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REVIEW ARTICLE

Cutaneous and Systemic Toxicology of Vesicant (Blister) Warfare Agents

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Abstract
Vesicants (blister) agents are a group of chemicals used in warfare. The most representative agent is yperite, also known as mustard gas. The blisters that appeared on those exposed to yperite during combat in the First World War are responsible for the current name—vesicants—for this group of chemicals. Their affects are produced mainly through localized action of liquid or vapor forms on the skin, eyes, and respiratory tract. However, the high absorption of the liquid form through the skin or the vapor form on inhalation may cause substancial systemic effects. Here we analyze these effects, treatment of intoxication, and long-term sequelae, drawing on our experience and a review of the literature.

PALABRAS CLAVE
Agentes químicos de guerra;
Agentes vesicantes;
Gas mostaza;
Iperita;
Lewisita

Toxicología cutánea y sistémica de los agentes vesicantes de guerra

Resumen
Los agentes vesicantes constituyen un grupo de agentes químicos de guerra cuyo principal representante es la iperita, también conocida como gas mostaza. Las ampollas que aparecían en los intoxicados por iperita en combate durante la Primera Guerra Mundial hicieron que a todos los agentes incluidos en este grupo se les denomine hoy en día agentes «vesicantes». Sus efectos se producen fundamentalmente por la acción local de la forma líquida o del vapor sobre la piel, los ojos y el tracto respiratorio. Sin embargo, la gran capacidad de absorción de la forma líquida a través de la piel o de la forma de vapor tras la inhalación puede dar lugar a efectos sistémicos importantes. Desde nuestra experiencia y tras una revisión de la literatura médica, en el presente trabajo se analizan estos efectos, el tratamiento de las intoxicaciones y las secuelas a largo plazo.

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Introduction

Modern chemical warfare made its first appearance during World War I, when commonplace industrial chemicals such as chlorine or phosgene were used as tactical weapons. The success of these attacks led both the Germans and the Allies to initiate research and development programs for chemical weapons. Their purpose was to discover chemicals whose physicochemical and toxicological properties made them appropriate for use in combat. Thus, research into the so-called vesicants began. These were a group of chemical weapons that included sulfur and nitrogen mustards, lewisite agents, and phosgene oxime (often denoted as CX).

The vesicants of main concern—important because different countries have used them in warfare and have stockpiled large quantities—are sulfur mustards, particularly bis(2-chloroethyl) sulfide, which is popularly known as mustard gas or yperite (Figure 1). Mustard gas was first synthesized between 1820 and 1860, and Guthrie[1] and Niemann[2] described its vesicant properties in 1860. In 1886, Meyer synthesized a purer mustard gas through the reaction of thiodiglycol with phosphorus trichloride.[3] But it was not until World War I when Lommel and Steinkopf developed the Meyer process for large-scale production and used thionyl chloride: mustard gas synthesized using this method was known as LOST, an acronym formed from the surnames of those 2 German scientists.[4] Coincidentally, the United Kingdom had also studied the possible use of mustard gas as a chemical warfare agent 15 months before the Germans used it for the first time on July 12, 1917.[5] The first attack took place at Ypres, and so mustard gas is sometimes known as yperite. The first soldiers affected reported a smell reminiscent of garlic or mustard, giving rise to the name mustard gas. Although this smell is often mentioned, the experience of those poisoned during the Iran-Iraq war shows that the nature of the smell is very subjective and may actually depend on the purity of the substance.[6] In fact, mustard gas is often denoted as H or HS (from the German *Hun Stoffe*) to refer to the agent when produced by the Levinstein procedure. This product contains 20% to 30% impurities, whereas the substance denoted as HD (where D refers to "distilled") refers to purer mustard gas. Another common denomination during the World War I was "yellow cross" as this was the marking used by the Germans for the shells that contained the agent.[7] The striking lesions and the effectiveness of the attacks earned it the title of "king of gases" during World War I.[8]

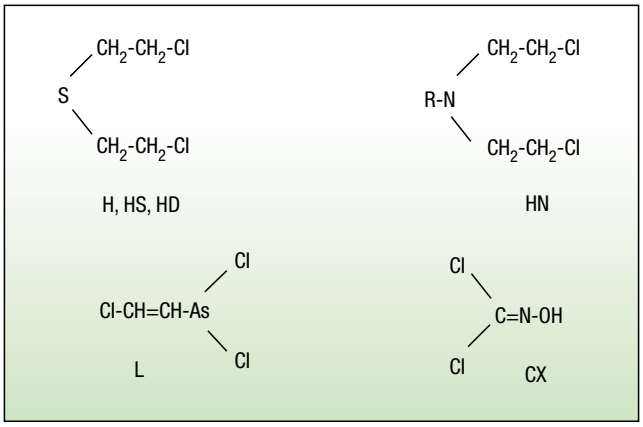

Figure 1 Chemical structures of the main vesicants.

According to some authors, chemical weapons were not used during World War II because Hitler refused to employ them after experiencing intense eye irritation after an attack by the British with mustard gas during World War I.[9] Although instances of use of mustard gas were not recorded during World War II, an attack by the German air force on the Italian port of Bari on December 2, 1943, hit the *USS John Harvey*, laden with 2000 bombs armed with 45 kg of mustard gas each.[10] The subsequent release affected more than 1000 people.

Other cases of use of mustard gas have been reported: Spain used it during the Rif War in the 1920s[11]; Italy in Ethiopia between 1935 and 1936 (the first attack with a chemical agent dispersed as an aerosol from aircrafts)[12]; Japan from 1938 onwards against China[13]; and probably Egypt in the Yemen Civil War in the mid-1960s.[14] More recently, Iraqi troops used mustard gas in the Iran-Iraq war, where chemical weapons caused more than 45 000 civilian and military casualties, although the exact figure varies according to the source.[15] From May 1983 through August 1988, the United Nations conducted 12 inspection missions, which found evidence that mustard gas had been used by the Iraqi Army (Figure 2).[16]

At the end of World War II, most of the German chemical warfare agents were dumped in the sea, particularly in the North Sea and the Baltic Sea. As a result, cases of poisoning by mustard gas among fishermen working those waters are not unheard of today.[17] The Allied chemical weapons in the European theatre of operations of World Wars I and II were also abandoned with no control at the end of the conflict. Chemical weapons continue to be found and, on occasions, there have been cases of poisoning of the civilian population.[18,19] Likewise, there have been cases of poisoning among workers at chemical weapons storage and destruction facilities.[20]

Although mustard gas is the most emblematic of sulfur mustards, other molecules have vesicant activity. In fact, the Chemical Weapons Convention (CWC) includes 9 sulfur mustards in its Schedules of chemicals for the application of verification measures.[21] The CWC is an international arms control treaty that bans the development, production, stockpiling, transfer, and use of chemical weapons. In addition, it is a disarmament treaty, as it requieres State Parties with chemical weapons and production facilities to proceed to their destruction. The CWC came into force in 1997 and, in accordance with Article VIII, the Organization for the Prohibition of Chemical Weapons was created, with headquarters in The Hague. This organization is responsible for ensuring the implementation of the CWL provisions.

During the 1930s, structural changes made to the sulfur mustards led to the discovery of nitrogen mustards, with similar properties to their sulfur analogues (Figure 1).[22] To date, no instances of use of this group of vesicants have been reported. The main nitrogen mustards are bis(2-

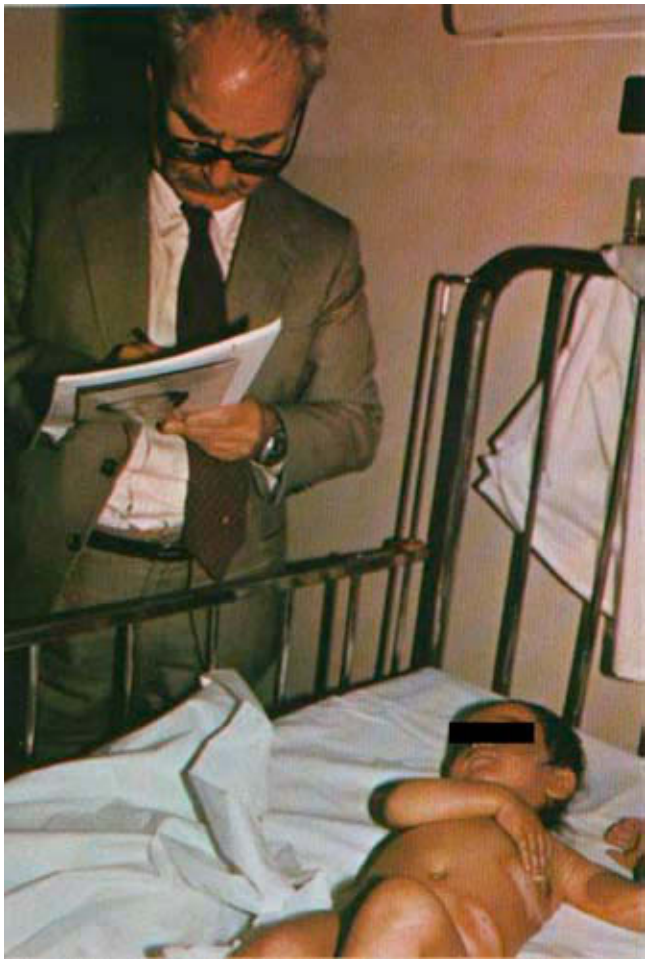

Figure 2 Dr Manuel Domínguez Carmona, member of the United Nations inspection team during the Iran-Iraq war, examines a child affected by mustard gas in 1987. Courtesy of Dr Shahriar Khateri.

chloroethyl) ethylamine, bis(2-chloroethyl) methylamine, and tris(2-chloroethyl) amine, all of which are included in the CWC's Schedules.[21] Bis(2-chloroethyl) methylamine is the most widely known, although as a cancer treatment rather than as a chemical weapon.

2-Chlorovinyldichloroarsine (Figure 1) was synthesized in 1903, but became known as lewisite or L when the team under the orders of Captain Lewis of the Chemical Warfare Service of the US army rediscovered it as a chemical weapon in 1918.[23,24] That same year, a shipment of 150 tons was sent to Europe, but the war ended and the cargo was dumped at sea.[25,26] There is no evidence of its use in combat, although some authors have suggested that it might have been used by Japan against China from 1939 onwards.[13] The main problem with lewisite as a weapon is that it hydrolyzes quickly and so would be deactivated in very humid conditions.[27] The former Soviet Union produced a mixture of mustard gas and lewisite, sometimes denoted HL. Mustard gas, with a melting point of 14.4°C, would be useless at low temperatures whereas the mixture, with a melting point below 0°C, would overcome this problem. As with mustard gas, cases of lewisite poisoning are not uncommon in individuals who come into contact with abandoned chemical munitions, particularly in Japan and China.[19,28] The Schedules of the CWC includes 2 molecules in the same group as lewisite: bis(2-chlorovinyl) chloroarsine (denominated L2) and tris(2-chlorovinyl) arsine (denominated L3).[21]

Some publications also consider CX as a vesicant (Figure 1), as it is thought that the former Soviet Union could have produced it for chemical warfare. However, this substance is not listed in the CWC Schedules.[21]

Although the main representative of mustards is popularly known as mustard "gas," in actual fact both sulfur and nitrogen mustards are liquids at room temperature (Table).[29] Mustards, unlike lewisite, are considered persistent agents due to their relatively low volatility. This means they remain in the area of the attack for a certain length of time. CX, in contrast, is a highly volatile crystalline solid.

Table Physicochemical Properties That Influence Environmental Persistence of the Main Vesicants[29]

Agent	Melting Point, ºC	Vapor Pressure, mmHg at 25°C	Volatility, mg/m^3 at 25°C
HD	14.45	0.11	910
HN3	−3.7	0.011	121
L	−1.2	0.35	3900
HL	−25.4	0.361	3900
CX	35-40	11.2	>20 000

Abbreviations: CX, phosgene oxime; HD, distilled or purified mustard gas; HL, mixture of mustard gas and lewisite; HN3, tris(2-chloroethyl) amine; L, lewisite.

Mechanism of Action

Although mustard gas was used for the first time in 1917, its mechanism of action is still unknown. Different hypotheses have, however, been proposed. Sulfur and nitrogen mustards undergo intramolecular cyclization reactions giving rise to sulfonium or immonium ions, respectively (Figure 3).[30] These intramolecular reactions are favored by the presence of water and high temperatures.[31] For this reason, the areas of the body that are moist are the most susceptible. Sulfonium ions are potent alkylating agents of molecules such as DNA, RNA, glutathione, and proteins. DNA alkylation leads to cross-linking and breakage of strands, and polymerases such as poly(adenosine-ribose diphosphate) polymerase are activated, leading to depletion of the substrate, nicotinamide adenine dinucleotide, and inhibition of adenosine triphosphate synthesis, leading to cell death.[32-34] The fastest-dividing cells are therefore the ones most affected by mustards.[31] Mustard gas appears to have a special affinity for N-7 of guanine.[35] Sulfonium and immonium ions also alkylate nucleophilic molecules such as enzymes that contain sulfhydryl groups and that are responsible for regulating calcium homeostasis in the cell.[36] Such processes would cause an increase in the

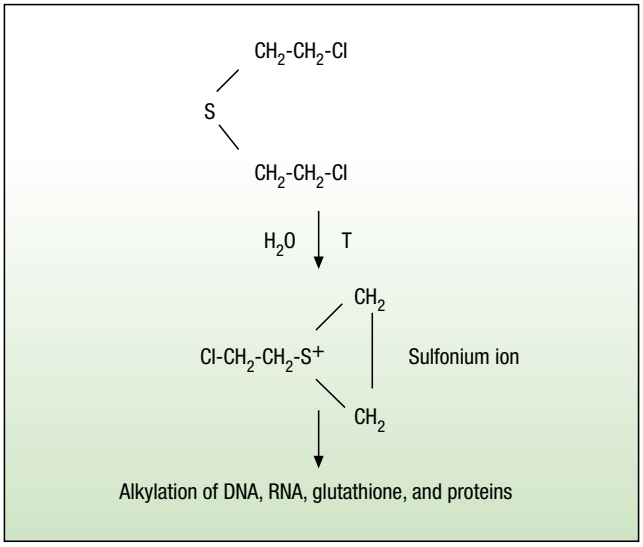

Figure 3 Formation of sulfonium ion, cause of mustard gas-induced alkylation.

intracellular calcium concentration, thereby disrupting the microfilaments responsible for cell integrity, with activation of endonucleases, proteases, and phospholipases, which finally induce apoptosis.[31] Moreover, mustards interact with glutathione and increase the concentration of free radicals which, through peroxidation of membrane lipids, affect the integrity and function of the membrane.[31,37] Some studies have suggested that oxidative stress due to reactive oxygen species plays an important role in the toxic mechanism of action of mustard gas.[38,39] Finally, mustards stimulate cytokine production and induce immune reactions and tissue lesions.[31]

The exact cytotoxic mechanism of action of lewisite is not known, but it seems to act at the mitochondrial level on lipoic acid of pyruvate dehydrogenase, thereby impeding the formation of acetyl-coenzyme A from pyruvate.[40-42] The mechanism of action of CX is unknown.

Clinical Effects and Pathophysiology

The information available on the clinical effects of vesicants pertains mainly to mustard gas and is derived largely from experience during World War I and the Iran-Iraq war. For this reason, recent experience in Western countries in the care of these patients has been limited, with a few exceptions. During Iran-Iraq war of the 1980s, Iran transferred more than 200 casualties from mustard gas attacks to European hospitals, including the Hospital Militar Central Gómez Ulla (today the Hospital Central de la Defensa Gómez Ulla) in Madrid, Spain. In 1986, this hospital received 20 Iranian mustard gas casualties—16 men (including both soldiers and civilians), 2 women, and 2 girls. Later, in 1987, 12 more victims arrived, mostly health-care workers who were evacuated from a hospital targeted by a chemical attack.

After exposure to mustard gas, there is an asymptomatic latency period before the first signs and symptoms of poisoning appear. This hinders both differential diagnosis and triage by health-care workers. The latency period varies between 2 and 48 hours according to dose (often expressed as the product of concentration and time, or Ct), temperature, humidity, and area of the body exposed. The most sensitive areas are the thinnest and most moist: the respiratory tract and eyes, and, on the skin, the axillas (Figure 4), neck, elbow creases, groin, genitals, and perineum.[43-45] Thus, local effects usually involve the skin, respiratory tract, and eyes, although ingestion of the agent (for example, by eating contaminated food) can also cause gastrointestinal lesions directly.

Mustard gas is absorbed through the skin and eyes, inhaled, and even when ingested into the gastrointestinal tract.[46] The skin is a good point of entry for mustard gas in both liquid and vapor form, given the highly lipophilic nature of the agent. Absorption is enhanced at higher temperature. Once absorbed, the systemic effects occur mainly in bone marrow, the gastrointestinal tract, and the central nervous system. It has also been observed that, after absorption, mustard gas accumulates in fatty tissue and the central nervous system because of its lipophilic properties.[47] Death in the first 24 hours after exposure is usually due to acute respiratory failure resulting from obstruction of the bronchial tree by pseudomembranes and from laryngospasm.[20] Death after the first 3 days is usually due to bacterial pneumonia (the bone marrow suppression induced by the agent predisposes the patient to infection). In World War I, mortality among mustard gas victims was 2% to 3%[47-49] whereas in the Iran-Iraq war it was 3% to 4%.[46] Mortality in the incident in Bari was 13% to 14%,

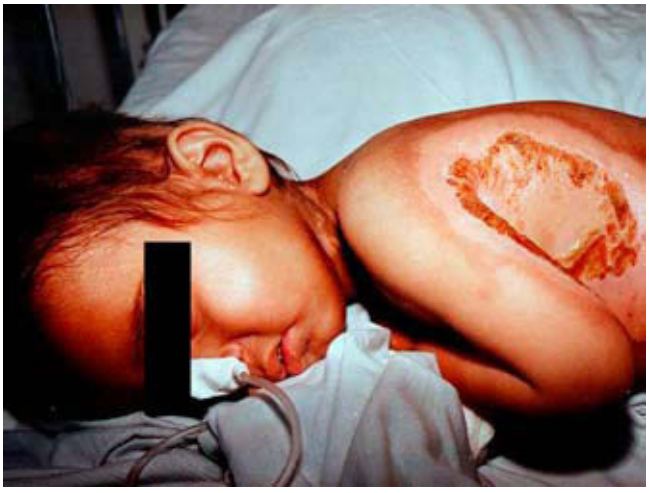

Figure 4 The moist areas of the body, such as the axillas, are the most susceptible to the action of mustard gas. The child in the photograph was 1 year old when she was exposed to the toxic effects of mustard gas in an Iraqi attack on the town of Aloot in Iran in 1987. Today, she has serious sequelae that affect the respiratory system, skin, and eyes. Moreover, she has serious psychological problems in relation to these lesions. Courtesy of Dr Shahriar Khateri.

but many of those deaths were caused by the mechanical and thermal effects of conventional munitions and not the toxic effects of mustard gas.[10] In fact, although vesicants are usually considered as lethal chemical agents, they are essentially disabling weapons.

Nitrogen mustards have similar effects to sulfur mustards, but their effects on the central nervous system are more severe and in vivo animal studies have shown convulsions after intravenous administration.[50] Lewisite is also well absorbed by the skin and mucosal tissues.[29] The main difference from mustards is that there is no latency period for the effects of lewisite: pain and irritation occur immediately. Although lewisite's effects are less widely studied than those of the mustards, in vivo studies in animals and cases of accidental exposure in humans have shown very similar effects.[7,51]

Skin

The levels above which the first signs and symptoms of skin poisoning occur are 100 to 300 mg·min/m^3 for mustard gas vapor and 10 to 20 μg/cm^2 for liquid mustard gas.[52-55] It has been observed that 20 μg/cm^2 of liquid mustard gas are sufficient to cause skin blistering, whereas only 4 μg/cm^2 of vapor can achieve the same effect.[54,56] The reason for this is that only 10% to 20% of liquid, on coming into contact with the skin, is absorbed thanks to its lipophilic properties whereas the remaining 80% to 90% is vaporized.[31,57] Of the 10% to 20% that penetrates the skin, 10% is fixed in macromolecules while 90% enters systemic circulation.[57,58] The speed of absorption is reflected by the fact that unmetabolized mustard gas is no longer detected in skin 30 minutes after exposure.[47] In our experience at the Hospital Gómez Ulla, analyses of serum and urine samples and the water from the first lavage did not detect the presence of mustard gas or any other chemical warfare agent.

Erythema appears between 2 and 48 hours after exposure and, subsequently, blisters develop on the erythematous areas. Initially, small blisters may appear at the edges of the erythematous area, producing a "string of pearls" appearance. These lesions then merge together to form larger blisters (Figure 5).[59] In severe lesions, particularly those due to exposure to the liquid agent, necrosis occurs and they become more susceptible to secondary infections that can complicate the course of the lesion. As mentioned earlier, given the high reactivity of mustards, no active agent is detected in the blisters and so there is no risk of poisoning from contact with the lesions.[60-63] The subsequent appearance of blistering in areas of erythema is not due to contact with mustard gas present in blisters but rather to friction giving rise to the Nikolsky sign.[45]

Reepithelization is slow due to DNA alkylation, which prevents the epidermal cells from proliferating at a normal rate.[62] Healing occurs in approximately 10 to 15 days, with few scars. In the cases we treated, only 1 patient developed hypertrophic scars on the legs (Figure 6). However, most patients showed an intense residual hyperpigmentation that started around the hair follicles then gradually spread to take on the appearance of an "oil slick" (Figure 7). Pigmentation is more evident in the skin folds, that is, the neck, axillas, groin, and genital region.

From the anatomopathological point of view, in early lesions, subepidermal blisters can be observed with degeneration of the basal layer (Figure 8).[45] The blisters appear between the epidermis and the dermis on formation of hemidesmosomes between the basal layer and keratinocytes in the epidermis. These blisters have scant inflammatory cell content, and the Schiff periodic acid-positive region of the basement membrane is located at the base of the blister. In other cases, the roof of the blister is completely necrotic. In the most advanced lesions, intraepidermal detachment of the blister may occur due to epithelial regeneration. This is when capillary dilatation and infiltration by mononuclear inflammatory cells may occur. During the phase of hyperpigmentation, a large accumulation of melanin may arise in all epidermal layers, including the horny layer. In addition, numerous melanophages with thick melanin granules can be observed in the upper dermis.

During the Iran-Iraq war, the Iraqi troops not only attacked military targets but also used mustard gas on civilians. One of the largest attacks took place on June 28, 1987, in the Iranian city of Sardasht, where 4 bombs with 250 kg of mustard gas poisoned 4500 individuals, mostly civilians. The experience gained from these attacks by Iranian physicians suggests that children are more

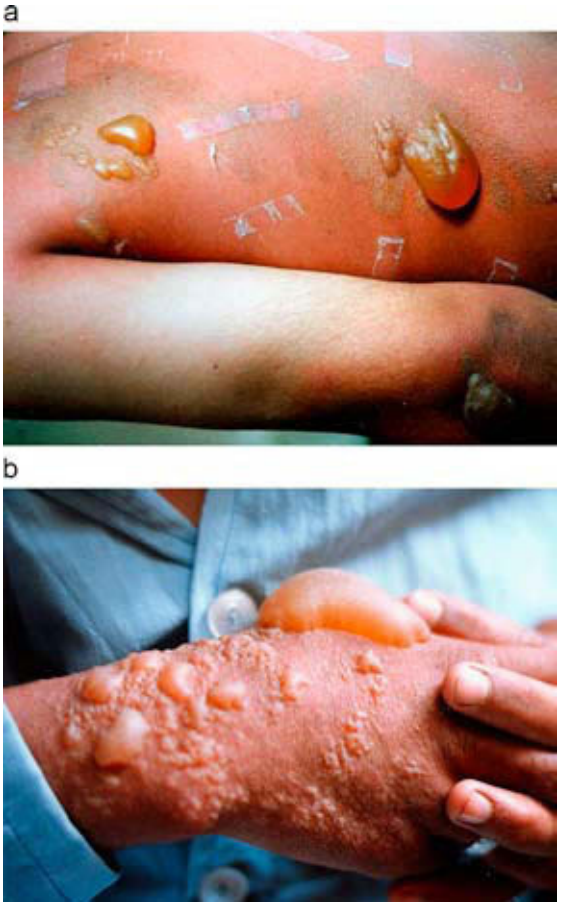

Figure 4 Blisters produced by mustard gas on Iranian casualties from the Iran-Iraq war. Courtesy of Dr Shahriar Khateri.

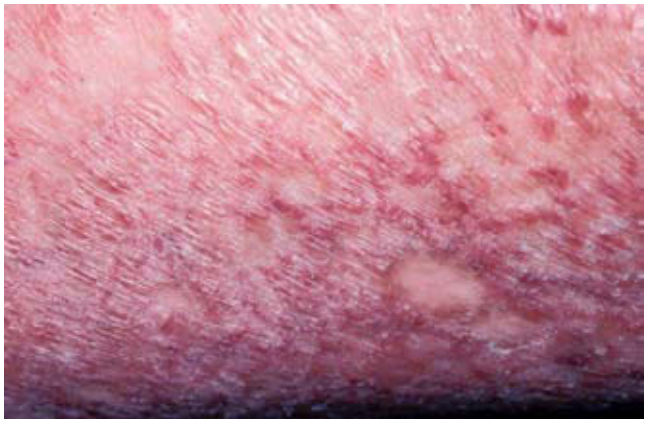

Figure 6 Hypertrophic scars from mustard gas lesions on a leg.

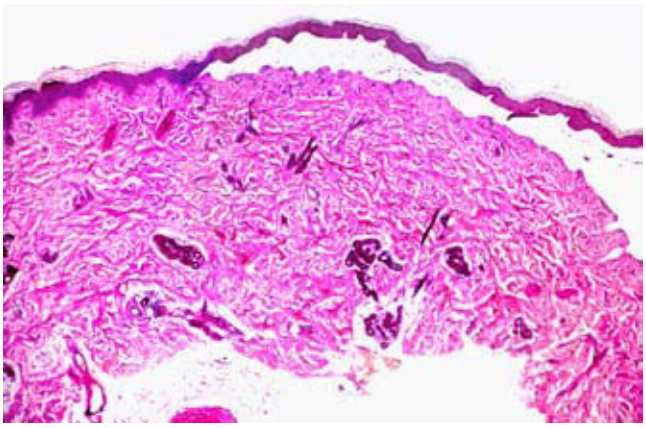

Figure 8 Subepidermal blister (hematoxillin-eosin,×100).

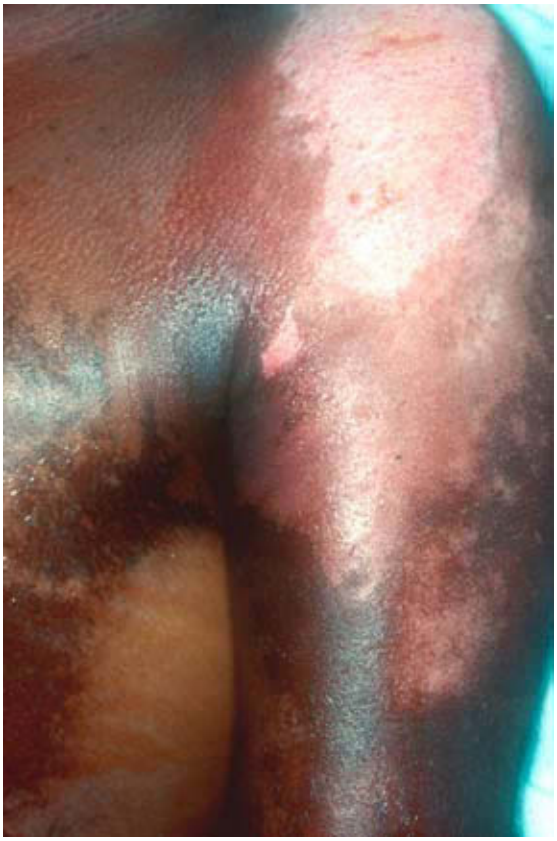

Figure 7 Cutaneous hyperpigmentation in an individual exposed to mustard gas.

susceptible than adults to cutaneous effects of mustard gas and that their lesions develop much more quickly.[64]

Unlike mustards, direct contact with lewisite causes immediate irritation and pain at the site of contact and it is absorbed more quickly through the skin (3-5 minutes).[7,27,62] Cutaneous lesions caused by lewisite are characterized by the initial appearance of a small blister at the center of the erythematous area. The blister then spreads to cover the whole affected area. Reepithelization of lesions caused by lewisite is faster and pigmentary abnormalities are less frequent than in the case of mustard gas poisoning.[65] Active agent has been detected in the fluid of lewisite-caused blisters. Oxidation products with vesicant action have also been detected.[62,65] CX also causes intense and immediate irritation on coming into contact with the skin, but blisters occur infrequently.[62]

Respiratory Tract

Acute poisoning by mustard gas is characterized by hoarseness and productive cough.[59,66-68] In severe cases, noncardiogenic pulmonary edema may develop. This was the cause of death of a patient 48 hours after he was admitted to our hospital. Initially, a mucosal lesion forms, with subsequent involvement of the muscle layer of the bronchial tree. These lesions may give rise to pseudomembranes between proximal and distal parts of the airways, resulting in obstruction.[69]

There is no direct information on the effects of lewisite on the respiratory tract in humans, but severe irritation may arise on contact with the vapor.[27] Pulmonary capillaries seem to be more susceptible to the action of lewisite. Thus if the skin comes into contact with the agent, there is a risk of hemoconcentration and hypotension (lewisite-induced shock), not just because of changes in local capillary patency but also because, on entering systemic circulation, lewisite reaches the lungs and affects the pulmonary capillaries, with a risk of pulmonary edema.[27]

Eyes

Eyes are very sensitive to vesicants in the vapor form. In fact, the latency period for onset of ocular signs and symptoms is shorter than for the skin symptoms.[70,71] Mustard gas penetrates the cornea more quickly than the skin.[72] An exposure to 50 mg·min/m^3 causes initial ocular symptoms and an exposure to 200 mg·min/m^3 completely disables an individual with very intense irritation and temporary blindness due to palpebral edema.[65] The

initial ocular irritation progresses to conjunctivitis with photophobia, blepharospasm, pain, and corneal lesions.[59] Permanent loss of sight is rare, except in cases of severe lesions caused by high concentrations or by direct contact with the agent in liquid form, which may cause corneal ulceration. In 2 patients attended at the Hospital Gómez Ulla, the corneal ulcers progressed to severe opacities requiring corneal transplantation (Figure 9).[45] In some cases, miosis due to the cholinergic activity of mustard gas also occurred, hindering differential diagnosis with nerve warfare agents.[62] In fact, sulfur and nitrogen mustards and, to a lesser extent, lewisite, are able to inhibit acetylcholinesterase.[73,74]

There is no direct information on the ocular effects of lewisite or CX in humans. In vivo studies in rabbits have found that lewisite leads rapidly to palpebral edema and myosis.[75]

Systemic Effects

Bone Marrow

The main systemic effect of mustards is generalized myelosuppression, and so its action is often referred to as radiomimetic.[72] Granulocytes and megakaryocytes seem to be the most susceptible to the action of mustard gas. In the first 3 days, leukocytosis may occur, followed by leukocytopenia at 7 to 10 days after exposure. In Iranian patients affected by mustard gas in the Iran-Iraq war, there were reports of total white blood cell counts below 200/μL.[59,76] The development of severe leukocytopenia or aplastic anemia are predictors of poor clinical outcomes.[7,59]

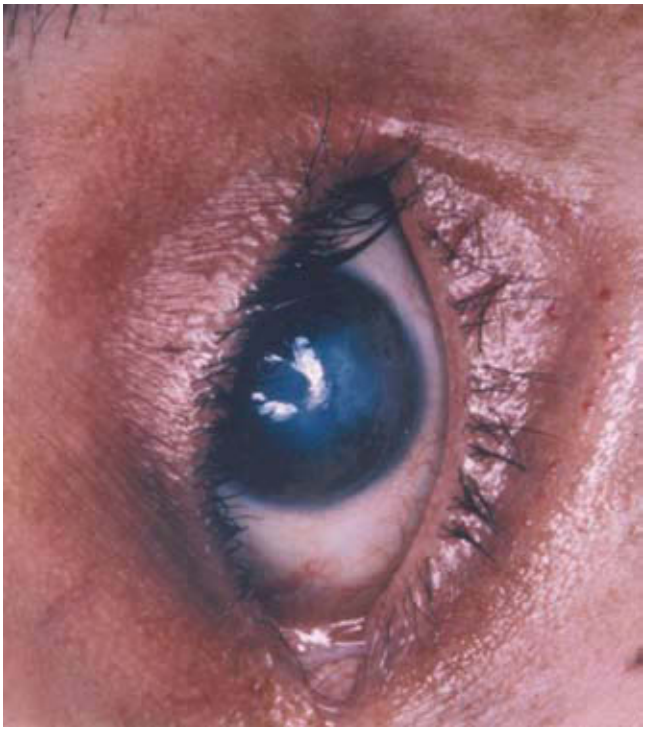

Figure 9 Corneal ulcers that progress to opacities may sometimes occur.

Gastrointestinal Tract

Gastrointestinal mucosa is very sensitive to mustards, not only due to local effects after ingestion but also due to systemic effects after inhalation or contact with the skin. The most common symptoms include nausea, vomiting, pain, diarrhea, and prostration.[72]

Central Nervous System

The experience in World War I and the Iran-Iraq war indicates that inhalation of high concentrations of mustard gas may lead to convulsions, followed by a depressive phase in which the individual is apathetic.[77]

Management

Once an individual has been evacuated from the area of exposure, the first critical step is full decontamination to stop any further contact between the agent and the individual and to prevent secondary contamination of the staff, including health-care workers who come into contact with the individual. Because of the rapid absorption of mustard gas and lewisite through the skin, decontamination should be performed quickly (within 30 minutes and 5 minutes, respectively).[7,27,47,62] In fact, the Nuclear, Biological, and Chemical Defense Regiment of the Spanish Army uses the expression "golden half hour," as a means of stressing the importance of a rapid evacuation and decontamination of affected individuals.

The short reaction time has led the US Army to include a product known as SERPACWA (for skin exposure reduction paste against chemical warfare agents) in the individual chemical warfare protection kit. This product impedes liquid agents from penetrating the skin, although vapor phases are still able to pass. The intention is for soldiers to apply the paste to the parts of the body most susceptible to mustard gas.

Although decontamination using only water gave good results for Iranian troops in the Iran-Iraq war,[78] there is a risk that the agents—given their low hydrosolubility—would be spread over a larger surface area, thereby extending the local effects and increasing the likelihood of systemic effects. The best approach is prior use of an absorbent material, such as Fuller earth, followed by rinsing with abundant water or a 0.5% sodium hypochlorite solution.[79,80] When the eyes come into contact with the agents, immediate rinsing with abundant water or normal saline is recommended.

Antidotes

There are currently no antidotes against mustard gas poisoning, although various scavengers with nucleophilic activity are under investigation (these include sodium thiosulfate, N-acetyl cysteine, and amifostine) as well as scavengers that oxidize mustard gas to its sulfoxide metabolite (a nontoxic product) but avoid further metabolism to the sulfone product (which is toxic), polymerase inhibitors, and calcium modulators.[47,61,81,82]

In the case of lewisite, there is an antidote available: 2,3-dimercaptopropanol, known as dimercaprol or

BAL (for British Antilewisite). Dimercaprol forms a hydrosoluble complex with arsenic, which is eliminated in urine.[83] Dimercaperol is available in different pharmaceutical forms, such as ophthalmic ointment, dermatological ointment, or ampules for intramuscular administration.[29,83] The ointments have the drawback that they have low stability and that they should be applied immediately after contact with the agent, and so their efficacy is, in practice, low. Intramuscular administration of dimercaprol is moderately effective in counteracting systemic effects, but it is very painful and associated with substantial adverse effects, such as arterial hypertension, tachycardia, nausea, vomiting, headache, and a sensation of burning in the mouth, lips, and throat.[24,83] Other alternatives to dimercaprol include *meso*-2,3-dimercaptosuccinic acid and 2,3-dimercapto-1-propanesulfonic acid.

Symptomatic Treatment and Support Therapy

Given that no specific antidote is available for mustard poisoning, the aim of treatment is to alleviate symptoms, avoid infections, and stimulate reepithelization and healing.[49,59] The experience of those affected by mustard gas in the Iran-Iraq war indicates that the final outcome and the healing process of skin lesions caused by mustard gas depend more on the initial severity of the lesion (dose, or Ct, to which the individual is exposed) than on the treatment applied. As the origin of skin lesions caused by vesicants differs from that of thermal burns, the Wallace rule of nines or the Lund-Browder chart are not useful for determining the initial severity and establishing the indication for fluid therapy. The dehydration observed in Iranian patients who were transferred to different European hospitals during the Iran-Iraq war was due to poor hygiene and sanitary conditions during evacuation and not a direct effect of mustard gas. Even so, an adequate metabolic state should be maintained, and lost fluids and electrolytes should be replaced, bearing in mind that this fluid loss is less serious than with thermal burns.

The main complication of skin lesions is infection. There is no consensus among authors as to whether or not the blisters should be lanced and what constitutes optimum therapy (whether or not to dress the wounds, and if so, whether to use a moist or dry dressing).[59] However, according to the US Army and the experience of health-care professionals in Iran, blisters should be lanced (except small ones under 2 cm) in a controlled fashion and antiseptic dressing applied.[46,62] The victims treated in the Hospital Gómez Ulla progressed favorably with antiseptic rinses and application of a 1% silver sulfadiazine cream which was widely used at the time to treat burns. It should be highlighted that in in vivo animal studies, good epithelial regeneration has been reported using dermabrasion and laser debridement after exposure to both mustard gas and lewisite.[49,84,85]

In ocular lesions, local analgesics can increase corneal damage and so systemic analgesics should be used.[29] Patients with corneal lesions should be given mydriatics to prevent the iris from adhering to the cornea. In the event that secretions accumulate, the eye should be irrigated with sterile saline and, to prevent the eyelids from sticking, sterile petroleum jelly (Vaseline) can be applied.

Although the efficacy of granulocyte-colony stimulating factor has not been proven, the US Army had this available in its logistical medical stock to treat possible leukocytopenia in the event of mustard gas poisoning.[46,86]

Long-Term Effects

In 236 Iranian veterans of the Iran-Iraq war, between 2 and 28 months after exposure, the main sequelae affected the respiratory system (78%), central nervous system (45%), skin (41%), and eyes (36%).[66] In a subsequent study of 34 000 Iranians who had been exposed to mustard gas 13 to 20 years previously, it was observed that the main complications occurred in the respiratory system (42.5%), eyes (39.3%), and skin (24.5%).[87] In a more recent study of 40 Iranian veterans who presented with signs and symptoms of mustard gas poisoning 16 to 20 years earlier, the respiratory tract (95%), peripheral nervous system (77.5%), skin (75%), and eyes (65%) were found to be affected.[88]

Skin

The most characteristic long-term cutaneous effect is changes in pigmentation, with the appearance of both hypopigmented areas due to melanocyte destruction, and hyperpigmented areas and dry skin.[49,61,66,88-90]

Respiratory Tract

In Iranian mustard gas casualties, the main long-term complications appeared some months, or even years, after exposure. These complications include chronic bronchitis, asthma, narrowing of the upper airways, bronchiectasis, and pulmonary fibrosis.[66,91,92] Ghanei et al[93] indicated that even subclinical exposure (that is, to mustard gas concentrations so low that they did not cause acute symptoms of poisoning at the time) may lead to bronchiolitis obliterans.

Eyes

In casualties of chemical weapons in the Iran-Iraq war, chronic and late-onset effects of mustard gas have been observed. These have been lesions of the ocular surface and cornea, giving rise to eye irritation and progressive deterioration in vision. Javadi et al[94] and Solberg et al[71] considered the possibility that these lesions resulted from immune processes.

Others

A significant increase in cancer, particularly involving the respiratory tract, has been reported in workers in mustard gas production facilities or in the dismantliny of these facilities.[77,95-103] However, in the case of isolated exposure to mustard gas, normally during combat,

epidemiological studies have not shown any significant increase in neoplastic processes compared to control groups.[77,99,104,105] In a recent study, Emadi et al[90] indicated that the number of cases of skin cancer associated with acute and chronic exposure to mustard gas is low, although they were of the opinion that such cases might be expected given the mechanism of action of the agent. Even so, the authors consider that it is not clear that the cases of cancer that were reported were related to the action of mustard gas on DNA or the presence of scars or chronic ulcers. The alkylating activity of mustard gas and its radiomimetic characteristics might trigger the particular poikilodermic clinical manifestations observed. These have been lesions with poorly defined borders, pigmentary abnormalities, reticular atrophy, and, occasionally, eruptive angiomas and telangiectasias. These differ from burn sequelae. In line with what would be expected with sequelae from other types of old wounds, the carcinomas observed are located on chronic ulcers and scars of old lesions caused by mustard gas. However, the greater frequency of basal cell carcinoma compared to spindle-cell carcinoma is exactly the opposite of what usually occurs in such cases.

In a study from 2004, Ghanei et al[106] did not observe any effect on fertility in Iranian casualties of these weapons. Finally, a high incidence of posttraumatic stress is reported both in those exposed to mustard gas during World War I and the Iran-Iraq war.[7,66]

Conclusions

Although these agents were first developed as weapons during World War I, the specific mechanisms of action of the vesicants have yet to be fully elucidated. Perhaps this is because, in view of their potent alkylation of macromolecules, they induce multiple processes which, taken together, are responsible for the clinical manifestations and pathophysiologic effects observed. The local effects occur mainly in the skin, respiratory tract, and eyes. However, given the good absorption resulting from the lipophilic characteristics of these agents, substantial systemic effects may arise particularly in bone marrow, the gastrointestinal tract, and the central nervous system. As a result of the nonspecific mechanism of action of these agents, antidotes for treating cases of poisoning are not currently available. The exception is dimercaprol, which can to some extent ameliorate the systemic effects of lewisite.

Vesicants can be considered disabling agents, as shown by the low mortality observed in armed conflicts where they have been used and, in particular, on comparison with other chemical warfare agents. In war, combatants disabled in large numbers pose a serious problem for a side as, unlike fatalities, they require decontamination, evacuation, and health-care treatment.

We should not underestimate the large negative impact on quality of life of patients with sequelae of mustard gas exposure, whose symptoms resemble those of atopic dermatitis. Likewise, we should not rule out the possibility of increased risk of malignization of old scars, especially given that it is important to avoid additional risk factors such as exposure to sunlight.

Conflicts of Interest

The authors declare no conflicts of interest.

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