**SULFUR MUSTARD GAS EXPOSURE: CASE REPORT AND REVIEW OF THE LITERATURE**


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**Introduction**

Sulfur mustard (SM) is a toxic, vesicant, blistering, alkylating nucleophile, and a strong lipophilic chemical agent. It was used extensively during the Gulf War, affecting potentially 100,000 United States (US) soldiers. SM exposure is uncommon in the US and therefore a paucity of data can be found related to its presentation and management. Nonetheless, because of its serious implications in various biological systems and with many cities around the world unfortunately witnessing terrorist attacks, a thorough understanding of presenting symptoms, diagnostic aspects, therapeutic options, and preventative measures is warranted. Here we describe a case of burn injury caused by SM exposure and review the salient clinico-pathologic features and treatment principles associated with exposure to this toxic gas.

**Case Report**

A healthy 21-year-old male, active duty marine sustained burns from mustard gas after a weapons cache exploded in Iraq. He was initially transferred to Germany for medical stabilization and then to Bethesda for definitive care. Follow-up was arranged at our outpatient burn center, as it was closer to the patient’s home. Upon follow-up, the patient complained of new onset burning pain to his left hand, right upper extremity, right thigh, and left calf persisting for approximately 2 weeks despite the use of oral narcotics. Physical examination revealed extremely tender areas of skin erythema with various size bullous lesions (Fig. 1). The patient was admitted to the burn service for local wound debridement, local wound care (with 1% silver sulfadiazine), and pain control. Debridement of blisters revealed a wound base with superficial partial thickness burn surrounding a central area of mid to deep partial thickness burn. Over the following 48 hours, his wound began to epithelialize, his pain was better controlled, and the patient was discharged. At 2 weeks follow-up, his wounds were noted to be fully epithelialized, and the patient had maintained full range of motion. His only complaints at that time were pruritus and unstable scars (Fig. 2).

**Discussion**

Sulfur mustard gas (dichlorodiethylsulfide) is the prototypical vesicant alkylating agent used in the fabrication of chemical weapons. It was first used by the Germans during World War I (1917) causing over 125,000 casualties. It was then used in World War II and during the Iran-Iraq war (1980-1988) affecting thousands of US soldiers. It is an oily liquid that can be easily aerosolized by spraying or dispersed by explosive blasts. In temperate climates (as in Europe during World Wars I and II), it vaporizes...
slowly, posing particular risk in prolonged, closed-space or below grade exposures. At higher temperatures (as in the Persian Gulf during the Iran-Iraq war), vaporization increases markedly and contributes to dispersion.

Due to its low volatility, in open areas with little wind, mustard gas can persist in the air for more than a week, especially in temperate climates. Battlefield air concentrations during World War I, for example, approached 19-33 mg/mm³. At such concentrations, exposure for several minutes can potentially lead to skin and eye injury. Longer exposures (30-60 minutes) can result in severe respiratory injury, systemic poisoning, or even death. Although SM exposure outside of war zones is rare, burn surgeons should be made aware of the clinical features and treatment of such injuries; and therefore we will outline the salient clinical manifestations, summarize its mechanism of action and histological features, and highlight management/treatment principles.

**Mechanism of action**

Sulfur mustard rapidly alkylates the purine bases (adenine & guanine) of DNA which triggers the activation of endonucleases for depurination (excision) of the alkylated bases, leaving apurinic sites where DNA breaks readily occur. This creates a considerable need for DNA repair, activating poly-(ADP ribose) polymerase enzymes that rapidly deplete NAD+. Depletion of NAD+, which typically occurs within an hour of exposure and is highest after four hours, inhibits glycolysis, leading to the release of multiple proteases that ultimately result in tissue necrosis. Tissue necrosis occurs in the affected system, namely in the skin (producing vesication of the epidermis), in the hematological system (leading to pancytopenia), in the respiratory system (causing respiratory failure), and in the gastrointestinal system (leading to mucositis). Death may occur, and mortality rates in the Iran-Iraq War were reported to be as high as 3-4%. Death was attributed to respiratory failure or bone marrow suppression.

**Clinical Manifestations**

A 4-12 hour asymptomatic latency period, depending on the extent and dose of exposure (Table I), is not uncommon; and victims generally present with multiple sites of involvement (Table II).

**Skin lesions**

Direct skin exposure to SM gas leads to a dose-dependent injury that ranges from mild erythema and edema

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**Table I - Onset of symptoms and exposure dose**

<table>
<thead>
<tr>
<th>Exposure dose (mg/min/m³)</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>Onset of eye pain</td>
</tr>
<tr>
<td>100 - 400</td>
<td>Onset of respiratory and skin effects</td>
</tr>
<tr>
<td>200 – 1000</td>
<td>Onset of skin burns</td>
</tr>
</tbody>
</table>

**Table II - Typical onset of symptoms and signs over time**

<table>
<thead>
<tr>
<th>Time after Exposure</th>
<th>Symptoms and Signs</th>
</tr>
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<tbody>
<tr>
<td>30 – 60 minutes</td>
<td>Nausea, vomiting, eye pain</td>
</tr>
<tr>
<td>2 – 6 hours</td>
<td>Eye pain, lacrimation, photophobia, rhinorrhea, sneezing, and sore throat</td>
</tr>
<tr>
<td>6 – 24 hours</td>
<td>Erythema, hoarseness, non-productive cough</td>
</tr>
<tr>
<td>24 – 48 hours</td>
<td>Skin blistering, productive cough</td>
</tr>
<tr>
<td>2 – 6 days</td>
<td>Ocular recovery starts, hyperpigmentation, secondary infections</td>
</tr>
<tr>
<td>6 days – 6 months</td>
<td>Resolution</td>
</tr>
</tbody>
</table>

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**Fig. 1** - Patient presentation to our outpatient burn clinic. Note diffuse erythema with multiple, large bullous lesions to the right forearm (top) and the dorsum of the left hand (bottom).

**Fig. 2** - Hyperpigmentation of left forearm (top) and right hand (bottom) noted at outpatient follow-up, 3 weeks after initial presentation.
to severe necrosis and vesiculation (Table III). Early onset skin lesions consist of erythema, purpura, and bullae of different sizes. Bullae typically appear over already erythematous lesions, but may also form on unaffected sites. Lesions do not form on palms or soles. They typically contain a yellow/straw colored fluid that forms a gel after 24 hours, making drainage of blister fluid more challenging as the clotted material adheres to the dermal bed. If bullae are debrided and drained within the first 24 hours, wounds heal favorably in 1-2 weeks. In contrast, wounds containing bullae drained after 24 hours may result in delayed wound healing (4-6 weeks). Large flaccid bullae may also develop, coalesce, and slough as large sheets of epithelium (Nikolsky’s Sign). The remaining wound bed is a raw, moist, blanching dermis, similar in appearance to a scald. While oral ulcerations are rare, moist or wet skin such as groins and axillae are especially prone to vesication.

Table III - Skin injury patterns due to liquid mustard

<table>
<thead>
<tr>
<th>SKIN INJURY</th>
<th>Clinical Manifestations</th>
<th>Mechanism of Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild Injury</td>
<td>Erythema, edema, first degree burn</td>
<td>Ambient doses of 50mg/min/m² or direct application of 0.1 to 1.0 mg/cm² liquid</td>
</tr>
<tr>
<td>Moderate Injury</td>
<td>Severe edema and vesication</td>
<td>Direct application of 1.0 to 2.5mg/cm²</td>
</tr>
<tr>
<td>Severe Injury</td>
<td>Full thickness skin necrosis surrounded by spreading vesication</td>
<td>Ambient doses of 200 to 1,000mg/min/m² or direct application of more than 2.5mg/cm²</td>
</tr>
</tbody>
</table>

Table IV - Ocular injury patterns due to sulfur mustard

<table>
<thead>
<tr>
<th>EYE INJURY</th>
<th>Clinical Manifestations</th>
<th>Mechanism of Injury</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild Injury</td>
<td>Erythema, edema, epiphora, or mild discomfort</td>
<td>Ambient doses of 12-70mg/min/m²</td>
<td>Within two weeks</td>
</tr>
<tr>
<td>Moderate Injury</td>
<td>Severe pain, blepharospasm, periorbital edema, scleral and conjunctival injection, chemosis, iritis, temporary blindness</td>
<td>Ambient doses of 100-200 mg/min/m²</td>
<td>Three to six weeks</td>
</tr>
<tr>
<td>Severe Injury</td>
<td>Permanent blindness</td>
<td>Ambient doses more than 200mg/min/m³</td>
<td>Very rare</td>
</tr>
</tbody>
</table>

In addition to delayed wound healing and its increased risk of secondary skin infection, patients often develop unstable scars (as our patient did) making them prone to blistering from minor shear forces. Still in the majority of cases, skin ulcerations heal with minimal to no scarring. Urticaria may present during follow-up, the pathophysiology of which is currently unknown; however, it may involve a hypersensitivity reaction or even a psychological component. Days to weeks after exposure, patients may develop areas of scaling over previously erythematous skin. More severe forms of scaling may occur, such as exfoliative erythroderma, but are extremely rare.

Late skin manifestations for SM gas exposure most frequently involve varying degrees of pigmentation. Such changes include:

1. Post-inflammatory hypo and/or hyperpigmentation at the site of a previous lesion;
2. Peri-follicular hypo and/or hyperpigmentation secondary to mild peri-follicular inflammation in the absence of a previous lesion;
3. Generalized hyperpigmentation, affecting the entire surface of the skin;
4. Generalized hypo and hyperpigmented macules and patches resembling tinea versicolor; and
5. Hyperpigmented lesions over areas subjected to chronic pressure.

Delayed onset of purpura and ecchymoses are rare manifestations.

Histological changes in SM exposed skin have been well described. Three to six hours after exposure, nuclear pyknosis of basal keratinocytes become pyknotic. Progression of injury leads to degeneration of basal cells with formation of intracellular and extracellular vacuoles, dissolution of the basal cell layer, and separation of dermis from epidermis. This becomes clinically evident as subepidermal bullae with mild dermal and epidermal necrosis.

Respiratory

Inhalation of sulfur mustard aerosol or vapor can rapidly lead to respiratory failure and death depending on the extent and dose of exposure. Victims initially suffer from tracheobronchitis, with nonspecific symptoms such as sore throat, hoarseness, chest pressure, and non-productive cough. Over the next 12 hours, progression of symptoms leads to sinus pain, tachypnea, bronchospasm, and a productive cough due to sloughed respiratory epithelium and an increase in secretions. Continued exposure may lead to secondary pneumonias, hemorrhagic pulmonary edema, and even respiratory failure within 24-48 hours. Chronic pulmonary manifestations include chronic bronchitis, bronchiectasis, reactive airway dysfunction syndrome and emphysema. There is also evidence to suggest a slightly
increased incidence of lung cancer after a latency of 20 years or more.9,20

Eye
Mustard reacts quickly upon contact with the tissues of the globe although frank clinical symptoms usually develop gradually, four to eight hours after exposure. Injuries to the globe are also dependent on dose and duration of exposure (Table IV). Initial symptoms include eye pain, photophobia, tearing, and blurred vision.21,22 Physical examination may reveal blepharospasm, peri-orbital edema, conjunctival and scleral injection/edema, and anterior chamber cellular infiltrates. Visual acuity is often decreased. After several hours, the corneal epithelium may vescicate and slough. Late recurrences of keratitis and worsening opacifications have been described and can lead to recurrent ulcerations, pain, and blindness.23

Gastrointestinal
Gastrointestinal manifestations are the result of systemic toxicity. Systemic toxicity is encountered with high dose exposures (more than 1,000mg-min/m3) or from swallowing contaminated food or saliva. Nausea and vomiting are common while diarrhea and gastrointestinal bleeding are not.1

Hematological
Bone marrow suppression is also the result of high-dose exposure (more than 1,000mg-min/m3) with subsequent systemic toxicity. Leukocytosis develops and lasts for several days before leucopenia manifests. Leucopenia may not be apparent for five to seven days but reaches a nadir in approximately ten days. Thrombocytopenia may ensue but anemia is noted less frequently. Mustard gas-induced bone marrow suppression is an extremely poor prognostic sign.24

Carcinogenicity
Sulfur mustard is a proven carcinogen. Prolonged and/or repeated exposure to a particular system/organ has been shown to increase its risk of cancer.19,20,24,25,27 World War I veterans who suffered mustard gas exposure in the battlefield had a small but probably significant increase in the incidence of lung cancer compared to veterans not exposed to the gas. Significant increases in the incidence of upper respiratory tract, oropharynx, and skin malignancies, have also been reported among patients who suffered occupational exposure to mustard gas.

Management and Treatment Principles
Regular clothing does not afford adequate protection. Specialized military protective garments are needed; these have a layer of charcoal to absorb the penetrating sulfur mustard and provide approximately six hours of protection after exposure.

Patients presenting with signs and symptoms of upper airway obstruction (i.e. stridor) require immediate endotracheal intubation or, in the presence of severe upper airway edema, tracheotomy.

Once the skin is exposed, rapid removal of the SM substance is crucial as it becomes irreversibly fixed in the tissues within minutes. Mustard scavengers, antioxidants, NAD+ precursors, polymerase inhibitors, and corticosteroids have all shown value in animal models; however, currently there is no accepted antidote for the treatment of SM gas exposure in humans.

Increased survival and fewer pathological organ effects were noted after administration of parenteral doses of sodium tiosulfate (3000mg/kg), vitamin E (20mg/kg), or dexamethasone (8mg/kg) within 15 minutes of exposure. The combination of all three was the most effective.25,26 It is likely that thiosulfate acts as a mustard scavenger, vitamin E as an antioxidant, and corticosteroids act by inhibiting lipoxygenase activity thereby decreasing the synthesis of prostaglandins and leukotrienes. In a rabbit model of mustard gas burns, the topical administration of cortisone following exposure decreased edema and led to shallower skin lesions. Healing time, however, was not affected.27 As mustard is relatively water insoluble, clothing and jewelry must be destroyed. The eyes should be copiously irrigated with water or saline. The skin is washed with mild soap and water with particular attention to the axillae, groin, and perineum. Should water supplies be limited, adsorbent powders such as talc, flour, and Fuller’s earth can be dispersed over affected areas and wiped with moist gauze. The skin can also be decontaminated with chloramine powder and 0.5% hypochlorite solution. These compounds inactivate sulfur mustard, producing free chloride.28 The U.S. military currently utilizes M258A1 kits for skin decontamination: these kits contain two sets of two towelettes, one containing phenol and hydroxide, the other containing chloramine.

Conclusion
Sulfur mustard is the first vesicant used as a chemical weapon causing a high number of injuries on the battlefields of World War I, and is still considered a major chemical agent. Owing to its ease of manufacture and extent of existing stockpiles, mustard was reportedly used in a number of isolated incidents since World War I. Its deleterious metabolic and tissue injury effects span almost every system in the body, and may lead to permanent disability and even death. A systematic multi-disciplinary approach is required for the care of injured patients, and this requires a comprehensive understanding of the various physiologic aspects of this type of burn. If mustard is ever used again, medical personnel must be prepared to accept and care for large numbers of casualties, who will require long-term care.
RÉSUMÉ. Ce rapport décrit un cas de brûlure suite à une exposition au gaz moutarde, un agent chimique utilisé dans la guerre. On présente un examen des caractéristiques de diagnostic, les manifestations cliniques et les mesures thérapeutiques utilisés pour traiter ce phénomène rare, mais extrêmement toxique. L’objectif de ce rapport est de mettre en évidence l’importance de considérer ce diagnostic dans toute victime de la guerre, surtout en ces temps malheureux de la hausse des activités terroristes.

Mots-clés: soufre du gaz moutarde, l’ypérite, brûlure, brûlure chimique

BIBLIOGRAPHY


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