Sulfur Mustard-Induced Ocular Surface Disorders

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ABSTRACT  Sulfur mustard is a vesicant agent with severe irritating effects on living tissues, including skin, mucous membranes, eyes, and respiratory tract. The eyes are the most susceptible tissue to mustard gas effects, and varying degrees of ocular involvement are seen in 75% to 90% of exposed individuals. Most cases resolve uneventfully; however, a minority of exposed patients will have a continuous process, which manifests clinically either as a persistent smoldering inflammation (chronic form) or late-onset lesions appearing many years after a variable "silent" period (delayed form). Distinctive features common to most cases with chronic involvement include chronic blepharitis, meibomian gland dysfunction, dry eye, limbal ischemia, limbal stem cell deficiency, aberrant conjunctival vessels, corneal neovascularization, and secondary degenerative changes, including lipid and amyloid deposition and corneal irregularity, thinning and scarring. Most cases can be managed with conservative measures, eg, preservative-free artificial tears, lubricants, and topical steroids. Punctal plugs or punctal cauterization is helpful in moderate and severe forms of injury. Surgical modalities, including lateral or medial tarsorrhaphies, amniotic membrane transplantation, lamellar or penetrating keratoplasty, and stem cell transplantation have been used.

KEY WORDS  chemical warfare agents, corneal burns, corneal transplantation, mustard gas, oxidative stress, sulfur mustard

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I. INTRODUCTION

Mustard gas was first produced by Meyer in 1886. It was used initially as a vesicant agent for chemical warfare in World War I by the German army.1,2 It is a vesicant agent with severe irritating effects on living tissues, including skin, mucous membranes, eyes, and respiratory tract.3-5 Because of its use as a weapon in World War I and in over 10 subsequent conflicts, including the Iraq-Iran war (1980-1988), its properties became more widely known in the 20th century.3, 4 Its late-onset, progressively destructive effects were recognized 15-20 years after its use.5 A minority of exposed patients will develop late destructive ocular complications, which are usually progressive and permanent and can lead to reduction of visual acuity and even corneal blindness.3, 4 The ubiquitous production, simple and cheap chemical synthesis, easy stockpiling, and toxic nature of this agent make it a worldwide threat. Because of its destructive properties, combined with the lack of an effective antidote, some experts have classified mustard gas as one of the most significant chemical warfare agents.6-8

II. PHARMACOLOGY

The mustard agent is a straw-colored, oily liquid and has the odor of onion, garlic, or mustard, hence its name.9 It mainly consists of two chemical forms: sulfur mustard [S(CH2-CH2-Cl), or (2,2'-dichloro-diethylamine; HD)], and nitrogen mustard [N(CH2-CH2-Cl) or (N-methyl-2,2'-dichloro-diethylamine; HN2)].2, 10 The former is longer acting and more commonly used in chemical warfare, but the latter is more toxic.2, 4, 5, 11 The popular term "mustard gas" is a misnomer, as this agent actually appears as an aerosol of small oily droplets.12 The toxicity of sulfur mustard (SM) as an incapacitating agent is of much greater importance than its capacity to kill via a lethal dose 50% (LD50).12, 13 The LD50 for humans is about 200 mg when the substance is swallowed, 4-5 g when it is applied to the bare skin over a long exposure time, and 1500 mg/min/m3 when inhaled.2, 14 It is a stable compound in low temperatures, which can persist in clothing or on the ground for months.3 On contact with human skin, 80% of the liquid evaporates and 20% penetrates; half of this remains in the skin and the other half is absorbed systemically.2 Additionally, due to free hydrolyzation by the interface organs, SM causes systemic effects only at very high doses.15
The measurement of biochemical markers in aqueous humor is a tool for evaluating SM-induced damages even before the onset of clinical signs. The concentration of protein in aqueous humor increases 4–6 hours following exposure; although it decreases after 28 hours, it still remains higher than in non-exposed controls. This increase, together with the presence of cellular lymphocytic infiltration, is indicative of an inflammatory reaction. Aqueous humor glutathione at the very early stages of SM exposure may change in a similar pattern. Alkylation products of SM with DNA and proteins (e.g., hemoglobin and albumin), as well as its urinary metabolites, have proved to be useful targets for diagnosing SM exposure in humans. Urinary markers are readily accessible, although their rapid elimination limits their use for retrospective detection. Adducts with macromolecules such as proteins offer longer lasting (possibly up to several months) biological markers of exposure to SM. The DNA adducts can also be detected in urine, processed skin, and blood samples.

III. PATHOPHYSIOLOGY
Mustard gas damages viable tissues only, and the exact mechanism for this is not clear. Theories include liberation of intracellular hydrochloric acid, formation of new compounds acting as alkylating agents, and, finally, formation of oxidative derivatives, which collectively can lead to more cellular damage.

SM causes a cross-linking of the 2 complementary strands in the DNA molecule by a monofunctional alkylating agent of the nitrogenous bases. The major alkylating site of nucleic acids is the nitrogen residue of guanine. The results are manifested in chromatid aberrations; inhibition of DNA, RNA, and protein synthesis; blocking of the cell’s cycle in the G2-M phase; and, eventually, cell death. SM tends to undergo intramolecular cyclization to create a hyperactive compound. Conversion to this derivative is facilitated in an aqueous solution, which accounts for the sensitivity of the eye to SM is due to the readily accessible aqueous-mucous surface of the cornea and conjunctiva, as well as the high turnover rate and intense metabolic activity of corneal epithelial cells.

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Mustard gas causes additional injury via skin and eye damage after absorption through the integument and the ocular surface; respiratory damage after inhalation; and systemic toxicity after ingestion or high exposures. As a result, it may further cause gastrointestinal, circulatory, and bone marrow toxicity. Hence, the destructive effects of SM are not localized to the site of application, as remote cells and tissues also become affected. The high sensitivity of the eye to SM is due to the readily accessible aqueous-mucous surface of the cornea and conjunctiva, as well as the high turnover rate and intense metabolic activity of corneal epithelial cells.

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Free radicals have already been shown to play a role in corneal inflammation after exposure to other ocular irritants, such as alkali substances. In such cases, tissue damage after corrosive injury to the cornea is exacerbated by penetration of reactive oxygen species to the corneal stroma, leading to fragmentation of DNA chains, polymerization or depolymerization of proteins and hyaluronate, and destruction of lipid membranes. Reactive oxygen species reduce ferric iron and copper and produce the highly reactive hydroxyl radicals. These reduced metal ions, in turn, can react with H2O2 to produce the hydroxyl radical, which causes further damage.

Other potential mechanisms of cell death are related to rapid inactivation of sulphydryl-containing proteins and peptides, such as glutathione. These sulphydryl compounds are critical for maintaining the appropriate oxidation-reduction state of cellular components. Glutathione is also thought to be critical for reducing reactive oxygen species in the cell and preventing peroxidation and loss of membrane integrity, which, in turn, prevents cytokine-mediated inflammatory response. Clinically impaired corneas display increased matrix metalloproteinase (MMP) activity, in particular, MMP-9 in the acute phase. There is a potential role for nitric oxide in tissue injury induced by SM and related analogs. Of particular importance is the reaction of nitric oxide with the reactive oxygen species superoxide anion, forming peroxynitrite. Peroxynitrite is a strong oxidant and nitrating agent and is known to trigger oxidative stress.

IV. IMMUNOLOGIC MECHANISMS

Animal and human studies have demonstrated that SM has short- and long-term influences on both humoral and cellular immune functions. The perlimbal site of the lesions, their similarity to Mooren’s ulcer, and mixed inflammatory infiltrate within substantia propria suggest the immunological basis of SM-induced delayed keratitis. Depression of cell-mediated immunity has been reported. Total white blood count and percentages of monocytes and CD3+ lymphocytes are significantly higher in SM-exposed patients. In addition, the percentage of NK cells (CD16+) is significantly lower in patients with severe respiratory complications up to 20 years after SM exposure. A significant positive correlation has been found between hemoglobin level and the severity of ocular complications. Increased levels of IgG, IgM, and C3 have been reported in the majority of SM-exposed patients during the first weeks and up to the sixth month after exposure. It has been noted that even 20 years after exposure, the percentage of patients with increased IgM, IgG, and IgE are still significantly higher than in the control group.

In study of rabbits with SM injury, a significant increase in interleukin (IL)-1, IL-6, IL-8, tumor necrosis factor, MMP-2, and MMP-9 activities in the aqueous humor was observed. The analysis of inflammatory mediators over time indicates that the SM injury progresses to the posterior part of the cornea, initiating the production of cytokines/chemokines, which, in turn, may activate MMPs. MMP-2 and MMP-9 degrade collagen, thus contributing to the deterioration of the stroma. It remains to be determined whether SM-damaged corneal stroma might elicit alloreactive responses that lead to further degradation, similar to Mooren’s ulcers. Abnormalities in the immune system may contribute to recurrent infections, septicemia, and a higher incidence of malignancies in these patients.

V. SYSTEMIC MANIFESTATIONS

Acute toxic effects appear after variable periods of latency, depending on the dose, mode of exposure, environmental temperature, and personal susceptibilities. Victims may have multiple sites of injury, including skin, eye, and respiratory systems. Organ damage is influenced by different concentrations of mustard gas exposure. The eye damage starts with exposure doses of 50 mg/min/m³. At 100-400 mg/min/m³ of exposure, respiratory and cutaneous systems are affected. At a dose of more than 200 mg/min/m³, severe ocular and respiratory afflications are observed. Skin burns occur at 200-1000 mg/min/m³, and severe incapacitation from skin burns ensues at 750–10,000 mg/min/m³. The reported fatality rates are less than 2% of the exposed soldiers during World War I and 3% to 4% in the Iraq-Iran conflict. Death usually results from either respiratory failure due to chemical bronchitis/pneumonia or bone marrow suppression.

A. Skin

The cutaneous effects of SM exposure begin after a latent period lasting for 0-24 hours. The characteristic skin lesion of SM is erythema followed by blisters. At higher doses, vesicles form at the periphery of the erythematous areas, which later merge into pendulous bullae containing large volumes of clear yellow fluid. Bullous lesions are particularly likely to occur on warm, moist areas, such as axilla, genitalia, and areas where tight clothing is worn. They tend to form within 24 hours of exposure, but sometimes appear 7–12 days later. Large blisters usually break, leading to erosions and full-thickness ulceration (Figures 1 A and B). Necrosis may occur at these sites, followed by

Figure 1. Facial bullous lesions in acute phase with use of silver sulfadiazine ointment (A) and without it (B).
formation of a scar at 72 hours post-exposure.

In the case of extensive bullae formation, fluid and electrolyte imbalance combined with secondary infection may complicate recovery.\textsuperscript{54, 65} Blistering and necrotic wounds may lead to permanent residual effects, including hyper- or hypo-pigmentation, atrophy, hypertrophy, dermal scar, dryness of the skin, erythematous papular rash, multiple cherry angiomas, local hair loss, eczema, chronic urticaria, vitiligo, psoriasis, and discoid lupus erythematosus.\textsuperscript{12,14,34,63-68}

Healing time varies depending on the extent of cellular damage and the ability of the body to replenish scavengers of electrophilic stress and reactive oxygen species.\textsuperscript{6,7} SM-induced lesions tend to heal slowly, and often ulcerate and vesciate repeatedly for reasons that are still unclear.\textsuperscript{6,7} One likely explanation is the propensity for SM to affect rapidly dividing cells, such as the basal cell layer of keratinocytes in the epidermis.\textsuperscript{6,7}

Other clinical forms of cutaneous lesions are pigmented exfoliation, superficial vesicular to bullous form, bullous necrotization, deep necrotizing non-bullous form, allergic and toxic contact reactions. The pigmented exfoliative form is often combined with severe lung damage.\textsuperscript{12,14,34,63-68}

B. Respiratory Tract

Depending on the dose of SM and duration of the contact, pain and discomfort may develop in the nose or sinuses with increasing secretions, sneezing, nonproductive hacking cough, and sore throat 4-16 hours after exposure. This can develop into epistaxis, aphponia, tracheobronchitis, dyspnoea, and possible hemorrhage into the alveoli and microbial bronchopneumonia.\textsuperscript{12} Necrosis of the mucosa with associated inflammation can lead to the formation of a diphtheritic-like membrane in the most severe cases, obstructing any level of the airways,\textsuperscript{69} and later, to the clinical picture of adult respiratory distress syndrome.\textsuperscript{35,70,71} Several years later, patients may be left with obstructive and restrictive pulmonary functions, bronchiectasis and bronchiolitis obliterans, chronic bronchitis, asthma, large airway narrowing, and pulmonary fibrosis.\textsuperscript{72-80} Chronic bronchitis has been reported as the most common late complication of the respiratory system.\textsuperscript{72,74-76,79,80} Progressive hypoxemia and hypercapnea are commonly observed in moderate-to-severe cases, leading to cor pulmonale and respiratory failure.\textsuperscript{53,63,80}

The infection of the respiratory tract is a common problem, often complicated by sepsis.\textsuperscript{42}

C. Bone Marrow

Bone marrow suppression can develop within 3-5 days of high-dose SM exposure, manifested as aplastic or ineffective hematopoiesis, leukopenia, and thrombocytopenia.\textsuperscript{52} In some cases, chronic bone marrow suppression appears 7-15 days after exposure, resulting in sepsis and pneumonia\textsuperscript{6,7} and higher mortality rates.\textsuperscript{12}

D. Other Organ Damage

Gastrointestinal symptoms in the acute phase of SM injury include nausea and vomiting, which is often accom-panied by respiratory distress resulting from immediate bronchospasm.\textsuperscript{6,7} Clinical findings are acute gastroduodenitis with hemorrhagic erosions, acute desquamative enteritis, and severe hemorrhagic necrotic colitis.\textsuperscript{6,12} Central nervous system involvement includes headache, anxiety, fear of the future, restlessness, confusion, lethargy, and convulsions.\textsuperscript{6,12} In addition, patients can develop pulmonary, nasopharyngeal and laryngeal cancers, basal cell and Bowen's carcinomas, adenocarcinoma of the stomach, and acute myeloblastic and lymphoblastic leukemia.\textsuperscript{66,81-86} Although an association between exposure to this chemical agent and ocular surface malignancies has not been reported, confocal microscopic findings have exhibited bizarre and abnormally enlarged pleomorphic keratocytes in all cases with SM-induced keratopathy.\textsuperscript{14,87,88}

VI. OCULAR INVOLVEMENT

The moistness of the ocular surface, the extreme lipophilic nature of the gas, and the high turnover rate and metabolic activity of corneal epithelial cells make the eye the most susceptible part of the body to the effects of SM exposure.\textsuperscript{2,6,11} Varying degrees of ocular involvement are seen in 75% to 90% of individuals exposed to mustard gas.\textsuperscript{6} The acute symptoms usually resolve completely without further inflammation after 2-6 weeks. However, photophobia may persist for some time. In a minority of patients, a continuous process clinically appearing either as a persistent smoldering inflammation (chronic form) or late-onset lesions appearing many years after a variable “silent” period (delayed form) may develop.\textsuperscript{2,3,6}

It remains unclear whether mustard gas actually induces a continuous process of progressive inflammation on the ocular surface with different speeds of individual progression. In the chronic form of injury, severe acute lesions abate, but symptoms such as photophobia, dry eye, and foreign body sensation persist, and sequelae such as corneal epithelial erosions, limbal ischemia, and, occasionally, peripheral corneal thinning and neovascularization may slowly progress.\textsuperscript{3} In the delayed form, patients become asymptomatic and enjoy improvement of their lesions several weeks after initial exposure, only to experience resurgence of symptoms several years later.\textsuperscript{2,3,6}

A. Acute Phase

Within several hours of SM exposure, symptoms begin to appear.\textsuperscript{6,15,51} The severity and timing of clinical symptoms and signs seem to be related to dose, concentration, and duration of contact.\textsuperscript{6,15} As early as 1 hour after exposure, clinical manifestations start with a sensation of grittiness, progressive soreness, and a bloodshot appearance before proceeding to edema and giving rise to “acute conjunctivitis.” At 2-6 hours, patients complain of severe ocular pain, lacrimation, photophobia, blepharospasm, and decreased visual acuity.\textsuperscript{6,12} The gradual spontaneous recovery usually occurs after 48 hours, with full regeneration of the corneal epithelium occurring within 4-5 days, although complete symptomatic recovery may take 6 weeks or longer.\textsuperscript{2,6,7,63}

Based on severity, immediate lesions can be divided into three groups: mild, moderate, and severe.\textsuperscript{2}
Mild lesions are caused by exposure to 12-70 mg/min/m² and manifest as mild eyelid erythema/swelling and conjunctival engorgement without significant chemosis. The cornea usually is spared, and recovery is complete within a few days.

Moderate lesions are caused by exposure to 100-200 mg/min/m² mustard gas. The eyelid, conjunctival, and corneal lesions are of the same type that occur with mild injury, but are more severe. Symptoms include a dry sensation, severe ocular pain, photophobia, and severe blepharoconjunctivitis. The corneal epithelium begins to vesicate and slough predominantly in the interpalpebral fissure, leading to superficial punctate keratitis, corneal abrasions, superficial infiltrations, corneal ulcers, and even perforation. The superior cornea is relatively spared, probably due to the protective effect of the upper lid. After 48 hours, pain and blepharospasm gradually decrease and the corneal epithelium usually heals completely within 4-5 days. Full resolution of symptoms may take up to 6 weeks or longer.

Severe lesions occur after exposure to more than 200 mg/min/m² mustard gas. Patients with such exposure often sustain associated systemic toxicity in the respiratory, gastrointestinal, and integumentary systems. In addition to the moderate lesions, limbal vasculature and deeper layers of the cornea are also involved. The eyelids may become ulcerated. The nasal and temporal limbi lose their normal vasculature and become white and necrotic. In addition to having marked congestion and chemosis, severe conjunctival lesions are characterized by areas of ischemia and necrosis, particularly in the interpalpebral fissure. There may be low-grade iridocyclitis, which usually leaves no synechia or cataract formation, and, rarely, the intraocular pressure is transiently elevated. Because conjunctival lesions are limited to the interpalpebral fissure, adhesions between the globe and eyelid are unlikely. The corneal epithelial irregularity and stromal edema combine to create an orange peel appearance, which usually does not stain with fluorescein; however, epithelial erosions and small corneal ulcers may be noted (Figure 2). They are prone to bacterial superinfection, including Pseudomonas aeruginosa, which can lead to severe intraocular infection necessitating evisceration or urgent tectonic penetrating keratoplasty (PKP). Corneal sensation may be affected to varying degrees. There may be pupillary constriction, iris vasodilatation, hemorrhages, and necrosis, with development of anterior uveitis. Improvement often begins within 1-2 weeks, when the corneal edema resolves and the uveitis subsides. A few weeks later, neovascularization begins. These tortuous blood vessels tend to bleed into the corneal subepithelial space and stroma. They eventually undergo rapid degeneration, leaving white opacities in the otherwise clear cornea.

**B. Chronic Phase**

A continuous process leading to a chronic form or a delayed form of injury develops in less than 1% of exposed individuals up to 40 years after their exposure. In contrast to acute lesions, chronic and delayed mustard gas lesions usually cause permanent reduction in visual acuity and can even lead to blindness. Distinctive features include chronic blepharitis, meibomian gland dysfunction, dry eye, limbal ischemia, limbal stem cell deficiency (LSCD), corneal neovascularization, lipid and amyloid deposition, and irregularity, thinning and scarring of the cornea. It remains unknown whether disease activity correlates with hotter and drier climates.

In the chronic form of injury, patients suffer from photophobia, injection, tearing, and foreign body sensation. Impaired corneal sensation, damaged limbal vasculature, and recurrent epithelial erosions produce corneal irregularity, thinning, and neovascularization, leading to descemetocytes and perforation. Corneal neovascularization can lead to intrastral exudation of plasma lipids and deposition of amyloids. Despite the ongoing inflammation, the eye may appear quiet. Nonetheless, this should not be considered as quiescence, as it may be the result of vascular necrosis resulting in ischemia. Patients suffer from foreign body sensation, tearing, redness, and severe photophobia. In early stages, the limbal region frequently presents a marbled appearance in which porcelain-like areas of ischemia are surrounded by blood vessels of irregular diameter. Varicose, tortuous, amputilliform and leaking vessels that characteristically are accompanied by blood islands and hemorrhages surround perilimbal ischemic areas. This may lead to lipid depositions in the adjacent cornea and trigger chronic stromal inflammation and thinning. It may also aggravate the clinical situation and produce severe photophobia and tearing. Later, vascularized scars of the cornea are covered with crystal and cholesterol deposits, leading to worsening of opacification, recurrent ulcerations, and sometimes corneal perforation. Opacification of the central and lower portions of the cornea is typical, while the upper sections are often protected by the eyelids. These lesions even recur after corneal transplantation. A minority of patients might develop corneal perforation and phthisis bulbi.

The presence of ischemic conjunctival areas, intrastromal corneal and conjunctival hemorrhages and bloody islands, lipid and amyloid depositions, and aberrant neo-
vascularization may be signs of chronic vasculitis induced by mustard gas. The chronic conjunctival and corneal inflammation can lead to chronic blepharitis with lid margin thickening and meibomian gland dysfunction. No cases with keratinization have been reported to date.

Ocular surface involvement can be graded as mild, moderate, or severe. Conjunctival vessel changes, including telangiectasia, tortuosity, and segmentation, are characteristics of the mild form, and the adjacent corneal quadrant is clear in this form. Limbal ischemia and peripheral vessel invasion with or without corneal opacity are features of the moderate form. If previous findings are accompanied by severe corneal thinning and melting, the involvement is considered severe (Figures 3 A-D).

The clinical picture of SM-induced ocular surface disease is a continuous spectrum of manifestations that make it difficult to clearly grade its severity. LSCD gradually begins in moderate forms and finally ends in total LSCD in most severe cases.

It appears that late clinical manifestations of SM keratopathy result from several underlying mechanisms. LSCD progresses from partial and asymmetric to total LSCD because of a direct and progressive detrimental effect of mustard gas or chronic limbal ischemia. We cannot ignore the likelihood that chronic ischemia or the detrimental effect of mustard gas may disturb the stem cell niche, resulting in progressive stem cell attrition. Damage to corneal nerves leading to the loss of corneal sensation also contributes to this detrimental process over time. In an animal study, degeneration of nerve fibers with a typical subsequent Wallerian degeneration was observed after exposure, and continued for weeks to months afterwards.

Autoimmune reactions to the corneal antigens altered by the mustard agent (collagen-mustard compound) have also been proposed. In delayed mustard gas keratopathy, limbal ischemia plays a significant role in the corneal neurotrophic and trophic changes, including thinning, descemetecle formation, and perforation. The role of known angiogenic factors in SM-induced angiogenesis has not been yet elucidated.

The clinical course of corneal injuries like alkaline/acidic burns is quite similar in all victims. The question of why some eyes are more vulnerable than others to the late response of SM is still unanswered. Vulnerability may be related to concentrations, total doses, contact duration, mode of exposure, environmental temperature, the extent of use of protective equipment, personal susceptibilities, individual closeness to the ground, age, and other factors.

Generally, children are more severely affected by SM exposure than adults, most likely because children have thinner skin and are closer to the ground, where mustard vapors accumulate. Reports of late response to SM exposure would also be related to type and duration of follow-up.

A puzzling feature in delayed mustard gas keratitis regards the unpredictable exacerbations and remissions in the clinical course, with peripheral corneal infiltrations, at times extending to the central cornea, mimicking Mooren's ulcer. Corneal infiltrations usually are accompanied by neovascularization (morphologically similar to conjunctival vessels), which is an unfavorable prognostic factor. Infiltrations may be accompanied by intrastromal hemorrhages,
corneal necrosis, thinning, descemetocoele formation, and perforation. Recurrent episodes lead to centripetal and deeper infiltrations, and degenerative changes finally take place and crystalline deposits are noted over time. However, corneal manifestations are not typical of the partial or total LSCD seen with severe chemical burns. With SM-induced keratopathy, the cornea is not covered by a total vascularized pannus; instead, corneal thinning with amyloid and lipoid depositions are prominent. In some areas, leaking telangiecatic vessels invade peripheral cornea. Corneal involvement is often asymmetric between the two eyes, and in each eye, severity of involvement is not the same in all quadrants. Most often, the interpalpebral (exposure) area of the cornea that is adjacent to conjunctival ischemic areas is more severely damaged. This may be due to direct contact of the interpalpebral fissure during the exposure or to more severe perilimbal ischemia in these areas. In turn, perilimbal ischemia may be due to direct exposure of tissues with consequent vascilitis.

In summary, corneal manifestations seem to be a mixture of progressive chronic limbal ischemia and stem cell deficiency. The differences in the clinical picture may be related to exposure pattern. In chemical burns, a high concentration of acid/alkali liquids is in direct contact with limbal stem cells, while aerosolized gas is in contact with the ocular surface during an SM attack. Numerous animal studies have investigated the clinical picture and pathophysiologic mechanisms of SM-induced keratopathy, but these are beyond the scope of this review.

C. Pathologic Findings

Light microscopic observation of corneas 48 hours after SM exposure reveals epithelial denudation and marked stromal edema accompanied by cellular infiltration, mostly of eosinophils. Endothelial destruction is occasionally observed. Epithelial regeneration starts 72 hours after exposure by migration of remaining noninjured corneal or conjunctival cells. The latter is confirmed by the presence of goblet cells scattered diffusely in the newly regenerated epithelium. The mosaic pattern of basal epithelial cells is delayed-onset forms of injury, abnormal confocal microscopic findings are observed in all corneal layers. The anterior and middle portions are affected more severely than the posterior parts. The mosaic pattern of basal epithelial cells is not apparent. Their density decreases and most of the cells look pleomorphic, with damaged or irregular high-contrast boundaries. Generalized decreased density of keratocytes has been reported, but their gradient pattern is controversial. Keratocyte density decreases progressively from the anterior to the posterior stroma in normal cornea. Within the anterior corneal stroma, spindle-like keratocytic nuclei (perhaps representing necrotic keratocytes) close to Bowman layer could be delineated. Normal keratocytes are capable of dividing and migrating after injury.

Histopathologic features of the conjunctival component in patients with chronic or delayed mustard gas keratopathy include chronic inflammation, perilimbal conjunctival ischemia, telangiectasis, vasculitis, subconjunctival hemorrhage, decreased number of goblet cells, thinning or thickening of epithelium, scar formation in substantia propria, lymphocytic infiltration, and dilated lymphatic vessels. There are no signs of dysplasia. Degenerative processes seem to dominate in chronic and the epithelium and Bowman’s layer, loss of keratocytes, conjunctivalization, superficial and stromal vascularization, squamous metaplasia, focal corneal thinning and ulceration, acute and chronic infiltration of inflammatory cells, lipoid/amyloid deposition, endothelial cell loss, calcific band keratopathy, and scarring in the stroma. Perilimbal conjunctival vascilitis and ischemia may contribute to the corneal cytopathologic features. Corneal squamous metaplasia, which is mild-to-moderate in most cases and has been suggested as a diagnostic factor in cases with mild or subclinical limbal deficiency, may be a reactive response to mustard gas (Figure 4).

D. Confocal Microscopy

Although SM cannot easily achieve deep corneal penetration, in the acute phase, it targets endothelial cells, inducing apoptosis at lower concentrations and both apoptosis and necrosis at higher concentrations. In chronic and delayed-onset forms of injury, abnormal confocal microscopic findings are observed in all corneal layers. The anterior and middle portions are affected more severely than the posterior parts. The mosaic pattern of basal epithelial cells is not apparent. Their density decreases and most of the cells look pleomorphic, with damaged or irregular high-contrast boundaries. Generalized decreased density of keratocytes has been reported, but their gradient pattern is controversial. Keratocyte density decreases progressively from the anterior to the posterior stroma in normal cornea. Within the anterior corneal stroma, spindle-like keratocytic nuclei (perhaps representing necrotic keratocytes) close to Bowman layer could be delineated. Normal keratocytes are capable of dividing and migrating after injury.

It has been suggested that the genetically altered keratocytes may lose their ability to repopulate the injured stroma in mustard gas keratopathy. Bizarre and abnormally enlarged pleomorphic keratocytes are observed in almost all cases. Intrastromal microdots, which are compatible with foci of stromal necrosis, may be observed. Foci of amyloid degeneration and lipid deposition and stromal neovascularization, have been reported, as well.

Degenerative processes seem to dominate in chronic and
delayed mustard gas keratopathy. The presence of dendritic cells without their dendrites and activated keratocyte nuclei may indicate ongoing inflammation at the microscopic level. These changes in the interstitial matrix of the cornea may be a potential barrier for repopulation of stromal keratocytes. Decreased sub-basal nerve plexus is observed in most of the cases, which could be secondary to destruction of the Bowman layer, occurrence of subepithelial fibrosis, and associated dry eye. However, the thickness of the midstromal irregular circular node-like nerve structure may increase (Figures 5 A-D). 

VII. INITIAL MANAGEMENT OF SYSTEMIC MANIFESTATIONS

There is no effective antidote for mustard gas exposure, so prevention is the most effective management strategy. Special protective garments and gas masks containing a charcoal layer to absorb penetrating sulfur mustard are highly effective in preventing dermal, respiratory, and ocular injuries. However, chemical goggles, gas masks, and protective clothing are cumbersome and inefficient for daily use in military or civilian populations.

The first priority of treatment after mustard gas exposure is to remove victims from the contaminated areas and initiate decontamination procedures. Contaminated clothes must be removed and destroyed. Rapid riddance from the skin is critical, as mustard penetrates the tissues within minutes of exposure, and its effects become irreversible. When available, absorbent powders such as calcium chloride, magnesium oxide, activated charcoal, talcum powder, Fuller’s earth, and flour, should be used to decontaminate the skin. The powder is sprinkled onto the exposed skin and allowed to absorb the mustard, and is then washed off with water.

When mustard exposure is suspected, the victim should be washed with hypochlorite 0.5%, calcium hypochlorite (72 g/L), neutrogenic soap/shampoo (pH around 7.0), and copious amounts of warm water for a prolonged period of time. Complete hydrolysis of mustard renders it nontoxic. Washing of the affected area with oil, kerosene, or gasoline, followed by washing with soap and water, has also been advocated.

Even in asymptomatic patients, the eyes should be washed as soon as possible with generous amounts of water, normal saline, and Ringer solution. Sodium bicarbonate 1.5%, dichloramine-T 0.5%, and saturated solutions of sodium sulfate or magnesium sulfate, as well as zinc or boric acid, have also been suggested. Because of the rapid and irreversible reaction of SM with ocular tissues, it may seem that irrigation would not be useful more than 10-15 minutes after exposure; however, irrigation at this later point is recommended, as it does no harm and may help. Of the many fluids studied for use in ocular irrigation, none has proved more effective than tap water.

Upon arrival at a medical facility, the victims should be quickly examined by medical doctors for severity grading of SM intoxication. The mild cases that do not reveal any sign of intoxication should be kept under observation and may be discharged after 24 hours. Those who show any sign of SM poisoning during observation should, along with moderate and severe victims, receive emergency management. If a large surface area is affected, fluid and electrolyte balance must be maintained. The management of skin lesions focuses on the prevention of secondary bacterial infections by applying sulfamylon (mefenide acetate),
sildavene (silver sulfadiazine), povidone iodine or bacitracin zinc to the affected areas, and administration of systemic antibiotics to prevent secondary infections.6,12,113,114 Biosynthetic dressings, ie, hydrogels and hydrocolloids, may accelerate healing. Steam inhalation, cough suppressants, oxygen therapy, assisted ventilation, early intubation, and bronchodilators are immediate measures for respiratory involvement. Systemic steroids and antibiotics may be helpful for severe affliction.6

Medical treatment can be divided into antidotal/general treatments and care of specific organs. In the antidotal treatment, up to 500 mg/kg sodium thiosulphate should be administered as soon as possible. It reacts with mustard gases when these agents are in the cyclized form. Thus, it is an effective antidote against systemic intoxication, especially when taken before exposure.6.12 Sodium thiosulphate can also be combined with a number of other drugs, such as cysteine, sodium citrate, dexamethasone, promethazine, heparin and vitamin E, to increase its protective activity against SM.115

VIII. MANAGEMENT OF OCULAR INJURY

A. Acute Phase

The ocular lesions can be differentiated into conjunctival only and corneal involvement by fluorescein staining performed immediately after ocular washings. Medical therapies in this stage include topical antibiotics, preservative-free lubricants, and corticosteroids.2,6,12 In the case of corneal involvement, close observation is necessary. Treatment should include daily ocular irrigation, artificial tears, therapeutic contact lenses, mydriatics (to reduce ocular pain produced by spasm of the ciliary muscle and to prevent posterior synechiae), antibiotic drops (to prevent secondary bacterial infections), and topical antiglaucoma medications (to control intraocular pressure).2,6,50,63 The use of lubricants is controversial, as they may concentrate mustard gas particles trapped under the eyelids.2 Ocular bandages should be avoided, as they might raise the corneal temperature and accelerate the toxic effects.2,12 Topical corticosteroids should be cautiously used.2,6,12 Although they may reduce eyelid, conjunctival, and corneal swelling and improve anterior uveitis, they may predispose the cornea to infection.6,12 Petroleum jelly can be used on the follicular margins to prevent sticking. However, it should not be used immediately after exposure, as mustard can become concentrated in this oily medium.2,3,113 Dark glasses and patient reassurance are very important, as the eye lesions produce severe photophobia and fear.9,113

Amniotic membrane transplantation can suppress inflammation and scarring and promote healing in patients suffering from a variety of ocular surface diseases.116-121 Used during the acute stage of Stevens-Johnson syndrome122 and acute chemical burn,123-127 its healing and anti-inflammatory effects have been shown to prevent late sight-threatening cicatrical complications. Therefore, it may be beneficial in the control of acute stages of SM-induced ocular surface disorders.

B. Chronic Phase

1. Medical Treatment

No definitive treatment for chronic and delayed mustard gas-induced ocular surface disorders is available.2,3,6,12 Current therapy is mainly conservative and directed at symptomatic relief, as it addresses tear deficiency and ocular surface instability (ie, artificial tears, temporary or permanent punctual occlusion, blepharorrhaphy, tarsorrhaphy and therapeutic contact lenses).2,6 Because the ocular surface is compromised, especially in the moderate and severe forms of injury, preservative-free artificial tears or gels should be used. Punctal plugs are usually beneficial.1,50,61 Permanent occlusion of one or both puncti of each eye by electrocoagulation may be preferable.95

Topical steroids can be used to control ocular surface inflammation and acute episodic corneal inflammatory infiltrates.2,3 Preservative-free topical steroids are beneficial, especially for short-term usage.3 Although systemic steroids are not usually necessary, in the case of severe corneal inflammations, they may be combined with topical steroids.3 However, long-term steroid-induced complications, including cataract and glaucoma, should be considered.2,6,12 Because of the loss of corneal integrity with mustard gas keratitis, the ocular surface is prone to secondary microbial infection; thus, topical steroids should be used cautiously.95,96

High DK silicone hydrogel contact lenses can improve punctate epithelial erosions and keratitis, as well as persistent epithelial defects (PEDs) in the context of partial LSCD. With total LSCD, they are not effective, and they can increase the risk of secondary microbial infections.2,3,6,12 Treatment of associated blepharitis is recommended in all cases. To improve visual acuity, spectacles and high DK soft/hard contact lenses may be cautiously used.3,5 Most cases with severe and recurrent inflammatory infiltrates respond well to conservative measures, including topical/systemic steroids.95,96 Adjuncts such as lubricants and topical antibiotics may help.2,3,61

2. Surgical Interventions

a. Tarsorrhaphy

In the case of nasal or temporal progressive corneal thinning with or without PEDs, medial or lateral tarsorrhaphy may halt progression of corneal thinning.3,95 It can also dramatically improve the symptoms of patients with chronic ocular surface irritation and dry eye.95 It is highly recommended after any type of stem cell or corneal transplantation.95,96

b. Amniotic Membrane Transplantation

Amniotic membrane transplantation can be used to treat PEDs that occur with partial LSCD.54,95 However, it is not useful when LSCD is severe or total.54 In severely irritated eyes with annoying photophobia due to corneal lipid deposition, superficial keratectomy combined with amniotic membrane transplantation is very beneficial (Figures 6 A and B).95 Amniotic membrane transplantation may also be used as a patch or graft as an adjunct to various kinds of
stem cell transplantation. It may also be used as an adjunct to medical therapy in cases with recurrent corneal inflammatory infiltrates to decrease ocular surface inflammation and reduce scarring. Multilayered amniotic membrane transplantation can be used in corneas with severe thinning.95,136

c. Stem Cell Transplantation

Candidates for stem cell transplantation include patients suffering from chronic irritation, redness, and tearing of the eyes with PEDs associated with severe corneal thinning, who are unresponsive to conservative treatments (artificial tears, lubricants, punctal occlusion, blepharorrhaphy and tarsorrhaphy).95 Limbal areas adjacent to the thinnest peripheral corneal areas with epithelial defects are selected as potential surgical sites. In some situations, simultaneous penetrating or lamellar keratoplasty can be performed.95,96

Limbal stem cells can be harvested from immediate family members, including parents, siblings, or children (living-related conjunctival-limbal allograft [lr-CLAL]) or cadaveric eyes (keratolimbal allograft [KLAL]). Human leukocyte antigen (HLA) matching is not obligatory. Various surgical techniques have been previously described.95,137-142

Tissue harvested from one or both eyes of an immediate family member is fresher and has closer genetic composition than KLAL. On the other hand, a KLAL graft is more accessible and has more stem cells. However, besides being less fresh than an lr-CLAL graft, it is more prone to chronic stem cell attrition and rejection. Due to partiality, bilaterality, and asymmetry of LSCD; and discrepancy in severity of quadrant involvement, complete 360-degree coverage of the limbal area by graft is unnecessary.95 Sectoral KLAL/ lr-CLAL in areas with the most severe thinning and LSCD appears to be adequate (Figures 7 A and B).

In a recent study, the rejection-free graft survival rate was reported to be 39.1% in the lr-CLAL group and 80.7% in the KLAL group at month 40, with a mean follow-up period of 24.9 and 68.8 months, respectively.143 Because simultaneous systemic problems exist in patients after mustard gas exposure, minimal necessary immunosuppression should be used.95,96 In some cases with severe ischemia, simultaneous resection of ischemic conjunctiva and advancement of near normal conjunctiva may be beneficial. It is not clear whether conjunctival advancement or tenonplasty should be used to correct ischemia before stem cell transplantation.
d. Corneal Transplantation

Penetrating or lamellar keratoplasty may be sufficient when LSCD is not severe and when visual acuity is decreased due to central corneal opacification caused by amyloid/lipoid deposition. In such circumstances, perilesional conjunctival ischemia is usually mild. Due to the recurrent and chronic nature of the disease, it is advisable to spare the posterior stroma and corneal endothelium, avoiding the associated ocular surface derangements; thus, lamellar keratoplasty (LKP) is preferred. A full-thickness graft is required for deeper lesions. Tectonic PKP may be needed in eyes with severe corneal thinning, large descemetoceles, and impending or frank corneal perforation. Tectonic LKP may also be performed in cases with small descemetoceles. Conventional LKP, or deep anterior lamellar keratoplasty (DALK; Melles and Anwar techniques) can be performed. 144,145 The rejection-free graft survival rate has been reported to be 39.0% in PKP patients and 90.3% in LKP at month 28, with a mean follow-up length of 29.6 and 85.0 months, respectively.143 Most often, due to corneal scar formation and variability of corneal thickness and its irregularity, conventional LKP and Melles techniques are preferred. Although, corneal transplantation can be simultaneously performed with limbal stem cell transplantation, it is advisable to perform it at least 3 months after stem cell transplantation. Because of the compromised ocular surface, corneal transplantation in cases with SM-induced keratopathy is considered high-risk. Cases with severe LSCD and severe limbal ischemia with peripheral corneal thinning may have a high rate of graft failure due to rejection reactions, recurrent opacity, and corneal thinning.

3. Treatment Algorithm (Figure 8)

Conservative management, which is the main modality in the mild form of SM injury, should be applied in all grades of delayed-onset SM-induced ocular surface disease. In the moderate form with partial stem cell deficiency, corneal opacity can be managed with corneal transplantation alone. In this grade, PED due to partial stem cell deficiency and limbal ischemia can be treated by AMT. In severe forms with severe LSCD associated with severe corneal thinning and melting, stem cell transplantation is the best option. Subsequent corneal transplantation can be used to improve visual acuity.

4. Postoperative Medical Regimen and Surgical Outcome

Topical antibiotic and steroid drops (especially preservative-free) are used when indicated, but tapered and discontinued when corneal epithelialization is complete and ocular surface inflammation declines. Topical 20% autologous serum, preservative-free artificial tears, and lubricating gels or ointments are also useful. Oral prednisolone 1 mg/kg should be started and tapered off during 6-8 weeks with decreasing inflammation, and antiglaucoma medications should be used as necessary. Because of the progressive nature of the disease, regular follow-up visits are highly recommended.

In general, optimization of the ocular surface by the aforementioned measures is required after corneal transplantation. The dose of systemic steroids should be increased for a period after corneal transplantation to decrease ocular surface inflammation. Immunosuppressive therapy may be required in the case of recurrent rejections, previous failure, or the presence of other risk factors. Different systemic and topical immunosuppressive regimens have been suggested for allogenic stem cell transplantation. Systemic cyclosporine A 3 to 5 mg/kg has been used in patients with SM-induced ocular surface disease. Combined systemic immunosuppression using more potent and safer immunosuppressives, including mycophenolate mofetil 1 to 2 gr/day and tacrolimus 2-6 mg/day, has been shown to be more effective than cyclosporine A in promoting survival in solid organ transplantations, as it lessens acute rejection. Doses should be adjusted according to ocular surface inflammation and systemic adverse effects. Given the multiple organ involvement in patients with SM-induced ocular surface disease, the optimal dose, combination, and duration of therapy should be carefully adjusted and evaluated in further studies. Because of the potential side effects of systemic immunosuppression, close collaboration with an immunosuppressive therapy expert is highly recommended.

Living-related limbal stem cell transplantation has been shown to be an effective way to stabilize the severely inflamed ocular surface in patients with advanced mustard gas keratopathy. This can markedly decrease subjective complaints, heal PEDs, and lead to regression of peripheral corneal neovascularization. The long-term results of sectoral KLAL have not yet been reported in such cases. Acute rejection, which is more prevalent in the early months after transplantation, is highly recommended.

Figure 8. Treatment algorithm for chronic/delayed-onset sulfur mustard-induced ocular surface disorders. See text for details. AMT = amniotic membrane transplantation; LSCT = limbal stem cell transplantation; PKP = penetrating keratoplasty; LKP = lamellar keratoplasty.
surgery, is manifested by the occurrence of limbal and perilimbal engorgement of vessels associated with conjunctival chemosis in the limbal transplant area. This can be treated by increasing the dose and frequency of topical and systemic steroids. The dose is gradually tapered with the elimination of vascular engorgement and local chemosis. Graft failure due to acute rejection is rare. Whether acute stem cell rejection(s) predispose the patient to chronic rejection has yet to be elucidated.

The results of PKP or LKP alone or combined with stem cell transplantation has been shown to be promising with proper case selection. Success may be related to the lack of structural defects in the ocular adnexa, symblepharon formation, partiality of stem cell deficiency, mildness of dryness, and absence of corneal exposure. Corneal transplantation in these patients is high-risk due to the compromised ocular surface, especially LSCD and perilimbal conjunctival ischemia, chronic inflammation, and decreased sensation. However, with appropriate management, graft clarity and visual outcomes have been reported to be favorable in long-term follow-up.

Even with successful corneal transplantation, SM-induced ocular surface disease may progress and recur (Figures 9 A and B). A rate of endothelial rejection up to 59% has been reported. Although endothelial immune reactions were relatively acute in these patients, most of them did not lead to graft failure. Optimization of the ocular surface and keeping it free of inflammation are critical for survival of the transplanted stem cells and corneal graft. It has been observed that corneal grafts performed after stem cell transplantation have better results than corneal grafts alone. Graft rejection may be more frequent in eyes that receive simultaneous corneal graft and stem cell transplantation than in those that have had the procedures sequentially. The major vision-limiting factors after a successful corneal transplantation are corneal epithelial breakdown, tear film instability, corneal astigmatism, steroid-induced glaucoma, and cataracts.

C. Novel and Potential Therapies for Mustard Gas Injury

Although progress has been made in understanding how the cornea responds to acute insults, the design of treatment strategies for SM injury is complicated by the lack of knowledge regarding the etiology of recurrent corneal disorders. In some animal studies, topical use of corticosteroids and nonsteroidal anti-inflammatory drugs, colchicine, a calcium-blocker (diltiazem), and MMP inhibitors (such as doxycycline) have been shown to reduce ocular inflammation. Reduced dermal and systemic injury has been reported after treatment with thiosulfate, nicotinamide, flavonoids, and topically applied iodine. Colchicine was found to inhibit the acute ocular response to nitrogen mustard in rabbits. Increased survival was noted in rats treated parenterally with vitamin E or dexamethasone within 15 minutes of exposure, while pre-exposure treatment of rats with nicotinamide (NAD+ precursor) decreased the severity of skin damage induced by sulfur mustard.

Thymosin β4 is a highly conserved, 43 amino-acid polypeptide that has been shown to influence cell migration, proliferation, and differentiation, promoting corneal wound healing, decreasing inflammation, and modulating activity of MMP when applied ectopically. This has been suggested as an antidote for SM injuries. Metallocomplexes, such as zinc- or gallium-desferrioxamine, are known to inhibit the formation of highly reactive free radicals. It has been hypothesized that either complex exerts its protective effect by intervening in a critical step of hydroxyl radical formation during acute phase damage. Nitric oxide synthase inhibitors, including topical iodine preparations and aminoguanidine, have been reported to protect or rescue cells in vitro from SM-induced toxicity. Ebelson, a peroxynitrite scavenger that did not affect nitric oxide synthase activity, has also been reported to be an effective inhibitor of SM-induced toxicity. Several studies have shown that glutathione or the its prodrug N-acetylcysteine can reduce oxidative stress and toxicity induced by SM or its analogs.
IX. SUMMARY

The vesicant agent sulfur mustard has been used as a weapon in several wars. Acute ocular manifestations of exposure include conjunctival redness, lacrimation, photophobia, blepharospasm, corneal edema, ulcer, iris vasodilatation/leukorrheamas, and anterior uveitis. Most cases resolve uneventfully; however, a minority of exposed patients develop a continuous process manifesting as a persistent smoldering inflammation (chronic form) or late-onset lesions appearing many years after a variable “silent” period (delayed form). Distinctive clinical features are chronic blepharitis, meibomian gland dysfunction, dry eye, limbal ischemia, vasculitis, stem cell deficiency, corneal neovascularization, lipid and amyloid deposition, corneal irregularity, thinning and scarring. The main pathophysiological mechanisms of injury consist of progressive DNA alkylation and formation of reactive oxygen species that ultimately lead to limbal stem cell deficiency and severe perilimbal conjunctival ischemia/vasculitis.

Conservative treatment, including preservative-free artificial tears, lubricants, topical steroids, and punctal plugs/cautereization are sufficient in most patients. Lateral or medial tarsorrhaphy, amniotic membrane transplantation, lamellar or penetrating keratoplasty and stem cell transplantation may be necessary for visual rehabilitation in eyes with moderate-to-severe disease.

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