Long-term ocular consequences of sulfur mustard in lung-injured war veterans

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Abstract

Purpose: Ocular and pulmonary involvement are the most important complications of sulfur mustard (SM) that may happen many years after exposure. This study aims to evaluate the severity of ocular involvement and the correlation between late ocular and lung complications in patients exposed to SM.

Methods: This descriptive cross-sectional study was conducted on SM lung-injured war veterans. Status of pulmonary involvement was categorized into normal, mild, moderate, and severe based on the “Forced Expiratory Volume in first second (FEV1)” Status of ocular involvement was also categorized into normal, mild, moderate, and severe, based on the slit lamp findings. Correlation between pulmonary and ocular involvements was evaluated by Spearman rank correlation test.

Results: Totally, 292 war veterans with clinical pulmonary involvement were included in the study. Status of pulmonary involvement was 3.8% normal, 11.2% mild, 16.1% moderate, and 68.9% severe. Status of the ocular involvement was 68.2% normal, 13.8% mild, 5.4% moderate, and 12.6% severe. Among all patients, 96.3% had pulmonary involvement and 32.5% had ocular involvement. There was a positive correlation between the severity of ocular and pulmonary involvements (p = 0.049 and r = 0.122).

Conclusion: The results of this study showed that although there was a positive correlation between the severity of pulmonary and ocular involvement, this correlation was weak. This might be due to the nature of the studied population or differences in the tissue susceptibilities, gas types, or exposure patterns.

Keywords: Sulfur mustard, long-term toxicity, lung injuries, ocular injuries

Introduction

Sulfur mustard (SM) is a well-known multiorgan toxic vesicant agent. Exposure of human beings to vesicant agents in the forms of liquid, aerosol, or vapor leads to severe chemical burns. Moist tissues such as the eyes, respiratory tract, and auxiliary areas are particularly more sensitive (1,2). The vital organs in SM war victims have shown some degrees of damages, even if they were several kilometers from the site of accident (3). Despite more than 90 years of experience with the serious consequences of SM, there is still no effective and specific antidote for this agent (4). More than 100,000 Iranians suffered from late-onset and chronic complications of mustard gas exposure. Lungs (42.5%), eyes (39.3%), and skin (24.5%) are the most sensitive target organs for acute or late-onset complications (5).
Pulmonary complications are known to occur in over half of the patients (6). About 45,000 Iranians (both civilians and veterans) are affected with late pulmonary complications of mustard gas (7). An in vitro study has showed that inhalation of 300 µmole of SM per liter of air (µmoll/L) for 12–24 h or 1000 µmoll/L for 8 h will lead to 50% reduction in barrier function of the pulmonary cell layers (8). In acute phase, respiratory problems are rhinorrhea, laryngitis, tracheobronchitis, and dyspnea. In chronic phase, main late respiratory complications are chronic obstructive pulmonary disease, bronchiectasis, asthma, large airway narrowing, small airway disease, and pulmonary fibrosis (9,10). Both the severity and incidence of late respiratory complications increase during the long-term follow-up (10).

Ocular injury is one of the most immediate and distressing problems (11). In acute phase, ocular manifestations are foreign body sensation, tearing, photophobia, blepharospasm, and corneal epithelial defects (9). Conjunctival dysplasia, mild inflammation, and squamous metaplasia have been reported in the early stages after exposure to mustard gas (12). In chronic phase, delayed keratitis that may appear many years after the initial exposure, appears as perilimbal conjunctival ischemia, corneal epithelial defects, neovascularization, amyloid depositions, lipoid depositions, thinning, and melting (9,13).

A positive correlation among severities of ocular, pulmonary, and cutaneous involvements has been reported in none selected group of patients with SM exposure (14–17). This study has exclusively reviewed the correlation between the severities of pulmonary and ocular involvements in a selected group of patients with severe SM-induced lung injuries, regardless of the severities of the other organs involvement.

**Materials and methods**

In this descriptive cross-sectional study, patients with SM-induced lung injuries were evaluated. The study protocol was based on the tenets of the Declaration of Helsinki and approved by the institutional review board and ethics committee of Shahed University Research Center and Janbazan Medical and Engineering Research Center (JMERC). Mustard gas exposure was confirmed by reviewing documented medical and military records of the patients. Enrolments of the patients were based on the presence of chronic pulmonary symptoms (chronic cough, sputum, hemoptysis, and dyspnea), signs (crackles, rales, wheezing), and history of hospitalization. Those patients who were smokers or had pulmonary disease other than SM lung injuries were excluded from the study. All eligible patients were recalled for simultaneous complete pulmonary and ocular examinations during 3 consecutive days. All patients with ocular and/or pulmonary involvements were under special treatment for their symptoms based on the severity of involvements since the time of exposure. An informed consent was obtained from all the participants. The status of the ocular and pulmonary involvement was categorized based on our previous reports and the standards of Organization of Veteran’s Affair (5,17–19).

All patients received complete pulmonary examinations and spirometry (Body box, Zan 530, Germany). Based on forced expiratory volume in first second (FEV1) results, status of pulmonary involvement was categorized as normal (FEV1 ≥ 80), mild (65 ≤ FEV1 < 80), moderate (50 ≤ FEV1 < 65), and severe (FEV1 < 50) at the time of examination.

A complete ophthalmic examination including uncorrected and corrected visual acuity measurement, slit lamp biomicroscopy, applanation tonometry, and funduscopy was performed. In each follow-up visit, digital photography was taken by a digital slit lamp (Topcon Digital Slit lamp SLD Seri 4 Japan). All digital photographs were reviewed and their clinical grades were categorized.

Ocular surface status was graded as normal, mild, moderate, and severe. Changes of conjunctival vessels including dilation, telangiectasia, tortuosity, segmentation, and subconjunctival hemorrhage were characteristics of the mild group. The adjacent corneal quadrant was clear (Figure 1). Limbal ischemia and peripheral vascular invasion with or without corneal opacity were features of the moderate group (Figure 2). If previous findings were accompanied by corneal thinning and melting, it was considered as severe (Figure 3).

Spearman rank correlation test was used to evaluate any correlation between the severity of ocular and pulmonary complications.

**Results**

Totally, 292 war veterans (all male) with clinical pulmonary involvement were included and all patients completed the study. The mean age of the patients was 46 ± 7.5 (range, 27–75) years. The mean time interval
between exposure and the examination was 21.2 ± 2.0 years.

Ocular surface manifestations were conjunctival vascular injection (18%), tortuosity (47.5%), and ischemia (12.3%), corneal opacity (26.7%), hyperpigmentation (21.2%), neovascularization (15.1%), thinning (12.3%), and epithelial defects (7.9%). There was no significant posterior segment abnormality.

Status of the ocular involvement was categorized as normal (68.2%), mild (13.8%), moderate (5.4%), and severe (12.6%).

Based on FEV1 results, the status of pulmonary involvement was categorized as normal (3.8%), mild (11.2%), moderate (16.1%), and severe (68.9%).

Among all patients, 96.3% had pulmonary involvement and 32.5% had ocular involvement. Simultaneous ocular and pulmonary involvements were seen in 31.8% of all patients. Severities of the ocular and pulmonary involvements are summarized in Table 1.

Although weak, there was a positive correlation between the severities of ocular and pulmonary involvements by Spearman rank correlation test ($p=0.049$ and $r=0.122$). Severities and correlations of the ocular and pulmonary involvements in SM-injured patients in different studies are compared in Table 2.

### Discussion

Delayed keratitis is the most dangerous sight-threatening complication of SM, which requires long-term ophthalmic surveillance and therapy. In this study, 31.5% of patients with pulmonary manifestations had simultaneous ocular involvement, of them 17.8% had moderate to severe keratitis.

Progressive limbal stem-cell deficiency (LSCD) induced by SM causes varying degrees of ocular surface

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
<th>Ocular status</th>
<th>Pulmonary status</th>
<th>Normal (%)</th>
<th>Mild (%)</th>
<th>Moderate (%)</th>
<th>Severe (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghassemi-Broumand et al.</td>
<td>2004</td>
<td>500</td>
<td>Normal (0%)</td>
<td>Normal (3.8)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>3.8</td>
</tr>
<tr>
<td>Etezad-Razavi et al.</td>
<td>2006</td>
<td>40</td>
<td>Normal (3.5)</td>
<td>Normal (9.6)</td>
<td>0.8</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
<td>11.2</td>
</tr>
<tr>
<td>Ghassemi-Broumand et al.</td>
<td>2008</td>
<td>600</td>
<td>Normal (45.6)</td>
<td>Normal (9.2)</td>
<td>4.6</td>
<td>0.4</td>
<td>4.6</td>
<td>10.3</td>
<td>68.9</td>
</tr>
<tr>
<td>This study</td>
<td>2010</td>
<td>292</td>
<td>Normal (68.2)</td>
<td>Normal (68.2)</td>
<td>13.8</td>
<td>5.4</td>
<td>12.6</td>
<td>11.2</td>
<td>100.00</td>
</tr>
</tbody>
</table>

$N=Numbers$ of cases.

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problems including corneal conjunctivalization and recurrent/persistent epithelial defects (20–24). Tear film abnormalities and secondary eyelid inflammations including meibomian gland dysfunction cause severe photophobia and tearing (21). In a report on 48 patients with moderate to severe ocular involvement, ocular manifestations were chronic blepharitis and decreased tear meniscus height (100%), perilimbal conjunctival ischemia (81.3%), conjunctival vascular abnormalities (50%), corneal opacity (87.5%), neovascularization (70.8%), thinning (58.3%), lipid deposition (52.1%), amyloid deposition (43.8%), and corneal epithelial irregularity or defects (31.3%) (22). In another report on 40 patients with moderate to severe forms, ocular findings were chronic conjunctivitis (17.5%), vascular tortuosity (15%), limbal ischemia (12.5%), corneal subepithelial opacity (15%), corneal thinning (15%), diffuse corneal opacity (10%), neovascularization (7.5%), and epithelial defects (5%). A significant correlation was reported between the severities of ocular and respiratory involvements ($r = 0.322, p = 0.043$) (23).

Pulmonary manifestations in acute phase are rhinorrhea, laryngitis, tracheobronchitis, and severe dyspnea. In late phase, main respiratory complications are chronic obstructive pulmonary disease, bronchiectasis, asthma, large airway narrowing, pulmonary fibrosis, bronchial wall thickening, interstitial lung disease, and emphysema (9, 17, 19, 25). Bronchiolitis has been shown as one of the main pathological mechanisms of lung lesions in SM-exposed patients (26). Acute lung injuries after SM inhalation are characterized by massive, localized hemorrhage, and alveolar edema, which implies severe disruption of the vascular and distal airway barriers (8). In vitro studies showed upper airway and deep lung epithelial cells apoptosis (27).

Late clinical manifestations of mustard gas keratopathy seem to be the result of four underlying mechanisms:
1. Progressive LSCD, which at the beginning is partial and asymmetric and finally leads to total LSCD (18, 22).
2. Chronic, progressive, and severe perilimbal conjunctival ischemia, which can lead to corneal neurotrophic and trophic changes (17, 18, 23, 28).
3. Lipid deposition resulting from invading telangiectatic vessels, triggering chronic stromal inflammation, and thinning (29).
4. Immune-mediated mechanisms that sometimes lead to inflammatory corneal infiltrates and melting (22, 30–35).

The same pathophysiologic mechanisms including progressive pulmonary airways epithelial or parenchymal stem-cell deficiency, ischemia, telangiectasia, vasculitis, lipid and amyloid depositions, and immune mechanisms may lead to pulmonary manifestations. Since the time of exposure and for a long period of time, all patients with SM-induced organ injuries needed to receive specific treatment based on the severity of involvements with comments relevant specialist.

In this study, there was a weak positive correlation between the pulmonary and ocular involvement. Logically, in none of the selected groups, simultaneous late pulmonary and ocular complications with the same severity would be expected. This controversy may be due to the type of the study that has been carried out on a selected group of patients with severe pulmonary involvement, differences in gas types/concentrations, exposure times, different protective equipments or personal devices (tissue versus mask, closing the eyes or holding the breath, using wet tissues in front of the eyes or mouth), genetic susceptibilities, availability and immediacy of medical managements.

In conclusion, the results of this study showed that there was a positive correlation between pulmonary and ocular involvement, but this correlation was weak. This might be due to characteristics of the studied population who were categorized as a group of patients with severe pulmonary involvement regardless of the severities of other organs involvement.

**Declaration of interest**

The authors declare no potential conflict of interest.

**References**