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# Original Article

# Delayed ocular complications of mustard gas poisoning and the relationship with respiratory and cutaneous complications

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## Abstract

**Background:** This study was aimed to determine the correlation between ocular complications and respiratory or cutaneous complications in a group of 40 Iranian veterans with late complications of sulphur mustard (SM) poisoning.

**Methods:** Thorough ophthalmologic examination was performed on all severely SM-poisoned veterans in the province of Khorasan, Iran. Spirometric evaluation of pulmonary function, as well as estimation of the burned skin area, was performed for all the patients. The severities of ocular, respiratory and cutaneous complications were classified into four grades in each patient and were compared with each other, using Spearman's rank correlation test.

**Results:** Forty male patients (aged 43.8 ± 9.8 years) with confirmed SM poisoning were studied 16–20 years after their initial exposure. Common symptoms were recorded as itching (42.5%), burning sensation (37.5%), photophobia (30%) and tearing (27.5%). Abnormal conjunctival and limbal findings were chronic conjunctivitis (17.5%), perilimbal hyperpigmentation (17.5%), vascular tortuosity (15%) and limbal ischaemia (12.5%). Abnormal corneal findings were subepithelial opacity (15%), corneal thinning (15%), diffuse corneal opacity (10%), neovascularization (7.5%) and epithelial defects (5%). A significant positive correlation was found between the severity of ocular and respiratory complications ($r = 0.322$, $P = 0.043$). Cutaneous complications revealed no significant correlation with either ocular or respiratory complications.

**Conclusions:** SM causes delayed destructive lesions in the ocular surface and cornea, leading to progressive visual deterioration and ocular irritation. Late complications of SM poisoning in the eyes, respiratory system and skin are mainly due to SM's local irritant effects.

**Key words:** chemical warfare agent, delayed keratitis, poisoning, sulphur mustard.

## Introduction

Sulphur mustard (SM) is an alkylating chemical warfare agent (CWA) that was widely used during World War I and by Iraqi forces against Iranian soldiers between 1983 and 1988.[1] Eyes, skin and the respiratory system are the three major targets for the local toxic effects of SM. When absorbed in large amounts, it can also damage rapidly proliferating cells of the bone marrow and may result in both short-term and long-term impairment of the immune system.[2–4]

The ocular complications of mustard gas were studied for the first time during World War I. Initial clinical signs occur about 1 h after exposure, starting with a sensation of grittiness, a progressive soreness and a bloodshot appearance, then proceeding to acute conjunctivitis. After several hours, the corneal epithelium begins to vesicate and slough, leading to severe pain, blepharospasm and decreased visual acuity. Gradual spontaneous recovery usually occurs after 48 h, with full regeneration of the corneal epithelium within 4 to 5 days. Complete symptomatic recovery, however, may take 6 weeks or longer.[5–8]

A most distressing ocular phenomenon, known from the First World War but has also now been observed in the Iranian veterans, is the development of delayed keratitis of the eyes after a long asymptomatic period. In the acute stage, the limbal region frequently presents a marbled appearance in which porcelain-like areas of ischaemia are surrounded by

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blood vessels of irregular diameter. Later, the vascularized scars of the cornea often contain deposits of cholesterol, calcium and fat. The lesions recur even after corneal transplantation and may lead to late-onset blindness.[9,10] The pathogenesis of this complication is unknown, but degenerative processes, as well as immune reactions against corneal proteins, have been suggested as the cause of long-term damage.[10,11]

Javadi *et al*. have suggested that delayed keratitis due to SM exposure generally occurs in patients who suffer multi-organ complications.[12] However, the correlation between delayed ocular complications and SM's long-term effects on other target organs has not been previously reported. We conducted this study in order to determine the correlation between ocular complications and respiratory or cutaneous complications in a group of 40 Iranian veterans with late complications of SM poisoning.

## METHODS

### Patients and study design

The Veteran Foundation provided us with the files of all CWA injured patients (1845 veterans) in the province of Khorasan, Iran. We reviewed the files and selected the patients who met the following criteria: (i) documented exposure to SM, as confirmed by toxicological analyses of their urine and vesicular fluid during the war, (ii) significant clinical complications of SM poisoning in their major target organs, namely the skin, eyes and respiratory system. Forty-seven male subjects fulfilled the above criteria. Patients with a known ocular disease before their exposure to SM (one patient with diabetic retinopathy, age 63 years), those with proven systemic illness other than SM poisoning (one patient with tuberculosis, age 48 years), as well as cigarette smokers (three patients, ages 37, 42 and 56 years), were excluded. Following these exclusions, 40 patients volunteered to participate in the study and signed the written informed consent. All these patients had their initial admissions in Imam Reza university teaching hospital between 1983 and 1988 and have had regular outpatient follow ups since then.

After approval by the medical ethics committee of the university, the patients were hospitalized in the Toxicology Ward of Imam Reza Hospital where they underwent a thorough history and physical examination by the experienced ophthalmologist on our research team. Dermatologic examination and spirometric assessment of pulmonary function were also performed for the severity grading of cutaneous and respiratory complications in each patient.

### Ocular examination

Distance and near visual acuity, both presenting the best corrected after refraction, were measured with logarithm of minimal angle of resolution (logMAR) charts under standard conditions. External ocular examination, assessment of pupillary reaction and anterior segment examination with slit-lamp biomicroscope were done. Intraocular pressure was measured with Goldman applanation tonometer. The pupils of all subjects were dilated unless contraindicated because of risk of angle closure. After dilation, the lens was examined with slit-lamp. Stereoscopic fundus examination was performed at the slit-lamp with a 78-diopter lens and with the indirect ophthalmoscope and a 20-diopter lens. Schirmer's test with anaesthesia was performed for all the subjects.

### Severity grading of ocular complications

The severity of ocular complications was classified into four grades as described below. (i) No specific ocular complications (grade 1): no objective sign with or without any of the following symptoms: photophobia, foreign body sensation, burning sensation, itching, tearing, eye pain and reading difficulties. (ii) Mild ocular complications (grade 2): any of the grade 1 manifestations plus conjunctival or palpebral abnormalities such as hyperemia, blepharitis, meibomian gland dysfunction, conjunctival concretion, giant papillary conjunctivitis, and vision <0.05 logMAR. (iii) Moderate ocular complications (grade 3): any of the grade 2 manifestations plus mild corneal lesions such as epithelial and subepithelial corneal opacity, superficial punctuate keratitis, early band keratopathy, micropannus (<2 mm), perilimbal hyperpigmentation, superficial corneal vascularization, tear film abnormalities (Schirmer test with anaesthesia = 5–10 mm in 5 min), and vision or red reflex of 0.05–0.3. (iv) Severe ocular complications (grade 4): any of the grade 3 manifestations plus severe corneal lesions such as melting, thinning, hyaline deposition, deep corneal vascularization, macro-pannus (>2 mm), diffuse corneal opacity, descematocele, severely impaired lacrimation (Schirmer test with anaesthesia <5 mm in 5 min), and vision of >0.3.

### Severity grading of cutaneous and respiratory complications

Pulmonary function variables were measured, using a flow-sensing spirometer (FUDAC 50; FUKUDA Sangyo, Chiba, Japan). The severity grading of respiratory impairment was based on the values of patients' forced vital capacity (FVC) and forced expiratory volume in the first second (FEV1). Normal respiratory function (grade 1) was defined as an FVC ≥ 80 and an FEV1 ≥ 80% of predicted. Mild respiratory impairment (grade 2) was defined as an FVC 60–79% or an FEV1 60–79% of predicted, moderate (grade 3) as an FVC 50–59% or an FEV1 40–59% of predicted, and severe (grade 4) as FVC < 50% or FEV1 < 40% of predicted.

The percentage of burned skin area in each patient was estimated, using Wallace's 'Rules of Nines.' Patients without specific objective findings were classified in grade 1 (no specific cutaneous complications). Those with burn scars involving 1–18%, 19–36%, and >36% of the total body surface area were classified in the grade 2 (mild), grade 3

(moderate) and grade 4 (severe) of cutaneous complications, respectively.

### Statistical analysis

The severity graded organ complications were compared with each other, using Spearman's rank correlation test. SPSS version 11.5 (SPSS, Chicago, IL, USA) was used throughout with the minimum level of significance set at $P = 0.05$ for all the comparisons.

## Results

The age range of the patients was 32–76 (43.8 ± 9.8) years. The patients were studied 18.0 ± 1.5 years (a range of 16–20 years) after their initial exposure. Some of our patients received medications such as artificial tears and lubricant ointments for ocular dryness. None of them had undergone any surgical interventions for ocular complications of CWAs.

### Subjective ocular findings

Only one patient had no complaints of eye complications. The symptoms were recorded as itching (42.5%), burning sensation (37.5%), photophobia (30%), tearing (27.5%), premature presbyopia with reading difficulties (10%), ocular pain (2.5%) and foreign body sensation (2.5%).

### Objective ocular findings

Patients' visual acuity varied considerably from 1.4 to zero of logMAR unit. Best corrected visual acuity was <0.05 in 25 (62.5%), 0.05–0.3 in 10 (25%) and >0.3 in five (12.5%) patients. Abnormal conjuctival and limbal findings were recorded as pinguecula in 25 (62.5%), pterygium in seven (17.5%), chronic conjunctivitis in seven (17.5%), perilimbal hyperpigmentation in seven (17.5%), vascular tortuosity in six (15%), limbal ischaemia in five (12.5%) patients. None of the patients revealed symblepharon. Abnormal corneal findings were recorded in the following order: subepithelial opacity in six (15%), corneal thinning in six (15%), diffuse corneal opacity in four (10%), micro/macro pannus in three (7.5%), corneal neovascularization in three (7.5%) and corneal epithelial defect in two (5%) patients. Lipid and hyaline deposits were found in eight (20%) patients. Abnormal findings in the 11 patients who had corneal lesions (grade 3 and 4 ocular complications) were mostly bilateral (9 patients) and symmetric (7 patients). Schirmer test with anaesthesia revealed normal function of the lacrimal glands in 28 (70%), mild dry eye (5–10 mm of wetting in 5 min) in eight (20%) and severe dry eye (less than 5 mm of wetting in 5 min) in four (10%) patients. Intraocular examination and fundoscopy were normal in all the patients.

### Comparison of severity graded organ complications

The severity grades of complications in the eyes, the respiratory system and the skin of patients are summarized in Table 1. Comparison of severity graded complications in these organs revealed a significant positive correlation between the severity of ocular and respiratory complications ($r = 0.322$, $P = 0.043$) as shown in Figure 1. No significant correlation was found between the severity of cutaneous complications and either ocular ($r = -0.068$, $P = 0.679$) (Fig. 2) or respiratory ($r = 0.011$, $P = 0.947$) (Fig. 3) complications.

## Discussion

Sulphur mustard [bis-(2-chloroethyl)sulphide] is a colourless to amber oily liquid which has the odour of onion, garlic or mustard, hence its name.[13,14] Eyes are the most sensitive

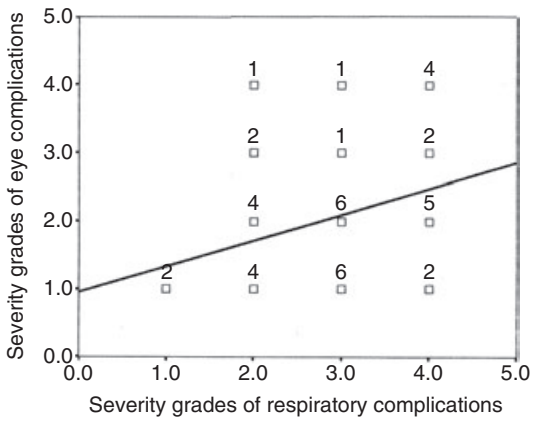


**Figure 1.** The comparison of severity graded ocular and respiratory complications in 40 Iranian veterans with long-term toxic effects of sulphur mustard poisoning. $r = 0.322$, $P = 0.043$.

**Table 1.** Severity graded organ complications in 40 Iranian veterans with long-term toxic effects of sulphur mustard poisoning

| Complication | Number of patients with | | | |
|---|---|---|---|---|
| | No specific complications (grade 1) | Mild complications (grade 2) | Moderate complications (grade 3) | Severe complications (grade 4) |
| Respiratory tract | 2 | 11 | 14 | 13 |
| Skin | 12 | 10 | 8 | 10 |
| Eye | 14 | 15 | 5 | 6 |

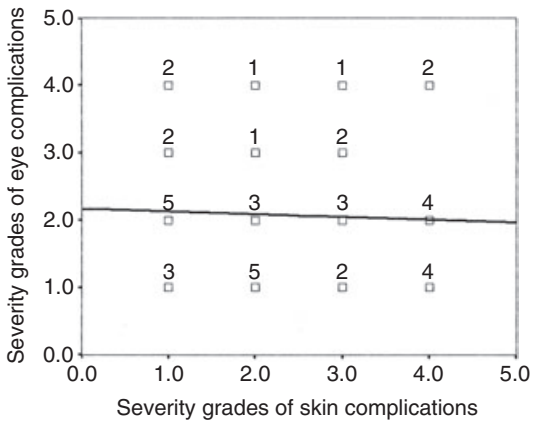


**Figure 2.** The comparison of severity graded ocular and cutaneous complications in 40 Iranian veterans with long-term toxic effects of sulphur mustard poisoning. $r = -0.068$, $P = 0.679$.

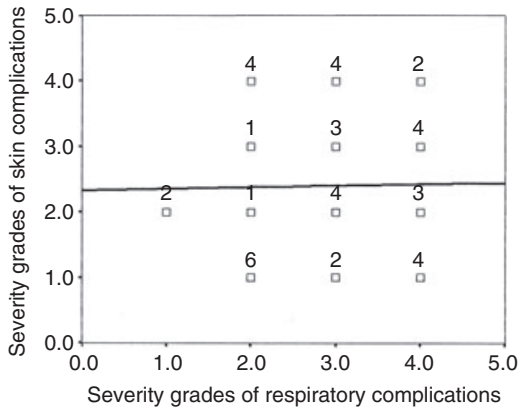


**Figure 3.** The comparison of severity graded respiratory and cutaneous complications in 40 Iranian veterans with long-term toxic effects of sulphur mustard poisoning. $r = 0.011$, $P = 0.974$.

organs to SM. This marked hypersensitivity is attributed to several ocular features including the aqueous-mucous surface of the cornea and conjunctiva, as well as the high turnover rate and intense metabolic activity of corneal epithelial cells.[7,15] Eye contact with mustard gas can cause lacrimation, oedema, discharge, and temporary blindness caused by blepharospasm within 3–12 h post-exposure. This might be followed later by conjunctivitis, opacity, and sometimes even corneal ulceration in cases of severe exposure. Most patients, however, usually recover completely after a few days to a couple of weeks.[6,7]

Unlike early ocular complications, a kind of delayed ulcerative keratopathy, may develop in severely poisoned patients, leading to permanent residual effects. This usually starts with a sudden onset of photophobia, tearing, and decreasing vision after a long latent asymptomatic period.[16–18] The maximum incidence usually occurs 15–20 years after the initial injury,[19] but latency periods as long as 40 years[9,10] and as short as 1 year[12] has also been reported.

Typically, patients develop late recurrence of keratitis and persistence of porcelain white areas in episcleral tissues, resulting in the worsening of the opacification, recurrent ulceration, pain and blindness. Accompanying this pathology is deep blood vessel ingrowth into the cornea, characterized by varicose and tortuous vessels. In advanced cases, the cornea is opaque and covered with crystal and cholesterol deposits.[9,10]

Revealing a combination of corneal vascularization, thinning, epithelial defect and opacity, 15% of our patients were diagnosed with delayed keratitis. In comparison to a 0.5–1% incidence of delayed keratitis, observed in the World War I SM casualties, the frequency of this complication was noticeably higher in our patients. This is probably related to our patient selection which included only severely intoxicated cases that were in the maximum incidence period for the development of delayed keratitis.

The exact pathogenesis of this condition, however, is still unkonown. Inhibition of respiratory enzymes resulting in the formation of free radicals has been suggested as the underlying pathomechanism affecting predominantly germinative epithelial cells in the ocular surface.[20] Byproducts toxicity,[21] necrotic changes after the initial injury,[22] destruction of the limbal vasculture, and degenerative processes[10,11] have also been proposed as causes of long-term damage.

Recent research suggests that the loss of ocular epithelium is a key factor in persistent epithelial defects of the cornea. Even when the cornea itself has not been damaged, loss of stem cells can result in persistent epithelial defects that will encourage inflammatory cell invasion, vascularization and scarring. To the best of our knowledge, no clinical trial has been done to study this problem, but numerous individual reports and clinical observations have shown that small conjunctival transplants from the limbus of an unaffected eye to the injured eye can eliminate these recurrent erosions and inflammation propensities.[23]

Another hypothesis suggests that SM reacts with and alters corneal proteins, resulting in collagen-mustard compounds that encourage autoimmune reactions against the cornea.[10,18] In a study of 48 SM-injured Iranian veterans with delayed keratitis, Javadi *et al.* indicated that the perilimbal site of the lesions, their similarity to Mooren's ulcer, and the histopathological findings, indicating lymphoplasmocyter infiltrate within substantia propria, may point to an immunological basis for SM-induced delayed keratitis.[12]

It is well documented that skin exposure sufficient to cause severe vesiculation and skin necrosis has been associated with systemic toxicity.[24] Boursnel *et al.* demonstrated that following intravenous administration of radiolabelled SM in rabbits, the level of radioactivity in tissues was highest in the kidneys, followed by the lungs and then the liver. Therefore, they suggested that some SM exposure of the respiratory tract, with subsequent biological effects, could occur following systemic absorption through skin.[25]

Comparing the severity of different organ complications in this study revealed a significant correlation only between the severity of ocular and respiratory complications. This can be simply attributed to the common site of exposure (face)

for both inhalation and eye injuries and the fact that these two organs are protected simultaneously with a gas mask, whereas a protective suit is required for prevention of skin exposure. Therefore, SM absorbed through the skin has either no significant effect on the respiratory system or it has only a minimal effect which is overshadowed by the severe local effects of the gas on these two organs. The absence of a reliable history regarding the use of protective equipment at the time of exposure is, however, a major limitation of this study.

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