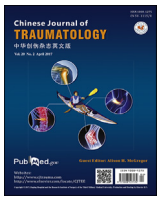
Chinese Journal of Traumatology 20 (2017) 114–117

Contents lists available at ScienceDirect

Chinese Journal of Traumatology

journal homepage: http://www.elsevier.com/locate/CJTEE



Original article

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

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ARTICLE INFO

Article history:
Received 6 December 2015
Received in revised form
10 April 2016
Accepted 12 May 2016
Available online 21 February 2017

Keywords:
Chemical warfare
Mustard gas
Iraq–Iran war, 1980–1988

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.

Iraq–Iran war (1980–1988) was one of the longest conflicts in the 20th century, during which Iraqi armies used more than 1000 tons of sulfur mustard (SM) gas against Iranian troops.[1,2]

SM is a potent toxic, vesicant, blistering, alkylating, nucleophile and lipophilic agent.[3] It affects different organs and causes various respiratory, cutaneous, ocular, gastrointestinal, hematological, immunological, reproductive, hormonal, neurological and psychological complications.[4–7] Khateri et al[8] evaluated the delayed toxic effects of SM on 34,000 Iranians who became chemical victims 13–20 years after exposure in the battlefield. They reported that SM caused respiratory problems in 42.5% of victims, dermatological problems in 24.5%, and ocular problems in 39.3%.

Iranian researchers published some articles regarding paraclinical evaluation of SM victims including their blood cell count, biochemical changes and serum immunological parameters using imaging tools like plain radiographs, high resolution computed tomography (CT), scans of the chest, and electro-diagnostic tests such as electromyography, nerve conduction velocity (NCV), and other tests like spirometry, gasometry and flow-cytometric analysis.[9]

This study aimed to assess paraclinical findings in Iranian veterans exposed to SM gas during Iraq–Iran war.

Materials and 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.[1] Totally 422 medical articles related to SM poisoning were reviewed. Considering the aim of our paper, 30 relevant articles were thoroughly assessed. The main criterion for validation of articles was publication in accredited journals indexed in the above-mentioned databases.

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Peer review under responsibility of Daping Hospital and the Research Institute of Surgery of the Third Military Medical University.

http://dx.doi.org/10.1016/j.cjtee.2016.05.005

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).[10] Various degrees of leukopenia are seen in 42% of victims with severe exposure to SM gas. Leukopenia is often associated with lymphopenia.[11]

Hooshyar et al[12] performed 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.[12] Thrombocytopenia could increase the bleeding time.[13]

In a study by Balali and Hefazi,[14] 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.[15]

Sohrabpour et al[16] 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.[17]

Biochemistry

Keramati et al[18] 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,[18] 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.

Ghanei et al[19] 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[20] 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[21] reported increased neutrophil (with chronic bronchitis) and eosinophil counts in SM victims. Leukopenia was often associated with lymphopenia and consequently decreased T-lymphocytes.[11] Additionally, Balali and Hefazi[14] and Razavi et al[21] reported increased levels of immunoglobulins G, M and E in victims. Naderi et al[22] 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.[22] Other studies showed increased C3 and CD3+,[14] 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.[21,23–25] The nitroblue tetrazolium test, chemotactic factors and plasma opsonins were normal in SM victims.[21,25]

Hormonal changes

There are some hormonal changes in SM victims such as decreased T3 and T4.[26] Naderi et al[22] 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.[27]

Azizi[26] 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[27] reported increased follicle stimulating hormone (FSH) in 57.6% and increased luteinizing hormone (LH) in 66.3% of the cases, respectively.

Ghabili et al[28] 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.[29] Several studies also confirmed this finding.[30]

Idani et al[31] 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[20] 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 obliterative bronchiolitis, in those cases, lung biopsy might be

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 and bronchoscopic secretions	12 SM-exposed veterans	4–17 days	Presence of *Staphylococcus aureus*, *Hameophilus influenza*, and *Pseudomona aeruginosa*	[36]
Sperm analysis	64 SM-exposed veterans and 64 SM-unexposed people	20 years	Low concentrations of sperm and abnormal sperm count	[37]
Neurologic examination	5 SM-exposed veterans	10–15 years	Neuropathic pain or other deafferenation symptoms	[38]
Nerve conduction velocity	40 SM-exposed veterans and 35 SM-unexposed people	16–20 years	77.5% of the SM-exposed revealed some degrees of abnormalities	[9]

helpful.[32] In addition, Rouhi et al[29] reported increased possibility of right ventricular pressure on echocardiography.

Myocardial perfusion scan

Saghari et al[33] 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[34] 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.[30]

Spirometry

The most common spirometric finding is presence of an obstructive pattern.[29,35] 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.[9,36–38]

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.[30]

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.[14] Therefore, the victims should be monitored for infection, even cancer.[15] Furthermore, decreased blood cell count may be related to bone marrow suppression induced by SM.[21]

During Iraq–Iran war, in addition to SM, organophosphorus nerve agents such as Sarin and Tabun were also used by Iraqi armies.[39] 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.[10,14] However, evidence is scarce on the acute and chronic effects of such agents.

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.

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