Paraclinical findings in Iranian veterans exposed to sulfur mustard gas: A literature review

Seyed Mansour Razavi, Masoud Saghaei b, Payman Salamati c, *

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Abstract

Objective: Sulfur mustard (SM) causes various systemic disturbances in human beings. This study aimed to assess paraclinical changes caused by exposure to SM gas in Iranian veterans during the war between Iraq and Iran.

Methods: A literature review was carried out in international and national medical databases including ISI, Medline, Scopus, Iranmedex and Irandoc. Both Farsi and English literature were searched.

Results: Search of the literature yielded 422 medical articles related to SM poisoning. Among them, 30 relevant articles were thoroughly reviewed. The most important reported complications were leukopenia, neutropenia, lymphopenia, eosinophilia, thrombocytopenia, increased bleeding time, positive C-reactive protein (CRP), rheumatoid factor (RF), antinuclear antibody (ANA), decreased T helper cells, natural killer cells, IL6, and IL8 levels, elevation of serum immunoglobulins, decreased levels of T3, T4 and cortisol, increased level of adrenocorticotropic hormone (ACTH), proteinuria, hematuria, and elevated liver enzymes. Also, there were some changes in chest assessments.

Conclusions: SM causes profound systemic complications in victims, even years after exposure. The paraclinical changes can be observed in hematology, immune system, biochemistry, hormonal profile and some imaging studies.

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Results

Blood test

Hematological changes

Leukocytosis is a common finding in the first few days after exposure. On the third and fourth days, the number of white blood cells starts to fall and reaches its minimum on the ninth day (full leukopenia). Various degrees of leukopenia are seen in 42% of victims with severe exposure to SM gas. Leukopenia is often associated with lymphopenia. Hooshyar et al. conducted the study on 85 Iranian chemical victims 10 years after exposure and found that the neutrophil count was below the normal range (neutropenia) in 6.7% of cases. Anemia occurred in the first week after exposure followed by thrombocytopenia. This was probably due to the effects of gas on the bone marrow. Thrombocytopenia could increase the bleeding time. In a study by Balali and Hefazi, white blood cell count and red blood cell count, hematocrit and the percentage of monocytes were significantly higher in severely exposed veterans than in control group (p < 0.042). In a study conducted on 7 patients, aplastic anemia was reported 6–12 months after exposure to SM. Sohrabpour et al. investigated late respiratory complications in 35 patients admitted for SM gas poisoning. In addition to complete clinical examination, spirometry and fiberoptic bronchoscopy, bronchoalveolar lavage (BAL) and transbronchial lung biopsy were performed for the patients. They showed decreased number of macrophages in 50% of BALs, increased number of lymphocytes and neutrophils and presence of eosinophils in 1%–5% of the BALs. Presence of eosinophilia in BAL might indicate asthma. Increased inflammatory cells in chronic lung involvement indicated active alveolitis.

Biochemistry

Keramati et al. conducted a case–control study on 42 male veterans (cases) and 30 healthy male volunteers (controls) in Khorasan Razavi Province of Iran. It showed no significant differences in fasting blood sugar, serum urea nitrogen, and creatinine or uric acid levels between cases and controls. But, levels of serum cholesterol and triglycerides were significantly higher in the cases compared with controls. Serum high density lipoprotein (HDL) and low density lipoprotein (LDL) were not significantly different between cases and controls.

Evaluation of alanine aminotransferase (ALT) enzyme is one of the most commonly used analyses for liver function assessment. Elevated level of this enzyme should be considered as a sign of damage or injury to the liver parenchyma. Normally, ALT is found in hepatocytes. If the liver is inflamed, ALT is released into the bloodstream. Measuring the blood level of this enzyme provides important information about the liver function, liver diseases, viral inflammations or drug intoxications. ALT increases in the metabolic syndrome, fatty liver disease, viral hepatitis and alcoholism. Enzyme activity is associated with body mass index, age, sex and height. Although significantly high level of ALT was detected in the liver of patients who died of exposure to SM gas, its chronic effects on the liver remained unknown. In the study by Keramati et al., there were no significant differences in aspartate aminotransferase (AST), ALT, alkaline phosphatase (ALP), lactate dehydrogenase (LDH) or bilirubin (both total and direct) between cases and controls. Total serum protein and albumin levels were significantly lower in cases than in controls. Chanet et al. conducted a cross-sectional study on 263 male victims with a mean age of (41.32 ± 5.84) years and body mass index of (26.52 ± 3.96). They found increased ALT level in about 16% of the chemically injured patients.

Agin found that serum magnesium level in asthmatic patients exposed to SM gas was lower than that in control group. Diagnosis and treatment of magnesium deficiency in this group of asthmatic patients might be helpful.

Immunity status

Razavi et al. reported increased neutrophil (with chronic bronchitis) and eosinophil counts in SM victims. Leukopenia was often associated with lymphopenia and consequently decreased T-lymphocytes. Additionally, Balali and Hefazi, and Razavi et al. reported increased levels of immunoglobulins G, M and E in victims. Naderi et al. performed a case–control study on 90 male chemically injured victims (cases) and 30 healthy individuals (controls) to compare humoral immunity parameters such as C3, C4 and immunoglobulins A, M and G. They reported that serum IgG significantly increased in victims while serum IgM dropped, IgA remained unchanged and the difference in serum complements was not significant between cases and controls. Other studies showed increased C3 and CD3 +, increased IL-6 in BAL, positive C-reactive protein (CRP) and rheumatoid factor (RF) and decreased number of leukocytes and lymphocytes (especially T-lymphocytes), natural killer cells (NKcs) and serum IL6 and IL8 levels in SM victims. The nitroblue tetrazolium test, chemotactic factors and plasma opsonins were normal in SM victims.

Hormonal changes

There are some hormonal changes in SM victims such as decreased T3 and T4. Naderi et al. studied thyroid hormones (TSH, T3 and T4) between 90 chemically injured cases and 30 healthy male controls, and found that the concentrations of T3 and T3 resin uptake increased while T4 significantly dropped.

SM inhibits DNA replication and mitosis and damages the cells. The most severe effect is on mitosis, particularly in testicular germinal layer cells. Therefore, one of the most common complications of SM is damage to the reproductive system and sexual cells in the testis.

Azizi reported that the levels of total and free testosterone in SM victims were significantly lower than those in healthy controls (p < 0.05).

In the study on 300 veterans in Kerman Province of Iran, Ketabchi reported increased follicle stimulating hormone (FSH) in 57.6% and increased luteinizing hormone (LH) in 66.3% of the cases, respectively.

Ghabili also reported a decrease in T3, T4, T3 resin uptake and cortisol and an increase in adrenocorticotropic hormone (ACTH) one week after exposure as common findings.

Chest assessments

Imaging changes

About 50% of the plain chest radiographs in SM victims were normal. Several studies also confirmed this finding.

Idani et al. evaluated high-resolution computed tomography (HRCT) findings in a cross-sectional study on 106 SM-exposed veterans 18–23 years after exposure. Air trapping and mosaic parenchymal attenuation patterns were the most common findings with a frequency of 65.09% and 58.49%, respectively. The main diagnosis was chronic obstructive pulmonary disease in 54.71%, bronchiolitis obliterans in 27.35% and asthmatic bronchitis in 8.49%. There was no significant relationship between clinical findings and HRCT changes.

In contrast, Agin stated that HRCT was a useful diagnostic tool for pulmonary evaluation of chemically injured veterans. Pulmonary function tests and HRCT were normal in patients with constrictive or obliterator bronchiolitis, in those cases, lung biopsy might be
helpful. In addition, Rouhi et al reported increased possibility of right ventricular pressure on echocardiography.

Myocardial perfusion scan
Saghari et al studied the myocardial perfusion scan patterns of 36 SM victims, 22 patients with cardiovascular diseases and 14 controls with less than 10% risk of cardiovascular diseases. They found that the frequency of myocardial ischemia was higher in exposed individuals compared with controls (p < 0.05).

Shariat-Panahi et al conducted a cohort study on 370 chemically injured veterans (167 inpatients and 203 outpatients) 20 years after exposure to SM and 128 ordinary patients as the control group in Sardasht and Rabat (two cities in the west of Iran). They studied rheumatologic disorders among the mentioned groups. The levels of pain and tenderness of the lower limbs in veterans were significantly higher than that in the control group. Moreover, clubbing and increased ANA were reported in hospitalized veterans more frequently than in the control group.

Bronchoscopy
The bronchial tree is usually full of pus in bronchoscopy and numerous bacteria can be isolated from the secretions. Antibiotics are not usually useful to prevent the production of purulent sputum because the respiratory cilia are destroyed.

Spirometry
The most common spirometric finding is presence of an obstructive pattern. The forced vital capacity (FVC) and forced expiratory volume in the first second (FEV1) are two important criteria for assessment of pulmonary function. Normal respiratory function is often defined as FVC and FEV1 > 80% of predicted values. Mild respiratory impairment is defined as FVC and FEV1 between 60% and 80% of predicted values, and moderate respiratory impairment is defined as FVC and FEV1 between 40% and 60% of predicted values. Severe respiratory impairment is defined as FVC < 50% or FEV1 < 40% of predicted values. Some other paraclinical findings in Iranian veterans exposed to SM gas are presented in Table 1. Furthermore, decreased blood cell count may be related to bone marrow suppression induced by SM.

During Iraq–Iran war, in addition to SM, organophosphorus nerve agents such as Sarin and Tabun were also used by Iraqi armies. Some complications induced by these agents were metabolic acidosis, hyperglycemia, decreased serum potassium, increased levels of creatine kinase, LDH and serum lipase and decreased blood butyrylcholinesterase.

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SM poisoning can change the results of paraclinical tests in chemically injured victims, including hematologic, immune system, biochemistry, hormonal profile and some imaging studies. Most of these changes occur many years after exposure to SM. Further research on the victims is needed.

Discussion
According to the present findings, it seems that the paraclinical tests for assessment of the respiratory system and systemic diseases are more useful than evaluation of localized disorders induced by SM.

Plain radiography is not a specific diagnostic tool for respiratory system and is not helpful for detection of SM victims. In general, spirometry and HRCT modalities are the most efficient diagnostic tools for assessment of respiratory system in SM-exposed veterans.

Although late complications of SM poisoning in the skin, eyes and respiratory system are mainly due to direct toxic effects, neuromuscular, hematological and immunological complications are probably the result of systemic SM toxicity. Therefore, the victims should be monitored for infection, even cancer.

Table 1
Paraclinical findings in Iranian veterans exposed to SM gas during war between Iraq and Iran.

| Assessment                               | Sample size                          | Time after exposure | Results                                                                 | Reference |
|------------------------------------------|---------------------------------------|---------------------|------------------------------------------------------------------------|-----------|
| Microbiological analysis of sputum        | 12 SM-exposed veterans                | 4–17 days           | Presence of Staphylococcus aureus, Haemophilus influenza, and Pseudomonas aeruginosa | 36-37     |
| and bronchoscopic secretions             |                                       |                     | Low concentrations of sperm and abnormal sperm count                    |           |
| Sperm analysis                           | 64 SM-exposed veterans and 64 SM-unexposed people | 20 years           | Neuropathic pain or other deafferentation symptoms                      | 38-39     |
| Neurologic examination                   | 5 SM-exposed veterans                 | 10–15 years         | 77.5% of the SM-exposed revealed some degrees of abnormalities          |           |
| Nerve conduction velocity                | 40 SM-exposed veterans and 35 SM-unexposed people | 16–20 years        |                                                                         |           |
| Spirometry                               |                                       |                     |                                                                         |           |

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