The effects of sulfur mustard on the skin and their management: reviewing the studies conducted on Iranian chemical victims

Seyed Mansour Razavi, MD [1]
Masoud Saghafinia, MD [2]
Seyed Masoud Davoudi, MD [3]
Payman Salamati, MD [4]

1. *Department of Community Medicine, Tehran University of Medical Sciences, Tehran, Iran*
2. *Trauma Research Center, Baghiyatallah University of Medical Sciences, Tehran, Iran*
3. *Department of Dermatology, Baghiyatallah University of Medical Sciences, Tehran, Iran*
4. *Sina Trauma and Surgery Research Center, Tehran University of Medical Sciences, Tehran, Iran*

Corresponding Author:
Payman Salamati, MD, MPH
Sina Trauma and Surgery Research Center, Sina Hospital, Hassan Abad Square, Imam Khomeini Avenue, Tehran, Iran
Email:psalamati@tums.ac.ir

Conflict of interest: none to declare

Background: The skin is among the main tissues affected by Sulfur Mustard (SM) in chemical attacks. Iranian researchers have performed extensive studies on the exposed victims and have reported a wide spectrum of information in this field. The main objective of this study was to develop a comprehensive revision of data on the pathology, pathogenesis, clinical findings, complications, and treatment of sulfur mustard exposure.

Method: This study was part of a systematic search which included all the war related studies on Iranian victims. Among nearly 300 retrieved articles, a total of 193 medical articles were approved in terms of quality and were related to the Iraq-Iran chemical war (1984-1988) out of which 48 were directly related to the dermatologic effects of sulfur mustard. We used known international databases such as ISI, Medline, Scopus, and Iranian databases such as Iranmedex, SID, and Irandoc in this study. Publishing the articles in approved journals was the main criterion for their quality.

Result: In this study, the most common symptom in the delayed phase of the exposure to SM was itching which was more frequently seen in women as compared to men. The most common sign was erythema in the skin. One of the chronic complications at the site of exposure was mustard scar. Lipoma and cherry angioma were the most common skin tumors which were reported. Iranian researchers have presented different approaches for the management of exposed victims.

Conclusion: In this study, in addition to the effects of SM on the skin, some methods were presented for decontamination, management of itching, vesicles, blisters and treatment of chronic skin lesions.

Keywords: chemical warfare, management, mustard gas, skin diseases

Received: 13 March 2013
Accepted: 19 May 2013

Iran J Dermatol 2013; 16: 21-30

INTRODUCTION

The Iraqi army used chemical weapons during the Iraq-Iran war. Sulfur Mustard (SM) was the most common chemical agent which they used in the war. SM causes many injuries in the body organs [1-5]. The skin is among the first tissues affected in chemical attacks with sulfur mustard gas (SMG). In a study by Khateri et al on 34,000 Iranian victims 13 to 20 years after exposure to SM, the rate of skin

involvement was 24.5%. [6] Balali et al evaluated the delayed toxic effects of the mustard gas on 1,428 chemical victims 3-9 years after the exposure and reported the frequency of skin lesions to be 88% [7]. In two other studies conducted on Iranian chemical warfare victims, this rate was 90% [8-9]. In another study, the delayed toxic effects of sulfur mustard on 236 Iranian chemical victims were assessed 2 to 28 months after the exposure and the authors reported the rate of skin involvement to be 41% [7].

In their study during 1992-1995 on 500 chemical victims in Kerman Province (South west of Iran), Fekri and Janghorbani stated the incidence of skin lesions to be significantly higher in chemical victims as compared to non-chemical victims [10]. The British scientist Frederick Guthrie found its powerful vesicant effects on its victims about 40 years after the development of sulfur mustard. After more than 80 years of investigation, no consensus has been reached about its main mechanism of action in causing skin vesiculation. The concentration of 0.1 to 1 mg/cm^2 is the minimum dose required to cause erythema and the concentration of 1 to 4 mg/cm^2 causes blisters and burns. Pigmentation disorders due to stimulation or necrosis of melanocytes occur with variable concentrations of mustard gas [11]. Diversity of skin and mucosal lesions due to exposure to sulfur mustard gas is very high. In this paper, we aimed to discuss the effects of this gas by reviewing the studies conducted in the field of dermatology on Iranian victims.

PATIENTS AND METHODS

This study was part of a systematic search which included all the war related studies on Iranian victims. Among nearly 300 articles which were obtained, a total of 193 medical articles related to SM were reviewed using known international medical databases such as Scopus, Medline, ISI, and Iranian medical databases such as Iranmedex, SID and Irandoc. Forty-eight articles were directly related to the dermatologic effects of SM. Chemical injury, chemical warfare, sulfur mustard and mustard gas was used as the key words. No special evaluation was conducted on the quality of the reviewed manuscripts and the credit of journal was considered sufficient. There were no ethical considerations in our study.

RESULTS

Pathology and Pathogenesis

After skin exposure, 80% of sulfur mustard evaporates and approximately 20% is absorbed which quickly enters the keratinocytes and hair follicle cell membrane. Of the absorbed amount, 12% remains in the skin, and 8% enters the systemic blood circulation. By increasing the temperature, the penetrating ability of this substance improves and it easily penetrates through the moist skin [6-7]. Keratinocytes of the *stratum basale* seem to have high sensitivity to SM cytotoxicity. This substance may result in histopathologic changes in keratinocytes, structural changes in the dermis and hyperplasia of epidermis [12]. In the acute phase, sulfur mustard leads to destruction of the skin appendages (eccrine and apocrine glands, pilosebaceous units and hair matrix) as well as dermal damages due to enzymatic changes and its proteases. In the late phase, it results in high production of collagen and mucoproteins, development of sclerodermoid lesions and partial atrophy [11].

Skin changes due to SM in the acute and chronic phases are similar to chemical burns. Histopathologic changes occur in several patterns: vascular or lichenoid type changes, spongiotic and vesicant dermatitis with or without acantholysis, pigmentation disorders, sclerodermoid changes and vasculopathy or inflammatory reactions. Also, it has been shown that the level of following factors increases in animal models or cultured human keratinocytes and fibroblasts exposed to SM: interleukin- 1, 6 and 8, macrophage inflammatory protein-1α (MIP-1 alpha), macrophage inflammatory protein-2 (MIP-2), monocyte chemoattractant protein-1 mRNA, growth-regulated oncogene (GRO), TNF-α, and granulocyte macrophage colony stimulating factor [8].

Vesiculation is among the main signs of SM exposure. Despite more than 80 years of investigation, the exact mechanism of skin vesiculation as the result of SM exposure has yet to be determined. Brimfield et al, suggested the inhibition of phosphatases in the tissue cytosol as the probable mechanism of vesiculation; Moreover, Arroyo indicated the role of cytokines in his study [13-14]. Also, some believe that SM impairs the action of glycolysis enzymes causing skin vesiculation [15].

SM can cause collagen vascular diseases like dermatomyositis and discoid lupus erythematosus through inhibition of immune system. Development of skin angiomas can also be related to this mechanism [16]. Also, development of angiomas may be due to the release of angiogenic cytokines during the recovery of skin vesicles or direct effect of SM on cellular DNA [15]. Hyperpigmentation may be due to the reduction of intracellular glutathione following SM exposure and subsequent increase in the activity of tyrosinase enzyme. Due to the changes in the basement membrane, fibrosis, inflammatory infiltration around the hair follicles and follicular destruction in the skin, hair loss may occur [9-10]. The burning sensation on the skin can be due to the effects of SM on nerve ends and nerve fibers. In histopathologic examination of the victims' skin, hyper melanogenesis, basal layer pigmentation, coagulative necrosis, fibrosis and mild dermal inflammatory changes can justify pigmentation changes, keloid formation and scarring. Lichenification and excoriation can be secondary to itching [17-18].

Davoudi et al, evaluated skin sebum and elasticity in their comparative study on 310 males. They divided their patients into four groups: patients exposed to SM with skin lesions, patients exposed to SM without skin lesions, patients with dermatitis and normal control group. They concluded that patients exposed to SM, whether or not causing dermatitis, showed no changes in the skin sebum and skin elasticity in comparison with unexposed patients or normal controls. They stated that SM mostly affected the epidermis rather than the dermis and its content [19]. Davoudi et al, in a similar study on the same number of patients, concluded that exposure to SM could affect biophysical properties of the skin, especially the function of stratum corneum as a barrier against loss of water, and moisture would be altered even several years after the exposure. Skin cancers due to SM exposure are usually localized to the scars [20]. Maleki et al, reported one case of Merkel cell carcinoma in a 60-year-old man in Mashhad [21].

Classification of skin lesions in terms of appearance

Skin lesions are categorized into the following forms in terms of appearance: erythematous, pigmentary exfoliation, vesicular or superficial blister, bullous necrotization, deep non-bullous necrosis, lesions due to allergic and toxic reactions [7]. Skin areas exposed to SM are more susceptible to chronic eczema, seborrheic dermatitis, skin atrophy, hair loss, and rash. Vascular changes such as telangiectasia and cherry angiomas are also seen [22]. Maleki et al, in a historical cohort study on 99 victims with and without history of SM exposure, concluded that the number of angiomas was significantly higher among chemical victims as compared to those who were not exposed to SM. They stated that SM could cause multiple and large cherry angioma several years after the exposure [16]. Burned skin usually heals spontaneously. However, deep burns are a candidate for skin graft [7]. Requena et al explained skin lesions in 8 chemical victims of Iraq-Iran imposed war. They reported that after an intensive exposure to SM, there was a latent period from 2 to 3 hours, and when the exposure is mild vapor exposure, the latent period lasts for 8 to 10 hours. After this time period, erythema, blisters, and other skin lesions develop [23].

Skin clinical signs and symptoms

Cutaneous symptoms manifest in 90% of the affected victims a few hours after exposure [20,24]. Cutaneous signs and symptoms in SM exposed victims may manifest in different forms such as erythema, itching, burning sensation or pain, vesicle, blister or deep burn, hyper-pigmentation, hypo-pigmentation, scaling, urticaria, dry skin, fissure, lichenification, and excoriation [22]. Table 1

Table 1. Distribution of skin complaints among SM victims in several studies.

Sample size, duration	Location of study N (%)	Itching N (%)	Burning sensation N (%)	Dryness Sensation N (%)	Excessive sweating N (%)	Complaining of hair loss N (%)	Reference
198, 20 years	Babol	187 (90.3)	103 (52)	34 (17.1)	–	26 (13.1)	26
5,668, 10 years	Tehran	4274 (75.4)	1426 (25.1)	645 (11.3)	1170 (20.6)	2260 (39.8%)	17
500, 6-11 years	Kerman	274 (54.8)	227 (45.4)	282 (56.4)	–	88 (17.6)	10

shows the frequency distribution of skin complaints (symptoms) in SM victims.

Toosi et al evaluated cutaneous signs, symptoms and delayed lesions in their descriptive study conducted on 5,668 chemical victims 8 to 10 years after exposure to SM, and reported that the most common skin complaint was itching which was present in 75% of the males and 83.5% of the females. They could not attribute itching to dry skin since only 2% of their study population had dry skin. Severe chronic itching irritates the patients and causes anxiety in their companions [17]. Fekri et al found that the incidence of itching was 6 times greater in chemical victims compared to controls [10]. Itching can cause sleep disturbances and decreases the victims' quality of life [25]. According to Toosi et al, all the cutaneous complaints (Itching, hair loss, burning sensation, and dryness sensation except excessive sweating) were more common in females than males [17].

Rezvani et al evaluated cutaneous signs and symptoms in a descriptive study conducted on 198 SM victims in Babol during 2001-2003 and found that over time, exposed victims developed new and different lesions. They reported erythema as the most common skin lesion and mentioned that the highest distribution of skin lesions was in the trunk (59.5%) especially the anterior trunk [26]. Some patients complain of the burning sensation or development of blisters on the skin, especially in warm weather [25]. Dabiri and Ghafarian Shirazi in a case control study on 180 cases and 40 controls during 2000-2004 evaluated lesions like acnes in chemical victims and concluded that the prevalence of these lesions did not significantly differ between cases and controls. They reported the prevalence of a form of lesions like acnes to be 53.9% among victims. However, the prevalence of acnes in another study on 800 victims 14 to 20 years after the exposure was 11.6% [27]. Mortazavi et al, in a descriptive cross sectional study on 800 chemical victims from various provinces of the country 14 to 20 years after SM exposure, reported a specific form of scarring in 44 subjects (5.5%) and called it the "sulfur mustard scar". This scar is characterized with an irregular margin and lesions ranging from localized leukomelanoderma to vascular lesions like telangiectasia and cherry angiomas, associated with atrophic or hypertrophic reticular regions surrounding small islands of apparently healthy skin [11]. Emadi et al, reported a type of scar tissue due to SM in a 37-year-old man with pigmentation and trophic and vascular characteristics 16 years after the exposure [22]. Fekri et al, evaluated and compared delayed skin lesions 6 to 11 years after the exposure between 500 chemical victims and 500 non-chemical subjects and reported that all types of cutaneous lesions except for acne and pityriasis versicolor fungal (yeast) infection were significantly more prevalent in the chemical victims. They reported that the most common cutaneous finding among chemical victims was dry skin (56.4%) and the most common complaint was itching (54.8%) [10]. Balali Mood et al, in their study on 40 victims, found xerosis as the most common cutaneous symptom in the lower limbs [7].

In summary, itching is the most prevalent complaints among the patients exposed to SM who suffer from chronic skin lesions, which may result in the development of psychological disorders and disturbs their quality of life. After itching, burning sensation, pain and redness are the most common symptoms in order of frequency. On clinical examination, xerosis (dry skin) is the most frequent finding followed by hyper-pigmentation, hypo-pigmentation, scar tissue formation, and skin diseases [22]. Table 2 shows the frequency distribution of skin findings (signs) among SM victims in some national studies in Iran.

Clinical progress of the skin lesions

Immediately after the exposure to SM, the victim feels nothing. Then, the skin becomes pale and after 2 to 24 hours, erythema develops which may be associated with severe itching. In the erythematous areas, vesicles develop following a slight pressure (Nikolsky's sign) [7,28]. About 2-14 hours after the exposure, erythema with severe itching develops; then, vesicles appear containing a yellowish fluid and gradually turn into blisters. After 48 hours, blisters rupture and later, lesions crust and become necrotic and edematous leaving a scar tissue [7].

Skin diseases, tumors and oral mucosal lesions

Mortazavi and Fekri evaluated an acceptable number of chemical victims in terms of skin diseases. The frequency of these diseases is summarized in table 3. In 1999, Mousavi et al conducted a

Table 2. Clinical findings of 6 national studies in Iran.

Location Number Exposure time	Erythema	Macule & Papule	Vesicle	Pustule	Blister	Ulcer	Plaque	Urticaria & Angioedema	Scar	Keloid
Babol 198 20y	99 (50%)	79 (39.8%)	23 (11.6%)	15 (7.5%)	2 (1%)	4 (1.5%)	4 (2%)	61 (30.8%)	9 (4.5%)	1 (0.5%)
Tehran 5668 10y	–	–	–	–	–	–	–	–	1717 (30.3)	95 (1.67)
Various Provinces 800 14-20y	–	–	–	–	–	–	–	41 (5.1)	44 (5.5)	13 (1.3)
Kerman 500 6-11y	–	–	–	–	–	–	–	10 (2)	–	–
Isfahan 535 acute	423 (79)	–	–	–	295 (55)	–	–	26 (4.85)	–	–

Table 2. Clinical findings of 6 national studies in Iran (Continue).

Location	Atrophy	Hyper-pigmentation	Hypo-pigmentation	Depigmentation	Dry skin	Hair loss	Lichenification	Excoriation	Scaling	Acne form lesions	Purpura	Ref.
Babol	7 (4.5)	16 (10.4)	15 (7.6)	4 (1.5)	31 (15.6)	20 (10.1)	3 (1.5)	13 (6.5)	27 (13.6)	–	–	26
Tehran	58 (1)	333 (5.6)	119 (20.09)	148 (2.6)	121 (2.13)	–	101 (1.8)	82 (1.4)	–	–	–	17
Provinces	–	152 (19)	18 (2.2)	–	–	–	–	–	–	93 (11.6)	–	11
Kerman	–	217 (43.4)	12 (2.4)	–	282 (56.4)	88 (17.6)	–	–	208 (41.6)	–	–	10
Isfahan	–	109 (20.3)	–	–	–	–	–	–	60 (11.2)	–	6 (1.1)	28

study on 222 subjects (101 chemical victims and 121 nonchemical victims) in Khouzestan Province (south west of Iran) and assessed the long term effects of SM on the skin after 10 to 19 years. The most common complaints were itching that exacerbated with heat or cold. Upon comparison of the skin lesions in exposed and unexposed people, androgenic alopecia grade 5-6 in the control group and alopecia areata, tinea versicolor, recurrent aphthous, cherry angiomas, melanocytic nevus and telangiectasia among chemical victims were significantly higher. The prevalence of other skin diseases such as keratosis pilaris, trichomycosis axillaris, vitiligo, psoriasis, leukoplakia, solar keratosis, skin tags, warts, solar lentigo, acne, and sebaceous dermatitis were not significantly different between the two groups. In this study, erythema of the scalp, folliculitis, hyper- and hypo-pigmentation and lichenification of the genital and lower body parts were significantly higher in chemical victims. The prevalence of dandruff, scalp and face hypo-pigmentation and lichenification of the upper limbs was not significantly different between cases and controls [9]. Afshari evaluated superficial skin fungus during 1996-1997 in a study on 300 victims in Isfahan (150 participants) and Kerman (150 participants) but could not find a correlation between exposure to chemical agents and the prevalence of superficial skin fungal infections [29]. Rashidi and Alamdari reported concomitant psoriasis and bullous pemphigoid

Table 3. Frequency distribution of skin diseases among SM exposed victims in 2 studies.

Author	Mortazavi [11]	Fekri [10]
Sample size	800	500
Exposure time	14 – 20 years	6 – 11 years
Location of study	Different Provinces	Kerman Province
Disease/Lesion	**Number (%)**	**Number (%)**
Sebaceous dermatitis	102 (12.7)	–
Eczema	99 (12.2)	37 (7.4)
Tinea versicolor	56 (7)	–
Melanocytic nevus	49 (6.1)	–
Lichen simplex	33 (4.1)	–
Keratosis pilaris	29 (3.62)	–
Vitiligo	29 (3.62)	18 (3.6)
Alopecia Areata	20 (2.5)	11 (2.2)
Lichen planus	7 (8)	–
Herpes	18 (2.2)	–
Psoriasis	16 (2)	–

in a 42-year-old woman from Sardasht who was exposed to SM in 1985, 5 years after her exposure [30].

Nakhaee et al evaluated a 37-year-old subject who was exposed to SM in 1988 reported that the patient first developed itching and erythema at the site of exposure and blisters developed after 24 hours. After one year, hair growth decreased and hypo-pigmentation of the skin and numerous separate red macules developed. Clinical and pathologic findings were compatible with cherry angiomas [7,31]. Some other studies have also evaluated skin tumors in chemical victims. For example, multiple basal cell carcinomas were reported in a woman from Sardasht who was exposed to SM in 1987 [32]. Moradi et al conducted a study on 1060 chemical veterans in Fars Province, Iran, and found only one patient with basal cell carcinoma [33]. In another study, chronic skin lesions were detected in 150 people residing in Sardasht 10 years after exposure to SM but no malignancy was observed among them [34].

Kakooiee et al performed a descriptive cross sectional study on 70 chemical victims from Kerman, Iran, in 2007 and reported the frequency of oral soft tissue lesions as wounds 20 (28.6%), erythema 7 (10%), leukoplakia 3 (4.3%), pigmentation 33 (45.7%), exophytic lesions 5 (7.1%), angular cheilitis 4 (5.7%). The prevalence of oral mucosal lesions was reported 42.8% in a study conducted on 390 subjects in Turkey, 4.9% in a study in Cambodia and 4.1% in another study in South India [35].

Treatment of skin lesions

The measures for the treatment of skin injuries with SM include:

Decontamination: After SM exposure, the first thing to do is to take off all the contaminated clothing as soon as possible. The SM sediment on the skin should be gently removed using a wooden spatula and the exposed skin surfaces should be immediately soaked in *calcium chloride* or *magnesium oxide* powder that act as an anti-gas and then washed with soap and water for 5 minutes. Then, the skin has to be washed with *sodium thiosulfate* for 20 minutes and washed or bathed again with water and soap for 5 minutes before starting the necessary medical treatment [36].

Washing and Disinfecting: The skin can be first washed with neutral soaps (pH of about 7.0) and the exposed areas should be soaked in *oil*, *kerosene*, or *gasoline* and then washed with soap again [4,37-38]. According to some other suggestions, the skin should be washed with home *bleach solution* or 0.5% hypochlorite solution [39], or based on another suggestion, the skin should be washed at least 6 times a day with 0.2 or 0.3% *chloramine solution* [40]. Momeni et al also recommended the irrigation of the skin with *potassium permanganate* solution 1/10,000 and warm water [28]. Bathing with fresh breast milk has also been recommended but further investigation is required in this respect [41].

Management of vesicles and blisters: Some investigators believe that the injured skin should be left open and uncovered but some others believe that the fluid of the blisters larger than 2 cm should be drained. Momeni et al demonstrated that when incision and drainage of the blisters larger than 2×2 cm during the first 24 hours was done, lesions healed more rapidly [28]. Usually blisters smaller than 2 cm should not be manipulated to allow them to rupture spontaneously [7,42-43]. The skin blisters should be incised and debridement under sterile conditions [7,28].

Use of topical creams & dressing: After draining the large blisters, debridement has to be done followed by normal saline or lactated Ringer's solution rinsing and using sterile dressing with topical creams such as mafenide acetate (Sulfamylon) or silver sulfadiazine 1% (Flamazine), furazolidon, metronidazole, paraffin gauzes, dexpanthenol, or flumetasone creams [7,42-43]. For armpits and scrotum, a combination of clioquinol-triamcinolone and Castellani solution should be used [39]. Also, application of W/O ointment (polysorbate, glycerin, monostearate, methyl alcohol, liquid paraffin, propylene glycol, and water) is recommended [28].

Itching management: Reassurance and compassionate care and psychological support of the patients are among the most important aspects of treatment in injured patients [7]. Calamine lotion can be applied to the erythematous areas [41]. Panahi et al performed a randomized double blind clinical trial on 80 male victims suffering from itching due to exposure to SM and concluded that local application of a combination of phenol 1% and menthol 1% was significantly effective for the treatment of itching due to SM compared to the placebo. They recommended starting the anti-

itching treatment at the early phases to prevent excoriation and scarring [25]. The use of diluted topical corticosteroids has proved beneficial in reducing irritation and edema. Long-term use of local corticosteroids on the skin is associated with side effects like skin atrophy, lines of striae and rosacea [44]; however, application of *Pimecrolimus* can be similarly efficacious without the above mentioned complications. Panahi et al compared the effect of *Pimecrolimus* 1% with betamethasone 1% ointment on chronic skin lesions due to SM in an investigator-blind study on 70 imposed war victims. They found that *Pimecrolimus*, similar to betamethasone, was effective in controlling itching, burning sensation, and dry skin [44]. Also, for controlling irritation and itching of the erythematous skin and vesicles, topical lotions like calamine or steroid solutions can be used [7,41]. Local *corticosteroid solutions* are effective in decreasing irritation and skin edema but have minimal or no impact on healing [28].

It has been well understood that itching due to SM exposure has a histaminic origin; thus, antihistamines are widely used to control it although neuroleptics and anti-depressants are also administered [45]. Administration of doxepin and hydroxyzine has a similar effect greater than that of cetirizine. Hydroxyzine is a first generation antihistamine. Cetirizine is the second generation antihistamine and doxepin is a tricyclic antidepressant (TCA) [45-46].

Pain Management: Use of analgesics from acetaminophen to morphine sulfate and use of anti-histamines like promethazine and sedatives like barbiturates, diazepam and in severe cases carbamazepine or morphine can be effective in decreasing pain or itching [7,41].

Other treatment measurements: During the treatment and care of the injured patients, other medical measures such as cooling the affected areas [41], and administration of high protein dietary regimens for the victims should be considered. Antibiotics should be used for infected lesions. Irrigation of the eyes with Ringer's solution, infusion of fresh blood in case of bone marrow suppression, venous treatment in the first 24 hours, and use of urinary catheters in case of genital skin involvement are recommended [28].

The effect of some other drugs like *N acetyl cysteine (NAC), 2 oxo-thiazolidine 4 carboxylate or OTC* and acetaminophen on sulfur mustard has also been evaluated. These drugs can decrease the toxic effect of SM on cells through affecting the glutathione stimulating hormone and inhibiting its release. Saberi and Zaree Mahmoudabadi, in a study on in-vitro tissue culture, evaluated the effect of administering NAC, TOC, and acetaminophen alone and together on SM and noticed that administration of these 3 therapeutic agents together before or after SM exposure may decrease SM toxicity [47]. Sawyer et al, in their study on pigs, exposed the pigs to sulfur mustard for 4, 8, 12 and 16 minutes. At early phases, they cooled down the resultant lesions with ice packs and examined histological changes in them. They concluded that moderate cooling of the skin exposed to SM decreased the severity of inflammation and wound. Thus, cold therapy is recommended for SM victims and its results are similar to cold compress immediately after burns [48]. Safari Nejad et al recommended the administration of 500 mg/kg/d *sodium thiosulfate* for the first 48 hours followed by oral N-acetyl-L-Cysteine for 10 days for medical therapy of SM victims. They suggested using the latter as follows: in the beginning, start with 10 gr, followed by 5 gr 2 hours later and then 5 gr every 4 hours for 10 days. Treatment with *sodium thiosulfate* results in methemoglobinemia for which administration of 1 gr vitamin C every 6 hours might be beneficial. Also, for excretion of SM metabolites, administration of *furosemide* for 3 days has been recommended. For the treatment of lactic acidosis, *trihydroxy-methyl-aminomethane* has been suggested [36]. Studies demonstrate that debridement with laser (Lasablation) facilitates wound healing at the cellular level [41]. For extensive burns, skin grafts may be required [7]. Patients may need to be hospitalized in the intensive care unit receiving charcoal and oral lactulose for 3 days. They may occasionally need dialysis and plasmapheresis. Administration of 250 cc thiosulfate sodium 10% daily for 5 to 7 days has also been recommended. Additionally, it has been suggested that patients receive prophylactic (low dose) heparin 10,000 units daily [49]. For the regulation of water and electrolytes, the protocols as for burns should be followed. In general, the course of recovery is slow and skin grafts may be required for repair for skin lesions [7,41]. Once the blisters are formed, fluid replacement may be indicated [49].

DISCUSSION

As we may notice, different frequencies have been reported (24.5% -94%) for the skin lesions. This variability may be due to different study designs, sample sizes, time and duration of exposure, concentration of the toxic gas, severity of the attack, climate of the area and many other factors.

In the literature, there is much evidence about the carcinogenicity of sulfur mustard gas. In a review study, Ghanei et al, described the acute and chronic effects of SM and its mutagenic, immunogenic, genotoxic and carcinogenic effects on skin using several studies conducted on this subject [8]. However, considering the distribution of the diseases and tumors of the skin reported in table 4, the rates of the above-mentioned effects in the Iranians who were exposed to SM are not too high [50]. According to Moradi's study in Fars Province, SM exposure is unlikely to enhance the risk of skin cancer [33] which may be due to the short duration of exposure of Iranian victims to SM.

The most common skin symptom in this study was itching [12] which can lead to unrest, agitation, depression, sleep disorders, secondary infection of the skin, and lowering the quality of life.

It has been well understood that itching due to SM exposure has a histaminic origin. Thus, antihistamines are widely used to control it. Shohrati et al, in a double blind randomized study on 75 patients suffering from chronic itching due to SM, administered 10 mg cetirizine daily for 4 weeks, doxepin 10 mg daily or hydroxyzine 25 mg and compared the results. They concluded that doxepin and hydroxyzine had a similar effect greater than that of cetirizine [45-46]. Therefore, hydroxyzine can be a safe and inexpensive drug for controlling itch. It seems that the frequency of oral lesions among the people exposed to SM is not higher than the unexposed population [45]. Most of the performed studies have focused on epidemiological and clinical aspects. To expand the frontiers of knowledge, we suggest more emphasis should be placed on molecular research to discover the mechanisms of chronicity and pathogenesis of SM and also definitive treatment of the skin problems.

Table 4. Frequency of skin tumors in two national studies in Iran

Author	**Mortazavi [11]**	**Davoudi [50]**
Sample size	800	9605
Exposure time	14 – 20 years	10 – 15 years
Location of study	From across the country	From 17 Provinces of country
Tumor	**Number (%)**	**Number (%)**
Lipoma	–	58 (1.66)
Melanocytic nevus	–	14 (0.15)
Syringoma	–	8 (0.083)
Warts	–	6 (0.06)
Dermatofibroma	1 (0.12)	4 (0.041)
Blue nevus	–	3 (0.031)
Angiokeratoma	–	2 (0.02)
Neurofibroma	–	1 (0.01)
Cherry angiomas	139 (17.3)	–
BCC	5 (0.65)	4 (0.41)
SCC	1 (0.12)	–

Acknowledgement

The authors are grateful to Ms. Ghadiri for initial typing of the article. We would like to express our gratitude to all the Iranian researchers for providing us with the results of their studies.

REFERENCES

1. Razavi SM, Salamati P, Saghafinia M, et al. A review on delayed toxic effects of sulfur mustard in Iranian veterans. DARU 2012, 20:2–8.
2. Razavi SM, Salamati P, Feizi S, et al. Mustard gas-induced ocular injuries: a review of manifestations and managements. Iran J Ophthalmol 2012; 24:11-8.
3. Razavi SM, Salamati P, Harandi AA, Ghanei M. Prevention and treatment of respiratory consequences induced by sulfur mustard in Iranian casualties: a review. Int J Prev Med 2013;4:383-9.
4. Razavi SM, Karbakhsh M, Salamati P. Preventive measures against the mustard gas: a review. Med J Islam Repub Iran 2013;27:83-90.
5. Razavi SM, Ghanei M, Salamati P, et al. Long-term effects of mustard gas on respiratory system of Iranian veterans after Iraq-Iran war: a review. Chinese J Traumatol 2013;16 (in press).
6. Khateri S, Ghanei M, Keshavarz S, et al. Incidence of lung, eye, and skin lesions as late complications in 34000 Iranian with wartime exposure to mustard agent. J Occup Environ Med 2003;45:1136-43.
7. Balali-Mood M, Hefazi M.The pharmacology, toxicology, and medical treatment of sulfur mustard poisoning. Fundam Clin Pharmacol 2005;19:297-315.
8. Ghanei M, Poursaleh Z, Harandi AA, et al. Acute and chronic effects of sulfur mustard on the skin: a comprehensive review. Cutan Ocul Toxicol 2010;29:269-77.
9. Mousavi ZB, Ebrahimi A, Mirian M. Long-term effects of sulfur mustard gas exposure on the skin of Iranian combaters. Iran J Dermatol 2001; 5: 9-19.

10. Fekri A, Janghorbani M. Delayed skin lesions in chemical victims of Kerman Province. J Kerman Univ Med Sci 1995;2:108-19.
11. Mortazavi H, Reziei M, Emadi SN, et al. Lesions in 800 Iranian victims of mustard gas, 14-20 years after exposure. Iran J Dermatol 2005; 8: 177-89.
12. Shakarjian MP, Heck DE, Gray JP, et al. Mechanisms mediating the vesicant actions of sulfur mustard after cutaneous exposure. Toxicol Sci 2010;114:5-19.
13. Brimfield AA, Zweig LM, Novak MJ, Maxwell DM. In vitro oxidation of the hydrolysis product of sulfur mustard. J Biochem Mol Toxicol 1998; 12:361-9.
14. Arroyo CM, Schafer RJ, Kurt EM, et al. Response of normal human keratinocytes to sulfur mustard (HD): cytokine release using a non-enzymatic detachment procedure. Hum Exp Toxicol 1999; 18: 1-11.
15. Firooz A, Komeili A, Dowlati Y. Eruptive melanocytic nevi and cherry angiomas secondary to exposure to sulfur mustard gas. J Am Acad Dermatol 1999; 40: 646-7.
16. Maleki M, Javidi Z, Soofi Zadeh V, Ebrahim Zadeh S. Multiple large cherry angiomas after exposure to sulfur mustard gas in Iranian veterans in Iraq-Iran war: A historical cohort study. Iran J Dermatol 2006, 9:40-45.
17. Toosi P, Amir Javanbakht AM, Heydarian Moghadam M, et al. Evaluation of delayed skin lesions in chemical victims. Pajouhandeh 2002; 3: 209-21.
18. Naraghi ZS, Mansouri P, Mortazavi M. A clinicopathological study on acute cutaneous lesions induced by sulfur mustard gas (yperite). Eur J Dermatol 2005;15:140-5.
19. Davoudi SM, Sadr B, Hayatbakhsh MR, et al. Comparative study of skin sebum and elasticity level in patients with sulfur mustard – induced dermatitis and healthy controls. Skin Res Technol 2010;16: 237-42.
20. Davoudi SM, Keshavarz S, Sadr B, et al. Skin hydration and transepidermal water loss in patients with a history of sulfur mustard contact: a case control study. J Eur Acad Dermatol Venereol 2009;23:940-4.
21. Maleki M, Tayebi Meybodi N, Javidi Z, et al. Merkel cell carcinoma on mustard eschar: a case report. Med J Mashhad Univ Med Sci 2007;50:444 -50.
22. Emadi SN, Hosseini-Khalili A, Soroush MR, et al. Mustard gas scarring with specific pigmantary, trophic and vascular characteristics (case report, 16 – years post exposure). Ecotoxicol Environ Saf 2008;69:574-6.
23. Requena L, Requena C, Sanchez M, et al. Chemical warfare.Cutaneous lesions from mustard gas. J Am Acad Dermatol 1988;19:529-36.
24. Thomsen AB, Eriksen J, Smidt-Nielsen K. Chronic neuropathic symptoms after exposure to mustard gas: a long term investigation. J Am Acad Dermatol 1998; 39: 187-90.
25. Panahi Y, Davoodi S.M, Khalili H, et al. Phenol and menthol in the treatment of chronic skin lesions following mustard gas exposure. Singapore Med J 2007; 48: 392-5.
26. Rezvani SM, Mahmoudipour A, Bijani A. Cutaneous signs and symptoms in chemical victims of Iraq-Iran imposed war (skin clinic of Shahid Yahya Nejad Hospital, Babol) during 2001-2003. J Babol Uni Med Sci 2005; 1:74-7.
27. Dabiri N, Ghafarian Shirazi HR. Prevalence of acne-like lesions in chemical victims in 2004. Armaghan Danesh J 2008; 1: 97-104.
28. Momeni AZ, Enshaeih S, Meghdadi M, Amindjavaheri M. Skin manifestations of mustard gas. A clinical study of 535 patients exposure to mustard gas. Arch Dermatol 1992;128:775-80.
29. Afshari MA. Epidemiologic study of common dermal fungal infections in chemichal veterans in Kerman and Esfahan Provinces. J Mil Med 2001; 3: 189-93.
30. Rashidi T, Alamdari Mahd A. Concurrent psoriasis and bullous pemphigoid in a chemical victim. J Tabriz Univ Med Sci 2004;64:110.
31. Nakhaee MM, Emadi SN, Toosi S, et al. Scar due to sulfur mustard gas on thigh with cherry angiomas, decreased hair growth and pigmentary disorder: A case report. Iran J Dermatol 2004;8(Suppl):26-30.
32. Rashidi T. Development of numerous basal cell carcinomas in a chemical victim. J Tabriz Univ Med Sci 2008; 30:141-2.
33. Moradi A. Evaluation of malignant skin lesions in SM victims. Abstract book of the 5th annual seminar of chronic complications of chemical warfare gases, Russia, 1996:34-75.
34. Gilasi HR, Holakooee Naini K, Zafarghandi MR, et al. Relationship between mustard gas and cancer in Iranian soldiers of imposed war in Isfahan Province: a pilot study. J Sch Pub Health Inst Health Res 2006; 4: 15-23.
35. Kakooyee SH, Rad M, Zia N. Incidence of oral soft tissue lesions in chemical victims of Kerman. J Isfahan Univ Med Sci 2009;5: 171-9.
36. Safarinejad MR, Moosavi SA, Montazeri B. Ocular injuries caused by mustard gas: diagnosis, treatment, and medical defense. Mil Med 2001; 166: 67-70.
37. Vedder EB. The medical aspects of chemical warfare. Williams & Wilkins, Baltimore.USA. 1925.
38. Chiesman WE. Lesions due to vesicants: diagnosis and treatment. Br Med J 1944; 2: 109-12.
39. Wattana M, Bey T. Mustard gas or sulfur mustard: an old chemical agent as a new terrorist threat. Prehosp Disaster Med 2009;24:19-31.
40. Heyndrickx A, (Ed.). Proceedings of the first world congress on new compounds in biological and chemical warfare, Rijksuniversiteit, Ghent, Belgium. 1984.
41. Rice P. Sulphur mustard injuries of the skin, pathology and management. Toxicol Rev 2003; 22: 113-8.
42. Marrs TC, Maynard RL, Sidell FR. Chemical warfare agents: toxicology and treatment. Wiley publishing, New York; 1996.
43. Dacre JC, Goldman M. Toxicology and pharmacology of the chemical warfare agent sulphur mustard. Pharmacol Rev 1996; 48:289-326.
44. Panahi Y, Moharamzad Y, Beiraghdar F, Naghizadeh MM. Comparison of clinical efficacy of topical pimecrolimus with betamethasone in chronic skin lesions due to sulfur mustard exposure: A randomized, investigator - blind study. Basic Clin Pharmacol Toxicol 2009;104:171-5.
45. Shohrati M, Tajik A, Harandi AA, et al. Comparison of

hydroxyzine and doxepin in treatment of pruritus due to sulfur mustard. Skinmed 2007; 6: 70-2.

46. Shohrati M, Davoudi SM, Keshavarz S, et al. Cetrizine, doxepin, and hydroxyzine in the treatment of pruritus due to sulfur mustard: a randomized clinical trial. Cutan Ocul Toxicol 2007;26:249-55.
47. Saberi M, Zaree Mahmodabady A. The protective effects of N-acetl-cysteine, oxo-thiazolidine-carboxylate, acetaminophen and their combinations against sulfur mustard cytotoxicity on human skin fibroblast cell line (HF2FF). Iran Biomed J 2009;13:215-21.
48. Sawyer W, Nelson P, Hill I, et al. Therapeutic effects of cooling swine skin exposed to sulfur mustard. Mil Med 2002;167:939-43.
49. Kehe K, Thiermann H, Balszuweit F,et al. Acute effects of sufur mustard injury -- Munich experiences. Toxicology 2009;263:3-8.
50. Davoudi SM, Shohrati M, Sadr B. Prevalence of skin tumors among chemical veterans in 17 provinces of the country and comparison with normal population. J Army Univ Med Sci Iran 2007;4:751-4.