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ORIGINAL ARTICLE

Acute intensive care unit management of mustard gas victims: the Turkish experience*

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ABSTRACT

Purpose: Sulphur mustard (SM) is an highly toxic and vesicant chemical weapon that was used in various military conflicts several times in the history. The severity of ocular, dermal, and pulmonary symptoms that may appear following a characteristic asymptomatic period are depending on the SM concentration and exposure duration. The aim of this study is to present the clinical features and share the intensive care unit (ICU) experiences for the medical management of mustard gas victims.

Materials and methods: Thirteen Free Syrian Army soldiers near Al-Bab region of North Syria were reportedly exposed to oily blackish smoke with garlic smell due to the explosion of a trapped bomb without causing any blast or thermal effect on 26th November 2016. None of them wore any chemical protective suits or gas masks during explosion. Since they observed skin lesions including bullous formation next day, they were admitted to the Turkish Field Hospital at the Turkish – Syrian border and then evacuated to the State Hospital of Gaziantep Province, Turkey for further management. Eight victims who were very close to point of explosion suffered burning eyes, sore throat, dry cough and dyspnoea after the chemical attack.

Results: On admission to hospital, all cases had conjunctivitis, hoarseness and bullae on various body areas. Blepharospasm and opacity were found in 8 patients and 5 of them had corneal erosions and periorbital oedema. Temporary loss of vision in 4 cases lasted for 24 h. Multiple fluid-filled blisters were observed especially on the scalp, neck, arms and hands, where direct skin exposure to the agent occurred. A definitive clinical care and infection prophylaxis measures along with the burn treatment and bronchodilators for respiratory effects were applied in ICU. Two patients received granulocyte-colony-stimulating factor due to the SM-mediated bone marrow suppression on the 16th day of exposure and one of them died because of necrotic bronchial pseudomembrane obstruction resulting in cardiopulmonary arrest.

Conclusions: SM was first used during the First World War and it is still considered one of the major chemical weapons recently used by non-state actors in Syria and Iraq. In case of SM exposure, medical treatment of SM-induced lesions is symptomatic because no antidote or causal therapy does exist even though SM is very well known for over 100 years. However, clinical management in intensive care medicine of SM victims have improved since the 1980s, this study which is one of the largest recent SM-exposed case series since that time is important for the contribution to the clinical experience.

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Chemical warfare agents; sulphur mustard; toxic exposure; intensive care unit; treatment; vesicants

Introduction

Sulphur mustard (SM), a vesicant chemical terror agent, is still a threatening factor from a military perspective. SM, which was first synthesized by Despretz in 1822, was also modified by Niemann and Guthrie in 1860[1]. It was the most devastating chemical warfare agent during the First World War[2]. During the Iran–Iraq War in the 1980s, SM exposure of approximately 100 000 Iranian soldiers was reported[3–5]. It is still considered one of the major chemical terrorism agents, and recent use of SM by various terrorist groups in the Syrian Civil War has been recorded[6,7].

SM, which is an oily liquid, dissolves in most organic solvents and is slightly soluble in water. As it interacts with cellular proteins in somatic cells, it initiates the alkylation of DNA strands, which leads to DNA and RNA damage. This metabolic effect becomes more apparent in cells found in tissues such as in the skin, cornea, bone marrow, trachea and gastrointestinal system, showing increased mitotic activity[2,8]. This tissue damage may lead to cell death and the following clinical findings of SM exposure: bullous formation, bone marrow depression, respiratory symptoms, and gastrointestinal symptoms[5,8].

Symptoms of exposure to previously used chemical agents may provide clues for identifying the clinical presentations of future SM-exposed casualties. Although studies on the effects of SM exposure have been carried out, the mechanisms related to SM pathology have not yet been clearly identified; therefore, proper treatment is still not available. However, great medical knowledge about SM victims was gained after the Iran-Iraq War and recent accidental exposures[4,5,9–11].

This article aims to evaluate the clinical features and medical management of 13 casualties due to SM exposure during

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the Syrian Civil War. The victims were evacuated to the hospital in Gaziantep, Turkey.

Materials and methods

According to the medical histories of the 13 casualties of SM exposure, they experienced a garlic-like scented, dark smoke following the explosion of a trapped improved explosive device (IED) at 2:00 PM on November 26, 2016 in the region of Al-Bab, Syria. None of them declared wearing any chemical protective suits. Five of them were 1–5 m away from the point of explosion, and 3 of them were 6–10 m away. The remaining five victims were inside the military vehicle and suffered slight effects.

All patients outside the vehicle smelled rotten egg or garlic and suffered from burning eyes, sore throat, dry cough and dyspnoea. Their complaints decreased when they left the explosion area. They washed only their hands and faces approximately four hours after exposure and spent the whole night without changing their clothes. The next morning, they observed skin lesions including bullous formation and were admitted to the Turkish Field Hospital, located at the Turkish-Syrian border.

All patients were decontaminated by RM 21 Decontamination Solution (Kärcher, Schwaikheim, Germany) and evacuated to the State Hospital of Gaziantep Province, Turkey. The ages of patients were between 16 and 48 (29.31 ± 9.87 years), and they were hospitalized in the intensive care unit for 10 days to three weeks for further medical diagnosis and treatment.

Results

Ocular injuries and treatment

There were 13 patients with conjunctivitis, 9 patients with photophobia, and 8 patients with blepharospasm and opacity. Five of them had corneal erosions and periorbital and palpebral oedema (Figure 1) and underwent treatment in the ICU. Temporary loss of vision was recorded in four patients during hospitalization, and it lasted for 24 h in all patients followed by total recovery.

A combination of mydriatic (cyclopentolate hydrochloride 1%), antibiotic (gentamicin), and local steroid (dexamethasone) eye drops was applied for 10 days in all patients. Patches were routinely added in patients with vision loss ($n = 4$) because of the adhesion risk. Daily eye examination was performed during the treatments.

Figure 1. Periorbital and palpebral edema (first day after sulfur mustard exposure).

Semi-dense corneal opacity was observed only in 2 of the 12 patients during the pre-discharge eye examination. No pathological ocular findings were observed in any patients one month after discharge from the hospital.

Respiratory injuries and treatment

During the admission, hoarseness, sneezing and progressive pharynx oedema were observed in all patients, and cough was observed in 8 patients. Chest X-rays, arterial blood gas analyses, sputum cultures, and auscultation findings were normal in all 13 patients. Although fiberoptic bronchoscopy was planned in order to control pseudomembrane formations in the lower airways, it was not performed because none of the patients gave formal written consent for this invasive procedure.

The thirteen patients were administered prophylactic parenteral steroids (methylprednisolone) for upper airway oedema for 3 days and inhaled corticosteroid (salbutamol) and parenteral mucolytic (N-acetylcysteine) for 10 days.

Although all bronchial lesions healed, the patient who was closest to the exploded IED died due to sudden respiratory and cardiac arrest on the 18th morning after exposure. In his autopsy, both pulmonary haemorrhage and necrotic bronchial walls were found.

Skin lesions and treatment

During the admission, superficial erythema in different parts of the body was observed in all patients. Multiple fluid-filled blisters were observed in 11 patients, especially on the scalp, neck, arms and hands, where direct skin exposure to the agent occurred. In addition, those patients showed blisters on the skin of body areas including the chest, abdomen and upper back where the agent penetrated the clothing. Formation of new blisters was also observed in patients admitted to the hospital with erythema, specifically on the upper extremities and axilla (Figures 2 and 3).

Biopsies taken from the blister floor and other erosive zones indicated subepidermal blister formation. Nikolsky's sign was positive. The percentage of the total body surface area showing the effects of mustard was more than 25% in 5 patients, between 10% and 25% in 3 patients, and less than 10% in 5 patients. First and second degree burn ratios were between 2% and 45%.

In all cases, parenteral antihistaminic (pheniramine maleate) was applied in order to relieve itching that continued for 7 days. None of the cases required surgical intervention. For the disinfection of skin lesions, antiseptic solution (0.1% octenidine dihydrochloride) and antiseptic gel (0.2% polyhexanide) were administered to skin lesions, including erythema and blisters, twice a day. The lesions were then left open to ease healing. Bed sheets were changed regularly after every antiseptic application. Re-epithelization was observed in all

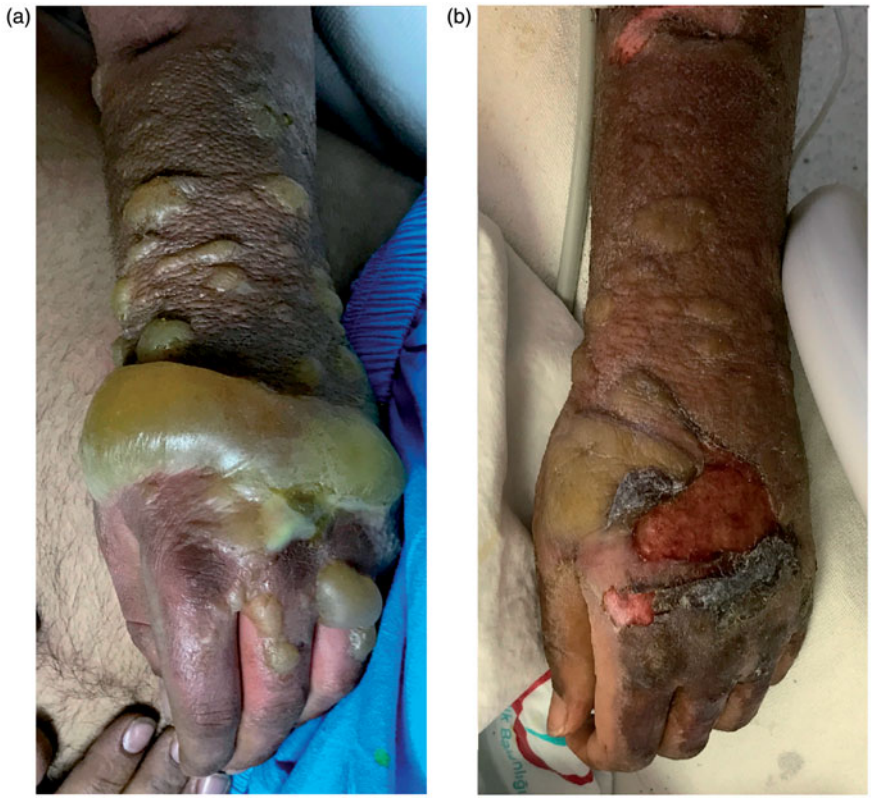

Figure 2. (a) large bullae and (b) scarification of bullae, scabbed lesions and re-epithelization.

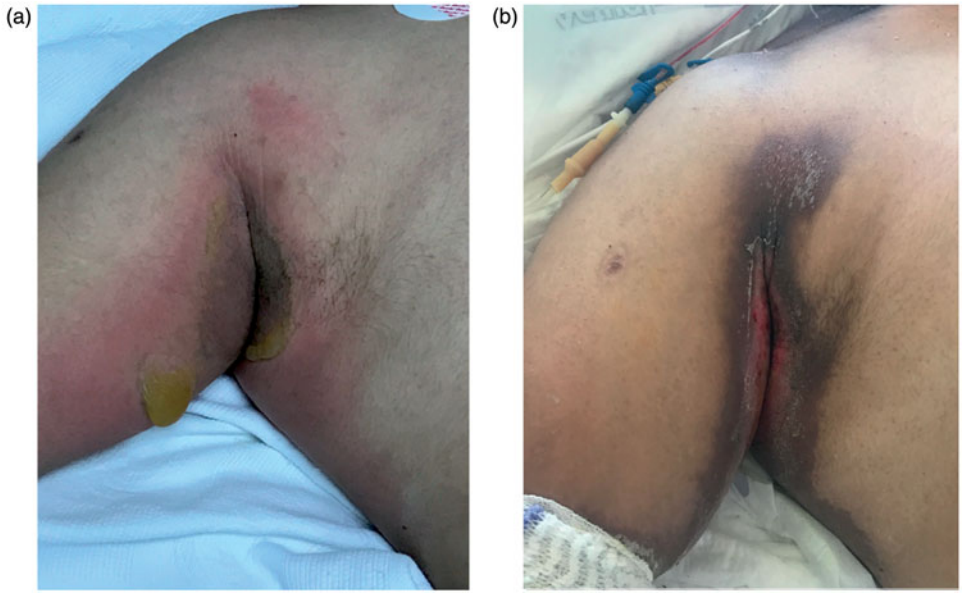

Figure 3. (a) bullae and erythematous lesions (first day after SM exposure), (b) erosions and hyperpigmented skin zones (11th and 13th days after SM exposure, respectively).

cases without any secondary infection. Hypopigmented and hyperpigmented zones were perceived as general characteristics of the healing process (Figure 3). Thirty days after admission, all skin lesions were almost completely healed.

Hematologic and systemic injuries

Haematologic and biochemical values (liver enzyme activity, plasma glucose and electrolyte levels) were within normal ranges. For the assessment of intravascular fluid and electrolyte balance, measurement of the internal diameter of the vena cava inferior was performed by ultrasound twice per day. All cases received 1 ml/kg/h normal saline solution intravenously for 10 days.

On the 6th day of treatment, bone marrow depression was observed in the two patients who were nearest to the explosion point. They showed decreased platelet count (18 000/μl, and 22 000/μl, respectively). Each patient received

pooled platelet suspension three times, and their platelet counts increased to over 40 000/μl. These patients received granulocyte-colony stimulating factor (filgrastim) on the 7th and 8th day of treatment.

General supportive therapy

On the first day, all patients received Oliclinomel N7® (Eczacibasi, Turkey), an olive oil based parenteral nutrition containing amino acid and glucose (60 ml/h). At the end of the day, parenteral nutrition was replaced with oral feeding. It was calculated that the energy requirement was 30 kcal/kg/day and the dietary protein intake was 2 g/kg/day. L-glutamine solution was given as an immunonutrient, and nutrition with omega-3 fatty acids, arginine, nucleotides, and soluble fiber was added to the daily diet of all patients. The patients were instructed to maintain routine diets after termination of nutritional support at the 10th day.

Additionally, all patients received parenteral multivitamin products for the first three days. A daily dose of 5 mg morphine was administered subcutaneously for 10 days to treat severe burn pains. Additionally, 40 mg of intravenous pantoprazole was added daily to treat stomach and esophagus problems.

As a result of our experience with the medical management of the patients exposed to SM, a consensus was reached to determine which criteria best indicated readiness for discharge from the hospital. The "Turkish Discharge Criteria" (TDC), which includes 5 criteria, was defined in order to determine the duration of hospital stay.

The TDC's are kindly proposed as follows:

1. Improved well-being with clear consciousness, orientation, and cooperativeness.
2. Regression in SM-induced cutaneous lesions or formation of new epidermal tissue.
3. Presence of normal breath sounds and signs of normal chest X-ray for at least 5 days.
4. Presence of normal complete blood count (CBC) and normal electrolyte balance for at least 5 days without medical intervention.
5. Recovery of eyesight and loss of SM-induced ocular lesions.

Discussion

It is known that chemical weapon attacks mostly occurred in the Middle East after the First World War. SM was extensively used by forces in Yemen (1963–1967) and by the Iraq Army against Iranian troops[12]. We presented short-term results regarding the treatment of SM victims of the Syrian Civil War who were hospitalized in the ICU. Our patients had shown typical signs and symptoms that were similar to other SM casualties in the Great War and the Iran-Iraq War. In addition to clinical findings, SM exposure was also confirmed by observing elevated thiodiglycol levels in the urine samples of casualties using a modified version of the method used by Kenar et al.[13].

Patients exposed to chemical agents should be decontaminated before hospital admission in order to reduce cross-contamination of health professionals. Additionally, health professionals should wear proper physical protective clothing[14,15]. All patients were decontaminated at the Turkish-Syrian border by professional first responder teams, and ICU staff wore "Level D" chemical protective equipment.

The main mechanism of tissue damage is poly-(ADP-ribose) polymerase (PARP) activation due to DNA alkylation and reduction of nicotinamid adenine dinucleotid (NAD), as well as ATP overuse in order to compensate for this cellular damage[9,16,17]. A latent period of 4 to 12 h is typical before the onset of clinical features after exposure to SM[5,12]. Following low-level exposure to SM, the latent period is prolonged, and the major mechanism of action is only DNA damage. On the other hand, the duration of the latent period is relatively short after high-level exposure to SM, and the onset of symptoms may be seen within hours after exposure due to cell damage (resulting from overactivation of PARP and depleted levels of NAD and ATP)[8,16,17]. None of the cases wore either personal protective clothing or gas masks, so they were vulnerable to high-level exposure to the agent; therefore, the time before onset of symptoms was relatively short.

Since eyes are more susceptible to SM than any other organ of the body, 12–70 mg/min/m^3 of SM causes mild irritation, and 100–200 mg/min/m^3 exposure causes moderate irritation. Severe eye lesions can occur if the exposure concentration is higher than 200 mg/min/m^3 (9). In our experience, conjunctivitis was observed in all patients at the 18th hour, but 5 cases had mild irritation and 3 cases had moderate irritation with corneal opacity and ulceration. Four cases had temporary loss of vision with periorbital edema and blepharospasm. According to the recommendations, our cases received treatment with mydriatics and appropriate anti-bacterial and steroid eye drops, resulting in complete eye symptom relief by the 15th day. The exceptions were the two cases with corneal opacity, which healed by the 30th day.

Hoarseness, sneezing, sore throat, and cough have been reported as the first symptoms of irritated upper respiratory tract after SM exposure[3,11,17,18]. Similarly, we also observed hoarseness, sneezing, sore throat, and rhinorrhea in all cases; however, cough was only present in 8 of them.

Depending on the SM concentration, bronchiotracheal inflammation may cause necrotic obstruction called "pseudomembrane formation", resulting in sudden cardiopulmonary arrest. These cases sometimes need immediate emergency airway tracheostomy[16,18]. Post-mortem examination of the case who died on the 18th day showed massive pulmonary hemorrhage and necrotic bronchial walls. For this reason, SM-exposed patients should be monitored for pseudomembrane formation, which may increase the risk of fatal complications.

Additionally, we used continuous supplemental oxygen, bronchodilators, and mucolytics in all patients. By using systemic methylprednisolone (1 mg/kg/day) for the first three days, we tried to improve respiratory system function without immune system suppression. A daily dose of 1 g ampicillin/sulbactam was given to all cases for systemic antibiotic

prophylaxis for the first 2 days. This prophylactic treatment lasted for 5 days in the 5 patients with severe skin lesions.

Skin blister formation is characteristic in patients who are exposed to a high concentration of SM (1000–1900 mg/minute/m^3)[19]. Histopathological examinations of skin lesions showed subepidermal blister formations with tense bullae[8,20]. The severity of skin lesions after SM exposure may vary depending on environmental temperature, humidity, and the affected anatomic region[4,16]. Especially thin and humid skin areas such as the scrotum, axilla and anal regions are much more sensitive to SM exposure[5,11,16].

Following a latent period of 2 to 8 h after the incident, erythema with intense itching was noticed in all cases, followed by blister formation on different body areas by the 18th hour. Blister formations following superficial reddening of the skin were mostly observed during the first 72 h after the exposure. All 8 patients who were less than 10 meters away from the explosion had erythema and blister formation on their hands, arms, axilla, and genital regions. Histopathological examinations of skin biopsies showed subepidermal blister formation. Additionally, positive Nikolsky sign was usually found in these patients.

There is still no medical consensus for the treatment of blisters that are greater than 1 cm in diameter. Health care professionals are advised not to discharge the content of large bullae, but to perform surgical debridement of bullae[4,21]. It has also been stated that healing may be seen within 2 weeks or less for blisters that were drained within the first 24 h[17]. For wound care and treatment of cutaneous lesions, the medical approach includes applying petrolatum gauze bandages, dexpanthenol for re-epithelization, topical steroid creams (flumethasone/clioquinol), topical antibiotic creams (furazolidone/metronidazole or silver sulfadiazine), and antiseptic octenidine hydrochloride solution; skin grafting may even be recommended[4,5,11].

No blister aspiration or debridement was performed. Once the blisters were broken spontaneously, their ragged roofs functioned as a kind of protective cover during the re-epithelization process. By the end of the second week, our patients showed significant re-epithelization and wound healing, which was faster than the cases reported by Graham et al[4], which healed within 5 to 8 weeks (Figures 2 and 3).

The focus of the present study has been on "good nursing care", measures for infection prevention, local wound care with topical agents, fluid replacement therapy, and especially the selection of an ideal nutrition method. Nutrition is an important factor for the medical management of ICU patients with thermal burns, especially since poor initial tolerance of gastric feeding is a risk factor for incomplete enteral nutrition[22–24].

In our experience, all patients were administered parenteral nutrition on the first day in the ICU followed by enteral nutrition with high-protein nutrients, arginine, and glutamine after the 2nd day. Well-planned and appropriate nutritional support was also observed to be a positive contributor to the wound healing process, as no wound infection was reported, and cutaneous lesions were almost resolved in less than two weeks.

In the Munich experience by Kehe et al, of the 12 study patients with SM injuries between 1984 and 1985, only one patient died due to bone marrow suppression-induced sepsis and airway obstruction on the 7th day after exposure[5]. Severe thrombocytopenia, leukopenia, and erythrocytopenia developed in 2 of the 13 cases we followed, and the bone marrow suppression due to SM exposure caused pancytopenia. We therefore administered granulocyte colony-stimulating factors (G-CSF) on the 7th and 8th days.

Because of the latent period following SM exposure, all surviving victims with or without symptoms should be followed in the ICU due to their increased risk of developing secondary infections resulting from bone marrow depression and respiratory system complications, such as pseudomembranous formation. During the follow-up period, a multi-disciplinary team of pulmonologists, dermatologists, ophthalmologists, hematologists, and infectious disease specialists should collaborate to examine SM victims. Avoidance of blister debridement, administration of short-course systemic antibiotic prophylaxis (not more than 5 days), adhering to standard infection control procedures, administering fluid replacement therapy, and adhering to a nutritional support plan are highly recommended basics for the medical management of SM victims. It may be considered that signs and symptoms of the eye are usually temporary and should be treated symptomatically.

Conclusion

After the First World War, mass casualties due to SM poisoning have been reported not only in the Iran-Iraq War but also in many conflicts that occurred in various regions of the world. SM attacks are a current threat and are still likely to occur throughout the Middle East and the rest of the world. Although there have been adequate data and experiences obtained regarding the clinical features of SM poisoning since The Great War, the medical management of SM victims was barely possible (especially for cases between 1986 and 1988) by Western physicians. However, clinical skills in intensive care medicine have improved since the 1980s, and have positively affected the care of patients exposed to SM. Therefore, the present study is important because it is the largest, most recent SM-exposed case series since 1988. Thus, we concluded that the current knowledge and experiences obtained from these patients can be used as an important guide for the medical management of future SM-exposed victims.

Disclosure statement

No potential conflict of interest was reported by the authors.

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