri-limbal hyperpigmentation (17.5%), vascular tortuosity (15%) and limbal ischemia (12.5%). Slit lamp examination of the cornea was normal in 26 patients. In the other patients, subepithelial opacity (15%), corneal thinning (15%), severe opacity (10%), micro/macro pannus (7.5% each), corneal vascularization (7.5%) and corneal epithelial defects (5%) were recorded.[25]

Mustard gas causes chronic and delayed destructive lesions on the ocular surface and cornea, leading to progressive visual deterioration and ocular irritation. Excised conjunctival and corneal specimens revealed a mixed inflammatory response without any specific features. Based on histopathological findings, an immune-mediated component seems plausible.[27]

The maximum incidence of delayed keratitis was observed to be 15 to 20 years after initial exposure, which is interesting in light of the finding that natural killer cells were significantly lower 16 to 20 years after exposure. These findings are also consistent with the suggestion that this is the main cause associated with malignancies and recurrent infections in these patients.[28] Living-related conjunctival-limbal allografts are effective in stabilizing the ocular surface in patients with delayed or chronic mustard gas keratopathy (MGK).[29]

Neuromuscular effects

In a study by Balali-Mood et al [25], nerve conduction velocity (NCV) in the pheripheral nerves of 40 SM exposed patients was evaluated. In this study, it was revealed that NCV disturbances were more common in the sensory nerves compared to the motor nerves, and more common in the lower extremities than in the upper extremities. Sensory and motor nerve disturbances in both upper and lower extremities were mostly symmetric.[25] In another study, the effect of SM on nerve conduction velocity and electromyography (EMG) patterns concluded that the findings are in favor of axonal

degeneration, but additional studies are needed.[30]

Hematological and immunological effects

The alkylating effects of SM have been demonstrated to disturb the deoxyribonucleic acid (DNA) of hematopoietic cells.[31, 32] A study by Tabarestani showed an initial marked increase in lymphopenia in 36% of exposed patients during the recovery phase, and lymphocyte counts increased past 40% in 18% of patients.[33] In another study, an increase in lymphocyte protease activity in human peripheral blood in response to SM exposure was reported.[34]

Ghanei & Vosoghi [35] also demonstrated that the risk ratio of CML developing in victims exposed to mustard gas (cutaneous or respiratory) was higher than it was in the general population, although confounding factors (e.g. the possibility of exposure to combined chemical agents, excluding patients who did not manifest blisters) may have limited the usefulness of these results.

An article by Ghanei [36] reported that there was no significant difference in mean red blood cell counts and hemoglobin levels between victims who were exposed to mustard gas and the control group, although the difference had increased over the five year period in which the data was recorded. In total, 20 cases with atypical lymphocytes in their PBS were found. Change in lymphocyte shape may be related to committed stem cell involvement, while the mild increase in erythroid cells and hemoglobin concentration may be due to chronic obstructive pulmonary disorder or other respiratory diseases in these patients.[36]The author concluded that further longitudinal studies on bone marrow cells and cell markers in exposed patients are necessary in order to assess the hematological complications of mustard gas exposure in humans.

The consequences of SM exposure on the immune system has been a highly studied area of research, with results indicating that this alkylating agent has short- and long-term influences on antibody production in both animals and humans.[37] In one study, it was concluded that the number of natural killer (NK) cells was significantly lower in SM exposed patients compared to the control group.[25] On the other hand, decreased cellular immunity due to the impairment of natural killer cells remains a major concern in the late phases of intoxication and is probably the main cause of recurrent and opportunistic infections, septicemia and the higher incidence of malignancies in these patients.[38]

In a study by Arroyo [39]), the responses of normal human epidermal keratinocyte (NHEK) cells to SM were defined by the release of interleukin-1 β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8) and tumor necrosis factor-α (TNF-α). According to the findings of that article, the cytokine changes that were detected could be used as potential biomarkers for cutaneous vesicant injury.

In a study by Balali-Mood & Hefazi [40], it was suggested that the primary factor behind the association between malignancies and recurrent infections was the

significantly lowered natural killer cell levels that have been observed in patients16 to 20 years after exposure.[41]

Teratogenicity and reproductive effects

In a study by Ghanei & Allameh [42], the prevalence of infertility (no conception after a 1-year attempt) was found to be approximately 16.2% in the group exposed to chemical warfare agents versus 15.1% in the general population. These findings suggest that there was no significant increase in the prevalence of infertility after a single exposure to chemical warfare agents.[42] In another study, the infertility rate was just 6% which is even lower than the worldwide average of 10-15%.[43] This conclusion was reinforced by results obtained from a historical cohort study that assessed fertility among 142 mustard-exposed residents of Sardasht.[44] In future studies, it may be useful to further evaluate the teratogenic effects of SM poisoning by examining the children of SM-exposed Iranian veterans.[25]

Carcinogenicity effects

Recent work has specifically shown that SM alkylates the O-6 position of guanine in DNA, and this is the primary factor responsible for the mutagenic consequences of cellular exposure.[45] Carcinoma of nasopharynx, bronchogenic carcinoma, adenocarcinoma of the stomach, as well as acute myeloblastic and lymphoblastic leukemia has already been reported in Iranian veterans.[25]

Conclusion:

There are still reports of recent industrial exposure to SM occurring around the world. Although it is best known as a blistering agent, sulfur mustard can also induce neutropenia in exposed individuals, increasing their susceptibility to infection. Despite extensive research efforts during the last century, efficient antidotes against SM have not yet been generated because its mechanism of action is not fully understood. However, deeper insights into these mechanisms gained in the last decade, in addition to promising pharmacological developments now offers new opportunities to minimize SM-induced organ damage and its latent effects. Polymerase inhibitors, anti-inflammatory drugs, antioxidants, matrix metalloproteinase inhibitors and regulators of DNA damage repair have been identified as promising approaches to improve treatment.[2]

Granulocyte colony-stimulating factor (G-CSF) and pegylated G-CSF (peg-G-CSF) have been approved by the U.S. Food and Drug Administration as hematopoietic growth factors that can be used to treat chemotherapy-induced neutropenia.[46] Further research is necessary to measure the health related quality of life in victims with different types of disabilities in order to support and enhance quality of life amongst this population.[47] The long term complications that these patients face due to exposure highlights the need for the development of effective preventive and therapeutic strategies in order to minimize the burden these latent effects have on the exposed individual. These strategies may be based upon immunopotentiating intervention and other types of therapy.[48]

Research into the health consequences of SM must include follow-up in this group of patients due to the well-documented latent carcinogenic, hematologic, and pulmonary effects that exposure has. We recommend yearly screening, educating patients on the long-term effects of SM exposure and the use of prevention strategies such as immunization.[22] In addition, an autopsy should be performed in all cases where death is the outcome.

Finally, it may be useful to instruct military experts to equip and train local chemical and biological response teams in order to establish strategies for inhibiting the production and use of chemical weapons. Ideally, we would like to see any remaining chemical weapons existing around the world safely destroyed.

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