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Mustard Gas-Induced Ocular Surface Disorders; an update on the pathogenesis, clinical manifestations, and management

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Abstract

Purpose: Mustard gas (MG) is a potent blistering and alkylating agent that has been used for military and terrorism purposes. Ocular surface injuries are common after exposure to MG. This review provides an update on the pathophysiology, ocular surface complications, and treatment options for MG-related ocular injuries.

Methods: Required information was obtained by reviewing various databases such as Cochrane Library, Google Scholar, and PubMed until March 2022. Data were collected by using keywords: “mustard gas” OR “sulfur mustard” AND “eye” OR “cornea” OR “ocular complication” OR “keratitis” OR “keratopathy” OR “limbal stem cell deficiency” OR “dry eye”.

Results: Chronic intracellular toxicity, inflammation, and ischemia have been shown to play an essential role in the pathogenesis of MG injury. Ocular surface injuries can have acute, chronic, and most distinctly a delayed-onset presentation leading to various degrees of limbal stem cell deficiency. To date, no treatment has been agreed upon as the standard treatment for chronic/delayed-onset MG keratopathy. Based on the authors’ experience, we propose a management algorithm for MG-related ocular surface injuries involving optimization of ocular health, anti-inflammatory therapy, and if needed surgical interventions. The management of chronic and delayed-onset presentation remains challenging.

Conclusion: MG keratopathy is a unique form of chemical injury which can lead to a range of ocular surface pathologies. Long-term anti-inflammatory therapy even in patients with seemingly

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mild disease may potentially reduce the likelihood of the development of more severe delayed-onset disease.

Keywords

Mustard gas; Ophthalmology; Mustard gas keratopathy; Eye; Management

Introduction

Mustard gas (MG) is a blistering and alkylating agent. Thousands of people were poisoned with MG during World War I and the Iran-Iraq War[1, 2]. The mustard agent has two chemical forms: the sulfur analog (sulfur mustard or 2,2-dichlorodiethyl sulfide; SM) applied as a chemical weapon, and the nitrogen analogs used previously for the treatment of cancer[3] and in experimental models.

Mustard gas is highly lipophilic and quickly penetrates the epithelial lining of tissues. Damage to the cell membrane, DNA cross-linking, the release of inflammatory cytokines, and oxidative stress result in various acute and chronic ocular, cutaneous and respiratory injuries[4]. It can lead to fluid-filled blisters and skin erythema, followed by permanent disfiguration by dermal scarring and hypo- and hyper-pigmentation. Lung injuries can lead to chronic bronchitis, bronchiectasis, interstitial lung disease, asthma, and emphysema[4].

The cornea is 10-fold more susceptible to MG-related injury than the skin and the lungs due to its exposure to the environment and high turnover of epithelial cells. It was reported that between 75%−90% of victims have ocular symptoms[5]. The dosage and duration of exposure, in addition to factors related to the host, determine the severity of the damage. There is a wide range of ocular surface complications resulting in vision loss[5]. This review provides an update on the pathophysiology, ocular surface complications, and treatment options for MG-related ocular injuries.

Methods

We collected the required information by reviewing various digital databases such as Cochrane Library, Google Scholar, and PubMed/Medline up to March 2022. Data were collected by using keywords: “mustard gas” OR “sulfur mustard” AND “eye” OR “cornea” OR “ocular complication” OR “keratitis” OR “keratopathy” OR “limbal stem cell deficiency” OR “dry eye”. No limitations on publication status and study design were imposed. Only articles in peer-review English language journals were included. The most relevant articles were selected and reviewed. The reference list of eligible research was also searched for additional resources.

Results

1. Pathophysiology of mustard gas-related injuries

The ocular damage caused by exposure to SM is multifactorial. Given its lipophilicity, mustard agent is rapidly absorbed through the tear film and ocular surface epithelium, where

it has alkylating, mutagenic, and cytotoxic effects. The high metabolic activity of the cornea increases its vulnerability to damage through the various mechanisms described below [2, 6].

1.1 Alkylation of nucleic acids and proteins—Mustard agents are known alkylating agents. This, in turn activates secondary signaling such as poly (ADP-ribose) polymerase (PARP), which can deplete nicotinic adenine dinucleotide (NAD)[7]. Cellular depletion of NAD inhibits glycolysis, followed by upregulation of the hexose-monophosphate shunt and release of tissue proteases which can cause cell necrosis and blistering[7].

1.2 Apoptosis induction—SM can activate both intrinsic and extrinsic signaling pathways that induce apoptosis. DNA breaks lead to cell death. Additionally, increased intracellular calcium levels due to homeostasis impairments may result in upregulation of calmodulin, an increase in nitric oxide synthetase, and activation of endonuclease, ultimately activating mitochondrial apoptotic pathways. Mitochondrial DNA alkylation causes cell death by releasing cytochrome C and activating caspase 9. Activation of Fas receptor and death receptors by SM and subsequent stimulation of caspase signaling cascade induce apoptosis[8].

1.3 Oxidative stress—SM can, directly and indirectly, lead to increased cellular oxidative stress. Increasing oxidative stress is evident in the presence of peroxidized lipid products and proteins. A 30-fold rise in Cu levels and diminished ascorbic acid in the anterior chamber (AC) are other indicators of oxidative stress following exposure to MG[9]. MG can directly inhibit the cellular respiratory enzymes and lead to glutathione (GSH) depletion[9].

1.4 Tissue inflammation—Dysregulation of the immunological system following MG exposure has been studied. SM activates the activator protein-1 and Nuclear Factor-kappa B (NF-κB). It also stimulates cyclooxygenase-2 (COX-2) and matrix metalloproteinases (MMP), leading to the release of inflammatory mediators, cytokines, prostaglandins, and serine proteases[10, 11].

Serum concentrations of interleukin (IL)-1α and Fas Ligand (FasL) in SM-exposed veterans with severe eye injuries were remarkably elevated compared to the healthy control group. Serum and tear levels of tumor necrosis factor-alpha (TNF-α) were lower in cases than in controls[10, 11]. A study on eye injuries secondary to SM showed the association of alterations in serum immunoglobulin levels, especially IgG1 and IgG2, with some ocular abnormalities[12]. Ghazanfari et al. stated that the level of IL-8/CXCL8 in tear film was associated with the intensity of ocular surface injuries[13]. The higher levels of soluble intercellular adhesion molecule 1 (ICAM-1) and changes in levels of selectins in serum of individuals with severe eye injuries caused by SM were previously demonstrated as a regulatory defense mechanism against the ocular damage by SM[14–16]. Higher serum MMP-9 in SM-exposed patients with ocular problems was also reported[17].

2. Mustard gas-related ocular surface disorders

MG-induced ocular surface disorders are divided into three main categories: Acute ocular lesions that occur within hours of chemical exposure, chronic disease which persists for

years, and late-onset disease, which occurs in patients who are symptom-free for years and then develop ocular complications.

2.1 Acute ocular injury

2.1.1 Acute ocular manifestations: Most victims will show at least some degrees of ocular surface toxicity. Generally, there is a latent period of approximately 1–6 hours before developing ocular symptoms and signs following MG exposure. The duration and level of exposure to MG are determining factors of severity in the acute stage[18].

The primary lesions are subdivided into three groups based on the severity, as shown in table 1[19, 20]. The most common acute ocular manifestations are conjunctivitis (in 75% of patients) and photophobia[21]. In mild cases, the cornea is usually spared. Moderate exposure usually involves the cornea. Loosening of the corneal epithelial layer and impairment of its barrier function may result in superficial punctate keratitis, corneal abrasion, corneal infiltration, and even perforation (Figure 1). There are reports of bacterial superinfection with *Pseudomonas aeruginosa*[22]. An orange peel appearance due to surface irregularity and stromal edema could be observed, which usually does not stain with the fluorescein. High dose exposure would additionally result in systemic toxicity (respiratory, gastrointestinal, and skin) and necrosis and ischemia of interpalpebral conjunctiva and deep corneal and limbal involvement. Anterior uveitis, posterior synechia, cataract, and full-thickness corneal damage are possible in doses higher than 200 mg/min/m^3. Transient intraocular pressure (IOP) elevation could be expected in severe cases[23]. Most mild to moderate injuries resolve completely[24]..

2.1.2 Pathologic findings in acute ocular lesions: Light microscopy may show epithelial denudation, stromal edema, and cellular infiltration (particularly eosinophils) within 48 hours after exposure. Corneal free nerve endings are exposed in the sites of epithelial loss. The epithelium starts to regenerate after three days[25]. Using electron microscopy, another study revealed a centripetal endothelial injury on the first day of exposure[26]. Damage to vascular endothelium and occlusion of conjunctival vessels accompanied by a severe decrease in density of conjunctival goblet cells are seen in moderate toxicities[7, 27].

2.2 Chronic Ocular Disease

2.2.1 Mechanism of chronic injury: Chronic complications can deteriorate the ocular surface and cause progressive visual impairment due to ongoing inflammation. However, it may be misleading that, secondary to vascular necrosis, the eye can appear quiet on slit lamp examination[7, 28].

2.2.2 Chronic ocular manifestations: Ocular findings of the late phase of MG-related eye injuries are classified into three categories: mild, moderate, and severe, as summarized in Table 2; however, the spectrum of disease is continuous and complete distinction is difficult. We previously introduced a practical approach for determining the severity of ocular surface involvement. The mild form is defined by changes such as tortuosity, telangiectasia, and segmentation of conjunctival blood vessels with a clear cornea. The moderate form is characterized by limbal ischemia and invasion of vessels to the corneal periphery with or

without corneal opacification. Corneal thinning or melting due to severe limbal ischemia and moderate to severe limbal stem cell deficiency are considered as severe forms[7, 22, 29–33].

Blepharitis, decreased tear meniscus, thickening of the eyelid margin, and meibomian gland dysfunction are associated with an increased risk of progression to more severe ocular problems[31]. Alterations in microbiological flora of the ocular surface, likely due to immune dysregulation, were also reported[34, 35].

Chronic conjunctival inflammation, ischemia, and hemorrhage are signs of chronic vasculitis[36].

One prominent feature of MGK is limbal stem cell deficiency (LSCD)[7]. The presence of prolonged inflammation and MMPs stimulation, accompanied by compromised innervation, abnormal increase in corneal calcitonin gene-related peptide (CGRP), perilimbal ischemia and low levels of growth factors have been described as possible mechanisms[37]. DNA injury results in decreased ability of epithelial cell repopulation and subsequent persistent epithelial defects[38]. In one study, impression cytology in MGK revealed at least one quadrant of LSCD in all patients[29]. The pattern of LSCD is different from chemical burns. It is usually bilateral, partial, and asymmetric between the two eyes. Damage is more pronounced in interpalpebral area. The superior and inferior regions are mostly spared due to eyelid protection[7]. In our experience, stem cell deficiency in MGK is progressive like congenital stem cell diseases and despite other chemical burns; this would complicate treatment (Table 3).

2.3 Delayed-onset ocular manifestation—Victims can present with ocular manifestations after a long asymptomatic period. There have been reports of delayed ocular complications as late as 40 years following the first exposure (usually 10–15 years before presentation)[22]. Less than 1% of mustard victims in World War I developed delayed keratitis[2]. The extent of ocular involvement is usually asymmetric between the two eyes. The pathophysiology of late-onset manifestations may be related to cytotoxic effects, long-standing inflammation, and ischemia. There may be a significant overlap between chronic and delayed onset manifestations[39].

A variety of corneal lesions are described. A marbled appearance is seen in the limbal area in the early stages[39] (Figure 2). A distinct type of vascularization consisting of varicose and ampulliform leaky vessels surrounding the perilimbal ischemic regions with blood islands may be present[40]. Because the eyelid protects the superior portion of the cornea in the acute phase, corneal manifestations mainly involve the nasal and temporal sides (Figure 3)[41]. Recurrent corneal ulceration often has an unpredictable course of exacerbation and remission and gradually involves deeper and more central cornea. Corneal neovascularization is an unfavorable prognostic factor in MGK[22]. We have observed more amyloidosis and lipid keratopathy cases in MGK, which could be due to leaky tortuous vascular abnormality and vasculitis due to long-standing inflammation and cellular toxicity. Corneal biomechanical properties in MGK indicate reduced corneal stiffness[42].

Corneal melt secondary to limbal infiltration has a similar appearance to Mooren's ulcer[22] (Figure 2). Corneal perforation and phthisis bulbi are reported in a minority of very severe injuries.

2.3.1 Pathologic findings in chronic and delayed-onset ocular lesions: The pathologic findings in chronic and delayed-onset injuries include thinning/thickening of corneal epithelium, chronic inflammation, conjunctivalization, reduced number of conjunctival goblet cells, telangiectasis, vasculitis, scarring in substantia propria, dilated lymphatics, and amyloid and lipid depositions. Mild-to-moderate corneal squamous metaplasia might be a diagnostic factor for mild or subclinical limbal stem cell deficiency[30] (Figure 4). Conjunctival cytology is helpful in the detection of conjunctival dysplasia[43]. Similar changes in the endothelial cells as well as Descemet's membrane were previously demonstrated[44]. Ongoing necrosis of basal and suprabasal corneal epithelial cells and the degeneration of the basal lamina are two critical early sequelae in MGK[38]. Damage to the corneal basement membrane and cytoplasmic vacuolization can be visualized using electron microscopy[30, 45]. Routine biopsy or impression cytology is not recommended unless with surgical procedures in patients with diagnostic dilemmas.

Kanavi et al. found that there was more severe damage in anterior corneal layers, although all corneal layers were affected to some degree[27].

2.3.2 Confocal microscopy in chronic and delayed-onset ocular lesions: Confocal scanning demonstrates abnormal findings in all corneal layers. The epithelial and basal epithelial cells are damaged with irregular high contrast boundaries. The keratocytes show pleomorphic change and a significant decrease in density. Spindle-like keratocytes and diffuse fibrillary inhomogeneities are reported in the anterior stroma. Foci of stromal necrosis are visible as intrastromal hyperreflective microdots. Also, the endothelial cells may be damaged[41, 46, 47].

3. Treatment

3.1. Management of acute ocular injury—No specific treatment is available to prevent or reverse mustard gas keratopathy. Mustard gas injuries are dose dependent. Hence, instantaneous corneal rinsing following exposure is critical[48].

Acute phase injuries can be treated as classic chemical burn; mainly offering symptomatic therapy and control of inflammation with daily ocular irrigation, lubricants, topical antibiotics, mydriatics, topical anti-glaucoma agents (in patients with high IOP), contact lenses, and anti-inflammatory eye drops[7]. However, serious concerns have been raised about the long-term use of steroids[49–52]. Also, the role of lubrication without prior irrigation in the clinic is controversial since it may release mustard particles entrapped beneath the eyelids. Some authors do not recommend ocular bandage lenses due to the potential effect on corneal temperature and accelerated toxicity[39]. We have not observed any cases of toxicity or infective keratitis patients treated with bandage contact lens and topical antibiotics. Although the application of Petroleum-based lubricating ointments should be delayed due to the risk of mustard concentration in this oily agent[53]. In our experience, there is less chance

for glaucoma, symblepharon and adnexal problems in MGK patients compared to routine chemical burns.

Amniotic membrane transplantation alone or combined with other procedures may be beneficial[54–58]. Punctal occlusion and tarsorrhaphy can also be used for dry eye symptoms and ocular surface disturbance[59, 60] (Figure 5).

3.2. Management of chronic/ late-onset ocular complications—Management of the chronic/late-onset complications of MGK is controversial and several interventions should be carefully considered to address dry eyes, blepharitis, corneal thinning or opacity, lipid or amyloid deposits, and stem cell deficiency[59]. Jadidi et al.[61, 62] found that topical cyclosporine A 0.05% could decrease tear osmolarity and improve dry eye symptoms as well as goblet cell density. In our experience, managing dry eye and blepharitis is fundamental in these cases, even more critical than routine chemical burns. A well-operated keratoplasty in cases of localized opacity could be easily failed if tear film problems are neglected during the management. Punctal occlusion or tarsorrhaphy would be essential for managing dry eye before considering any keratoplasty.

It appears that combination of corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) is more effective than using a single agent for corneal neovascularization[50, 51]. There are some reports about the efficacy of topical doxycycline in preventing neovascularization[51, 63, 64] and also topical or subconjunctival administration of anti-VEGF agents may be useful[65, 66]. The effect of fine-needle diathermy and photodynamic therapy is unpredictable[67].

Besides frequent lubrication[7] and prophylactic topical antibiotics, autologous serum, platelet-rich plasma eye drops (E-PRP), or autologous platelet-rich plasma enriched with growth factors are potential options for improving corneal healing in persistent epithelial defects (PED)[19, 68, 69]. Cultured stem cells from bone marrow, adipose tissue, umbilical cord, and orbital fat are some of the emerging therapies under investigation [7, 67, 70, 71]. Topical thymosin ß-4 may effectively improve corneal healing[72]. A recent report showed that curcumin was effective in the treatment of ocular lesions[73].

Corneal thinning, scarring, and degeneration in the visual axis necessitate optical corneal grafting including lamellar and penetrating keratoplasty. It was shown that in most cases with corneal involvement, the damage was limited to the anterior cornea[57]. So, lamellar keratoplasty is a suitable alternative option[74]. It seems that performing conventional lamellar keratoplasty or Melles technique is more suitable for these cases rather than using Anwar big-bubble technique, since making a proper big bubble in mustard gas keratopathy is hardly achievable due to malformed corneal structure[27, 74]. Penetrating keratoplasty can be an option for late stages when full thickness of the cornea is involved. The risk of graft failure in such cases is considerably high due to prolonged inflammation, neovascularization, perilimbal ischemia, and stem cell deficiency[75, 76].

In cases with severe limbal ischemia and stem cell deficiency, limbal stem cell transplantation with the least possible manipulation of healthy cells is needed. Since the

injury is bilateral in almost all cases, the available options are limited to transplantation of allogeneic stem cells, whether living-related conjunctival limbal allograft (lr-CLAL) or keratolimbal allograft (KLAL). Although an acceptable success rate has been reported for lr-CLAL, advantages of the KLAL include containing more stem cells and simultaneous resolving of scleral and peripheral corneal injury[57, 59, 74, 77–79]. In a study by Javadi et al.[59] the outcomes achieved with KLAL were better than those achieved with lr-CLAL. Due to its availability and the load of stem cells which can be harvested, KLAL has priority. We showed that complete 360-degree transplantation is unnecessary and sectoral KLAL/lr-CLAL in areas with the most severe injury seems to be adequate[7, 57]. Debridement of ischemic perilimbal area followed by advancement of normal conjunctiva has been previously used in some of our patients with severe compromised limbal vasculature and it might be a potential beneficial procedure in MG-related LSCD.

A remarkable number of patients required both simultaneous or staged limbal stem cell transplantation and keratoplasty. It was reported that simultaneous versus staged approach had no significant differences in terms of visual and refractive outcomes or graft survival[74]. However, outcomes of stem cell transplantations were better in the simultaneous cases[74]. In contrast, some studies have shown worse outcomes with simultaneous surgeries[76, 79]. Some experts recommend that keratoplasty should be performed at least 3 months after limbal stem cell transplantation to have a less inflamed eye[57]. On the other hand, fewer operations and anesthesia, less antigen load to the host's immune system, and shorter duration of oral steroid therapy are advantages of simultaneous strategy[74]. Recurrence after keratoplasty is possible (Figure 4). In our experience, stem cell deficiency in MGK is mostly partial; thus, a lamellar or penetrating keratoplasty is preferred to limbal stem cell transplantation which may be more invasive and require systemic immunosuppression. In cases that limbal stem cell transplantation is inevitable, we usually recommend KLAL in one session with one donor for both stem cell transplantation and keratoplasty and tapering off the systemic immunosuppression after 18 months following transplantation. Topical immunosuppressive agents such as cyclosporine plus systemic doxycycline or minocycline are used to control the long-standing inflammation in these cases.

Mustard gas can have a direct pain-stimulating effect on corneal nerves. Hence, cutting the nerves during autorotation keratoplasty may lead to pain relief[80]. The presence of necrotic tissue may irritate corneal nerves and cause pain. This may explain the efficiency of debridement of necrotic tissue[81].

3.3 Treatment algorithm—We provide algorithms for managing MG-related ocular surface disease during acute and chronic phases after the injury (Figures 6&7). Stepwise management is recommended to avoid complications of more complex procedures in milder forms of injury. Management of dry eye disease is extremely important[81–83].

3.4 Experimental approaches and future directions—Topical diltiazem was effective in preventing IOP rise and congestion in rabbits[84]. Also, using MMP inhibitors such as doxycycline for eight weeks may be helpful in decreasing acute and late phase damages. Doxycycline drops seem to be more effective in improving corneal edema, whereas hydrogels significantly reduce neovascularization[49]. Topical iron-chelating agents

may lead to faster corneal epithelialization, lower rates of corneal opacification and neovascularization, cataract, PS formation, and inflammation, and also better IOP control in animal models[85]. The combination of desferrioxamine-zinc with dexamethasone had additive effects[86].

Recently, a mixture of topical eye drops, including ketorolac, suberoylanilide hydroxamic acid, enalapril, and vitamin C, has been formulated to attenuate mustard gas-related ophthalmic injuries in animal models[48]. It was found tolerable and effective for improving central corneal thickness, Schirmer's test result, corneal edema and haze, and inflammation[48]. Several studies are available on the role of biological products in the treatment of MGK[54]. A combination of epidermal growth factor (EGF) with corneal collagen membrane (CCS) and fibronectin (FN) enhance attachment of the corneal epithelium to the basement membrane and improve epithelial cell migration in rabbits[87]. In another animal study, in cases treated with fibronectin, corneal epithelial healing was better and the breakage rate was lower than in the controls. An in vivo study reported resolving corneal injuries with a combination of dexamethasone, doxycycline, and silibinin[63]. Basic fibroblast growth factor was highly effective in improving the healing process in rabbits' cornea[88]. Fagerholm et al. introduced recombinant human collagen as a promising safe material for partial regeneration of sub-basal nerves[89]. Antioxidants such as N-acetylcysteine and curcumin may help reduce oxidative damage in both acute and chronic phases[72].

Recent studies on the signaling pathways and factors involved in late manifestations of SM-related ocular injuries may help scientists develop novel biological therapies that specifically target these pathways[90, 91]. Suberoylanilide hydroxamic acid is used to reduce transforming growth factor β1 (TGF-β1) signaling pathways and decreases corneal haze by decreasing myofibroblast production. Enalapril, an angiotensin-converting enzyme (ACE) inhibitor has antioxidant properties and reduces TGF-β1 expression[48]. A new investigational product, INV-102 is a topical preparation that modulates the activity of p53, and could be an effective treatment for ocular conditions associated with DNA damage including delayed eye injury after SM exposure[36]. Another new hypothesis is that hypercitrullination is critical in nitrogen mustard injury by causing chronic glial reactivity and fibrosis. Peptide arginine deiminase (PAD4) is an enzyme discovered to be involved in hypercitrullination. Small molecule inhibitors against PAD4 and gene therapy to turn off PAD4 production are under investigation for possible use in MG-related eye injury[72,92].

Developing new technologies for cultivating stem cells would be helpful but still expensive[92]. Mesenchymal stem cells (MSCs) have regenerative potential, immunomodulatory and anti-scarring effects and are more resistant to SM compared to epithelial cells. MSC transplant may represent a new modality that can be used for promoting corneal healing and reconstruction of the ocular surface in advanced injuries[54, 93].

Conclusion

Ocular surface tissues are highly susceptible to mustard gas-related damage. Irreversible and vision-threatening ocular surface injuries could occur following severe exposures.

The pathophysiology involves DNA and microstructural involvement, oxidative stress and inflammation. There are various medical and surgical treatment options available based on the severity and phase of injury. Timely management is critical in preventing the sight-threatening sequelae. Overall, although management of acute phase MGK is similar to routine cases of chemical burn, chronic/ delayed-onset MGK is more complicated. No specific treatment has been proposed for late-onset disease; however, the treatment of dry eye disease is of utmost importance in these patients. Chronic uncontrolled ocular surface inflammation likely leads to the progression of the disease. Therefore, we recommend regular use of anti-inflammatory therapies such as topical cyclosporine as well as oral agents such as doxycycline/minocycline.

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References

1. Graham JS, Schoneboom BA. Historical perspective on effects and treatment of sulfur mustard injuries. Chemico-biological interactions 2013;206:512–22. [PubMed: 23816402]
2. Ghasemi H, Ghazanfari T, Yaraee R, et al. Systemic and ocular complications of sulfur mustard: A panoramic review. Toxin Reviews 2009;28:14–23.
3. Panahi Y, Gholami N, Ghojazadeh M, et al. Complications and carcinogenic effects of mustard gas-a systematic review and meta-analysis in Iran. Asian Pacific Journal of Cancer Prevention 2015;16:7567–73. [PubMed: 26625763]
4. McNutt PM, Hamilton TA, Lyman ME, et al. Ocular toxicity of chemical warfare agents. Handbook of Toxicology of Chemical Warfare Agents: Elsevier; 2020. p. 567–88.
5. Ghassemi-Broumand M, Aslani J, Emadi S-N. Delayed ocular, pulmonary, and cutaneous complications of mustards in patients in the city of Sardasht, Iran. Cutaneous and ocular toxicology 2008;27:295–305. [PubMed: 18756385]
6. Ghabili K, Agutter PS, Ghanei M, et al. Mustard gas toxicity: the acute and chronic pathological effects. Journal of applied toxicology 2010;30:627–43. [PubMed: 20836142]
7. Baradaran-Rafii A, Eslani M, Tseng SC. Sulfur mustard-induced ocular surface disorders. The ocular surface 2011;9:163–78. [PubMed: 21791191]
8. Panahi Y, Abdolghaffari AH, Sahebkar A. A review on symptoms, treatments protocols, and proteomic profile in sulfur mustard-exposed victims. Journal of cellular biochemistry 2018;119:197–206. [PubMed: 28657650]
9. Kadar T, Turetz J, Fishbine E, et al. Characterization of acute and delayed ocular lesions induced by sulfur mustard in rabbits. Current eye research 2001;22:42–53. [PubMed: 11402378]
10. Ghasemi H, Javadi MA, Ardestani SK, et al. Alteration in inflammatory mediators in seriously eye-injured war veterans, long-term after sulfur mustard exposure. International Immunopharmacology 2020;80:105897. [PubMed: 31685435]
11. Ghasemi H, Ghazanfari T, Yaraee R, et al. Evaluation of relationship between the serum levels of inflammatory mediators and ocular injuries induced by sulfur mustard: Sardasht-Iran Cohort Study. International immunopharmacology 2009;9:1494–8. [PubMed: 19733692]

12. Ghazanfari T, Mostafaie A, Talebi F, et al. Alteration in serum levels of immunoglobulins in seriously eye-injured long-term following sulfur-mustard exposure. International immunopharmacology 2020;80:105895. [PubMed: 31787572]
13. Ghazanfari T, Ghasemi H, Yaraee R, et al. Tear and serum interleukin-8 and serum CX3CL1, CCL2 and CCL5 in sulfur mustard eye-exposed patients. International Immunopharmacology 2019;77:105844. [PubMed: 31669888]
14. Heidary F, Ardestani SK, Ghasemi H, et al. Alteration in serum levels of ICAM-1 and P-, E-and L-selectins in seriously eye-injured long-term following sulfur-mustard exposure. International Immunopharmacology 2019;76:105820. [PubMed: 31480003]
15. Ghasemi H, Yaraee R, Hassan ZM, et al. Association of ophthalmic complications in patients with sulfur mustard induced mild ocular complications and serum soluble adhesion molecules: Sardasht–Iran Cohort Study. International Immunopharmacology 2013;17:980–5. [PubMed: 23370300]
16. Yaraee R, Ghazanfari T, Faghihzadeh S, et al. Alterations in the serum levels of soluble L, P and E-selectin 20 years after sulfur mustard exposure: Sardasht-Iran Cohort Study. International immunopharmacology 2009;9:1477–81. [PubMed: 19733695]
17. Ghasemi H, Yaraee R, Faghihzadeh S, et al. Tear and serum MMP-9 and serum TIMPs levels in the severe sulfur mustard eye injured exposed patients. International Immunopharmacology 2019;77:105812. [PubMed: 31677500]
18. Uhde GI. Mustard-gas burns of human eyes in World War II. American journal of ophthalmology 1946;29:929–38. [PubMed: 20994632]
19. Panahi Y, Rajaee SM, Sahebkar A. Ocular effects of sulfur mustard and therapeutic approaches. Journal of Cellular Biochemistry 2017;118:3549–60. [PubMed: 28106291]
20. Fuchs A, Giuliano EA, Sinha NR, et al. Ocular toxicity of mustard gas: A concise review. Toxicology letters 2021;343:21–7. [PubMed: 33600921]
21. Shohrati M, Davoudi M, Ghanei M, et al. Cutaneous and ocular late complications of sulfur mustard in Iranian veterans. Cutaneous and ocular toxicology 2007;26:73–81. [PubMed: 17612976]
22. Javadi M-A, Yazdani S, Sajjadi H, et al. Chronic and delayed-onset mustard gas keratitis: report of 48 patients and review of literature. Ophthalmology 2005;112:617–25. e2. [PubMed: 15808253]
23. Safarinejad M, Moosavi S. Ocular injuries caused by mustard gas: diagnosis, treatment, and medical defense. Military medicine 2001;166:67–70.
24. McNutt PM, Tuznik KM, Glotfelty EJ, et al. Contributions of tissue-specific pathologies to corneal injuries following exposure to SM vapor. Annals of the New York Academy of Sciences 2016;1374:132–43. [PubMed: 27310673]
25. McNutt PM, Nguyen DL, Nelson MR, et al. Corneal endothelial cell toxicity determines long-term outcome after ocular exposure to sulfur mustard vapor. Cornea 2020;39:640–8. [PubMed: 32044824]
26. McNutt P, Tuznik K, Nelson M, et al. Structural, morphological, and functional correlates of corneal endothelial toxicity following corneal exposure to sulfur mustard vapor. Investigative ophthalmology & visual science 2013;54:6735–44. [PubMed: 24045986]
27. Kanavi MR, Javadi A, Javadi MA. Chronic and delayed mustard gas keratopathy: a histopathologic and immunohistochemical study. European Journal of Ophthalmology 2010;20:839–43. [PubMed: 20491046]
28. Saladi R, Smith E, Persaud A. Mustard: a potential agent of chemical warfare and terrorism. Clinical and Experimental Dermatology: Clinical dermatology 2006;31:1–5.
29. Baradaran-Rafii A, Javadi M-A, Kanavi MR, et al. Limbal stem cell deficiency in chronic and delayed-onset mustard gas keratopathy. Ophthalmology 2010;117:246–52. [PubMed: 20018379]
30. Rajavi Z, Safi S, Javadi MA, et al. Clinical practice guidelines for prevention, diagnosis and management of early and delayed-onset ocular injuries due to mustard gas exposure. Journal of ophthalmic & vision research 2017;12:65. [PubMed: 28299009]
31. Ghasemi H, Ghazanfari T, Ghassemi-Broumand M, et al. Long-term ocular consequences of sulfur mustard in seriously eye-injured war veterans. Cutaneous and ocular toxicology 2009;28:71–7. [PubMed: 19514930]

32. Ghasemi H, Owlia P, Jalali-Nadoushan MR, et al. A clinicopathological approach to sulfur mustard-induced organ complications: a major review. Cutaneous and ocular toxicology 2013;32:304–24. [PubMed: 23590683]
33. Ghasemi H, Ghazanfari T, Babaei M, et al. Long-term ocular complications of sulfur mustard in the civilian victims of Sardasht, Iran. Cutaneous and ocular toxicology 2008;27:317–26. [PubMed: 19037764]
34. Karimian F, Zarei-Ghanavati S, Baradaran-Rafii A, et al. Microbiological evaluation of chronic blepharitis among Iranian veterans exposed to mustard gas: A case-controlled study. Cornea 2011;30:620–3. [PubMed: 21282998]
35. Ghasemi H, Owlia P, Ghazanfari T, et al. Conjunctival microbial florae in patients with seriously sulfur mustard induced eye injuries. Cutaneous and ocular toxicology 2013;32:13–7. [PubMed: 22668347]
36. Panahi Y, Naderi M, Zare MA, et al. Ocular effects of sulfur mustard. Journal of Current Ophthalmology 2013;25:90.
37. Kadar T, Dachir S, Cohen M, et al. Prolonged impairment of corneal innervation after exposure to sulfur mustard and its relation to the development of delayed limbal stem cell deficiency. Cornea 2013;32:e44–e50. [PubMed: 23132440]
38. McNutt P, Lyman M, Swartz A, et al. Architectural and biochemical expressions of mustard gas keratopathy: preclinical indicators and pathogenic mechanisms 2012.
39. Balali-Mood M, Hefazi M. The pharmacology, toxicology, and medical treatment of sulphur mustard poisoning. Fundamental & clinical pharmacology 2005;19:297–315. [PubMed: 15910653]
40. English F, Bennett Y. The challenge of mustard-gas keratopathy. The Medical journal of Australia 1990;152:55–6.
41. Pleyer U, Sherif Z, Baatz H, et al. Delayed mustard gas keratopathy: clinical findings and confocal microscopy. American journal of ophthalmology 1999;128:506–7. [PubMed: 10577594]
42. Jadidi K, Mohazzab-Torabi S, Pirhadi S, et al. A Study of Corneal Biomechanics in Delayed-Onset Mustard Gas Keratopathy Compared to Cases With Corneal Scarring and Normal Corneas. Eye & contact lens 2019;45:112–6. [PubMed: 30005052]
43. Safaei A, Saluti R, Kumar PV. Conjunctival dysplasia in soldiers exposed to mustard gas during the Iraq-Iran war: scrape cytology. Acta cytologica 2001;45:909–13. [PubMed: 11726116]
44. Kadar T, Cohen M, Cohen L, et al. Endothelial cell damage following sulfur mustard exposure in rabbits and its association with the delayed-onset ocular lesions. Cutaneous and ocular toxicology 2013;32:115–23. [PubMed: 23106194]
45. ESCAMOSA DDGDM, DEL EPITELIO CCFD, DE INSUFICIENCIA L. Corneal epithelium squamous metaplasia determination as diagnostic factor in limbal deficiency. Arch Soc Esp Oftalmol 2006;81:281–8. [PubMed: 16752320]
46. Jafarinasab M-R, Zarei-Ghanavati S, Kanavi MR, et al. Confocal microscopy in chronic and delayed mustard gas keratopathy. Cornea 2010;29:889–94. [PubMed: 20489576]
47. Lagali N, Fagerholm P. Delayed mustard gas keratitis: clinical course and in vivo confocal microscopy findings. Cornea 2009;28:458–62. [PubMed: 19411968]
48. Tripathi R, Balne PK, Sinha NR, et al. A novel topical ophthalmic formulation to mitigate acute mustard gas keratopathy in vivo: A pilot study. Translational Vision Science & Technology 2020;9:6-.
49. Gordon MK, DeSantis A, Deshmukh M, et al. Doxycycline hydrogels as a potential therapy for ocular vesicant injury. Journal of ocular pharmacology and therapeutics 2010;26:407–19. [PubMed: 20925577]
50. Amir A, Turetz J, Chapman S, et al. Beneficial effects of topical anti-inflammatory drugs against sulfur mustard-induced ocular lesions in rabbits. Journal of applied toxicology 2000;20:S109–S14. [PubMed: 11428620]
51. Kadar T, Dachir S, Cohen L, et al. Ocular injuries following sulfur mustard exposure—pathological mechanism and potential therapy. Toxicology 2009;263:59–69. [PubMed: 19061933]
52. Phulke S, Kaushik S, Kaur S, et al. Steroid-induced glaucoma: an avoidable irreversible blindness. Journal of current glaucoma practice 2017;11:67. [PubMed: 28924342]

53. Murray V, Volans G. Management of injuries due to chemical weapons. BMJ: British Medical Journal 1991;302:129. [PubMed: 1822079]
54. Sun M, Yang Y, Meng W, et al. Advanced biotherapy for the treatment of sulfur mustard poisoning. Chemico-biological interactions 2018;286:111–8. [PubMed: 29572074]
55. Joseph A, Dua HS, King AJ. Failure of amniotic membrane transplantation in the treatment of acute ocular burns. British Journal of Ophthalmology 2001;85:1065–9. [PubMed: 11520758]
56. Tsai RJ-F, Li L-M, Chen J-K. Reconstruction of damaged corneas by transplantation of autologous limbal epithelial cells. New England Journal of Medicine 2000;343:86–93. [PubMed: 10891515]
57. Javadi M-A, Baradaran-Rafii A Living-related conjunctival-limbal allograft for chronic or delayed-onset mustard gas keratopathy. Cornea 2009;28:51–7. [PubMed: 19092406]
58. Figueiredo F, Glanville J, Arber M, et al. A systematic review of cellular therapies for the treatment of limbal stem cell deficiency affecting one or both eyes. The Ocular Surface 2021;20:48–61. [PubMed: 33412337]
59. Javadi MA, Jafarinasab MR, Feizi S, et al. Management of mustard gas-induced limbal stem cell deficiency and keratitis. Ophthalmology 2011;118:1272–81. [PubMed: 21397949]
60. Wolffsohn JS, Huarte ST, Jones L, et al. Clinical practice patterns in the management of dry eye disease: A TFOS international survey. The ocular surface 2021;21:78–86. [PubMed: 33964411]
61. Jadidi K, Panahi Y, Ebrahimi A, et al. Topical cyclosporine a for treatment of dry eye due to chronic mustard gas injury. Journal of ophthalmic & vision research 2014;9:417. [PubMed: 25709764]
62. Jadidi K, Ebrahimi A, Panahi Y, et al. Topical cyclosporine a for mustard gas induced ocular surface disorders. Journal of Ophthalmic & Vision Research 2015;10:21. [PubMed: 26005548]
63. Tewari-Singh N, Jain AK, Inturi S, et al. Silibinin, dexamethasone, and doxycycline as potential therapeutic agents for treating vesicant-inflicted ocular injuries. Toxicology and applied pharmacology 2012;264:23–31. [PubMed: 22841772]
64. Horwitz V, Dachir S, Cohen M, et al. The beneficial effects of doxycycline, an inhibitor of matrix metalloproteinases, on sulfur mustard-induced ocular pathologies depend on the injury stage. Current eye research 2014;39:803–12. [PubMed: 24502433]
65. Kadar T, Amir A, Cohen L, et al. Anti-VEGF therapy (bevacizumab) for sulfur mustard-induced corneal neovascularization associated with delayed limbal stem cell deficiency in rabbits. Current eye research 2014;39:439–50. [PubMed: 24215293]
66. Gore A, Horwitz V, Cohen M, et al. Successful single treatment with ziv-aflibercept for existing corneal neovascularization following ocular chemical insult in the rabbit model. Experimental Eye Research 2018;171:183–91. [PubMed: 29548928]
67. Panahi Y, Roshandel D, Sadoughi M, et al. Sulfur mustard-induced ocular injuries: update on mechanisms and management. Current pharmaceutical design 2017;23:1589–97. [PubMed: 27774903]
68. Shtein RM, Shen JF, Kuo AN, et al. Autologous serum-based eye drops for treatment of ocular surface disease: a report by the American Academy of Ophthalmology. Ophthalmology 2020;127:128–33. [PubMed: 31561880]
69. Giannaccare G, Versura P, Buzzi M, et al. Blood derived eye drops for the treatment of cornea and ocular surface diseases. Transfusion and Apheresis Science 2017;56:595–604. [PubMed: 28844373]
70. Gu S, Xing C, Han J, et al. Differentiation of rabbit bone marrow mesenchymal stem cells into corneal epithelial cells in vivo and ex vivo. Molecular vision 2009;15:99. [PubMed: 19156227]
71. Lin K-J, Loi M-X, Lien G-S, et al. Topical administration of orbital fat-derived stem cells promotes corneal tissue regeneration. Stem cell research & therapy 2013;4:1–12. [PubMed: 23290259]
72. Beigi Harchegani A, Khor A, Tahmasbpour E, et al. Role of oxidative stress and antioxidant therapy in acute and chronic phases of sulfur mustard injuries: a review. Cutaneous and ocular toxicology 2019;38:9–17. [PubMed: 29969302]
73. Batal M, Rebelo-Moreira S, Hamon N, et al. A guanine-ethylthioethyl-glutathione adduct as a major DNA lesion in the skin and in organs of mice exposed to sulfur mustard. Toxicology letters 2015;233:1–7. [PubMed: 25562541]

74. Jafarinasab MR, Feizi S, Javadi MA, et al. Lamellar keratoplasty and keratolimbal allograft for mustard gas keratitis. American journal of ophthalmology 2011;152:925–32. e2. [PubMed: 21871601]
75. Rall DP, Pechura CM. Veterans at risk: The health effects of mustard gas and lewisite 1993.
76. Javadi MA, Yazdani S, Kanavi MR, et al. Long-term outcomes of penetrating keratoplasty in chronic and delayed mustard gas keratitis. Cornea 2007;26:1074–8. [PubMed: 17893537]
77. Daya SM, Ilari FL. Living related conjunctival limbal allograft for the treatment of stem cell deficiency. Ophthalmology 2001;108:126–33. [PubMed: 11150276]
78. Tsubota K, Shimmura S, Shinozaki N, et al. Clinical application of living-related conjunctival-limbal allograft. American journal of ophthalmology 2002;133:134–5. [PubMed: 11755849]
79. Solomon A, Ellies P, Anderson DF, et al. Long-term outcome of keratolimbal allograft with or without penetrating keratoplasty for total limbal stem cell deficiency. Ophthalmology 2002;109:1159–66. [PubMed: 12045060]
80. Richter MN, Wachtlin J, Bechrakis NE, et al. Keratoplasty after mustard gas injury: clinical outcome and histology. Cornea 2006;25:467–9. [PubMed: 16670487]
81. Alio JL, Rodriguez AE, WróbelDudzinska D. Eye platelet-rich plasma in the treatment of ocular surface disorders. Current opinion in ophthalmology 2015;26:325–32. [PubMed: 26058033]
82. Nair AP, D'Souza S, Shetty R, et al. Altered ocular surface immune cell profile in patients with dry eye disease. The Ocular Surface 2021;21:96–106. [PubMed: 33862224]
83. Ma B, Zhou Y, Liu R, et al. Pigment epithelium-derived factor (PEDF) plays anti-inflammatory roles in the pathogenesis of dry eye disease. The Ocular Surface 2021;20:70–85. [PubMed: 33412338]
84. Gonzalez GG, Gallar J, Belmonte C. Influence of diltiazem on the ocular irritative response to nitrogen mustard. Experimental eye research 1995;61:205–12. [PubMed: 7556484]
85. Banin E, Morad Y, Berenshtein E, et al. Injury induced by chemical warfare agents: characterization and treatment of ocular tissues exposed to nitrogen mustard. Investigative ophthalmology & visual science 2003;44:2966–72. [PubMed: 12824239]
86. Morad Y, Banin E, Averbukh E, et al. Treatment of ocular tissues exposed to nitrogen mustard: beneficial effect of zinc desferrioxamine combined with steroids. Investigative ophthalmology & visual science 2005;46:1640–6. [PubMed: 15851563]
87. Jiping C, Jie Z, WeiGuo H, et al. Therapeutic effects of combination of three drugs on healing of rabbit corneal wound caused by mustard gas. Bulletin of The Academy of Military Medical Sciences 2001:126–9.
88. Jiping C, Weiguo H, Mingxue Z. Effect of basic fibroblast growth factor on healing of rabbit corneal wound caused by mustard gas. Di 2 jun yi da xue xue bao= Dier Junyi Daxue Xuebao= Academic Journal of Second Military Medical College 2002;23:67–8.
89. Fagerholm P, Lagali NS, Carlsson DJ, et al. Corneal regeneration following implantation of a biomimetic tissue-engineered substitute. Clinical and translational science 2009;2:162. [PubMed: 20443883]
90. Horwitz V, Cohen-Gihon I, Egoz I, et al. A comprehensive analysis of corneal mRNA levels during sulfur mustard induced ocular late pathology in the rabbit model using RNA sequencing. Experimental eye research 2019;184:201–12. [PubMed: 31022400]
91. Panahi Y, Shahbazi A, Naderi M, et al. Sulfur mustard-related ocular complications: a review of proteomic alterations and pathways involved. Current pharmaceutical design 2018;24:2849–54. [PubMed: 30179120]
92. Gore A, Kadar T, Dachir S, et al. Therapeutic measures for sulfur mustard-induced ocular injury. Toxicology Letters 2021;340:58–66. [PubMed: 33440228]
93. Shojaati G, Khandaker I, Funderburgh ML, et al. Mesenchymal stem cells reduce corneal fibrosis and inflammation via extracellular vesicle-mediated delivery of miRNA. Stem cells translational medicine 2019;8:1192–201. [PubMed: 31290598]

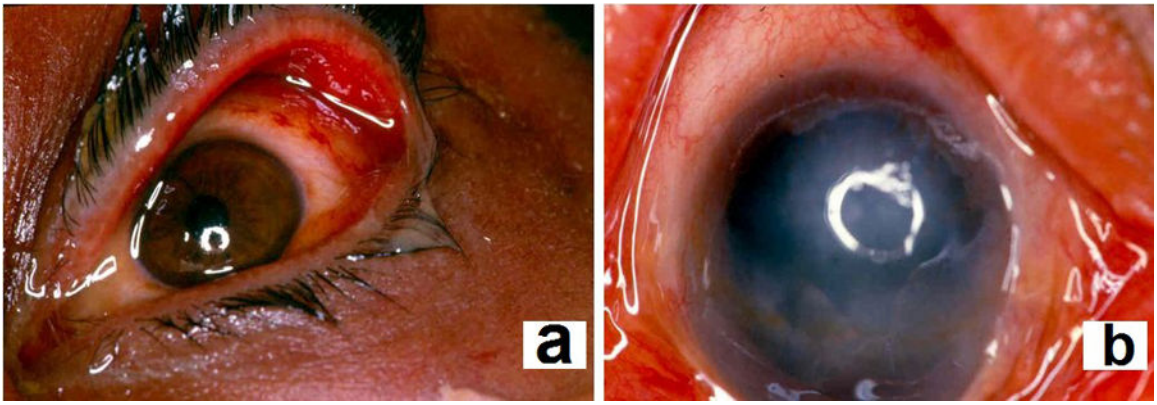

Figure 1.

Acute phase of mustard gas-induced ocular surface disorders. **a.** Chemosis and conjunctival injection. **b.** Corneal epithelial sloughing.

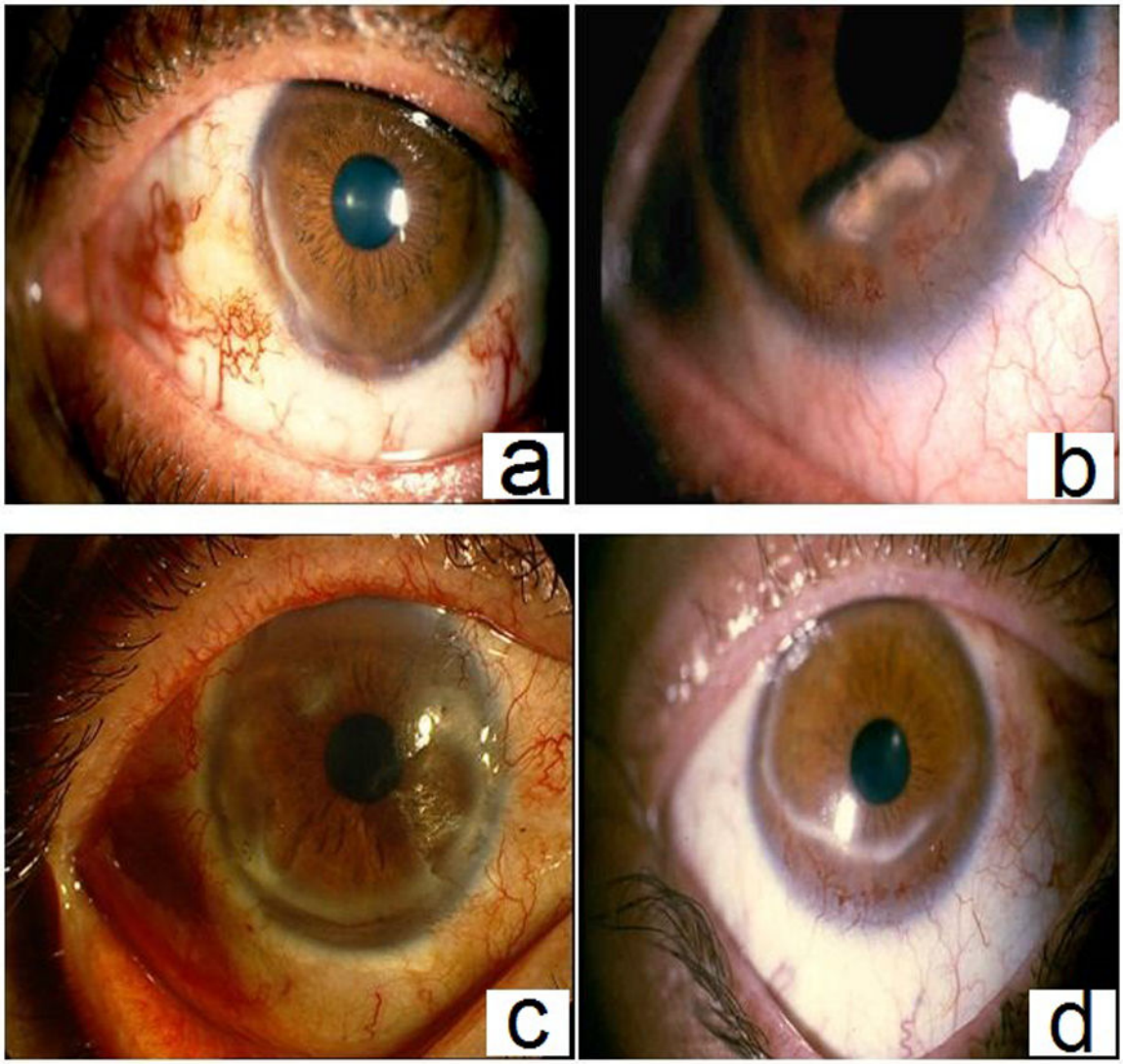

Figure 2.

Delayed-onset phase of mustard gas-induced ocular surface disorders. **a.** Telangiectatic ampulliform leaky vessels with peripheral corneal thinning and lipid deposition. **b.** A patch of inferior corneal thinning and intrastromal lipid and amyloid deposits. **c.** Corneal surface irregularity, thinning and peripheral corneal infiltration. **d.** Peripheral corneal melt (healed) following MGK similar to a Mooren's ulcer.

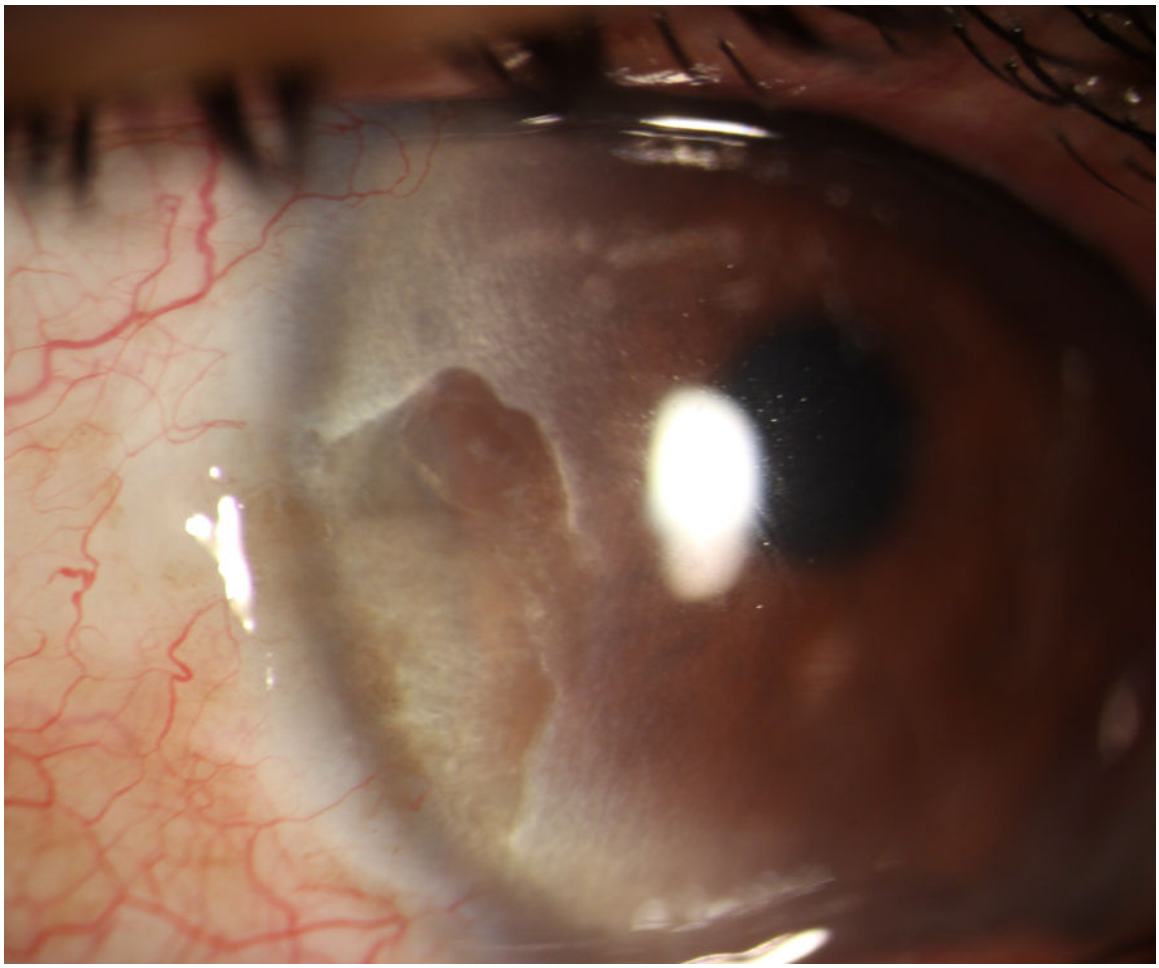

Figure 3.
Interpalpebral involvement in MGK.

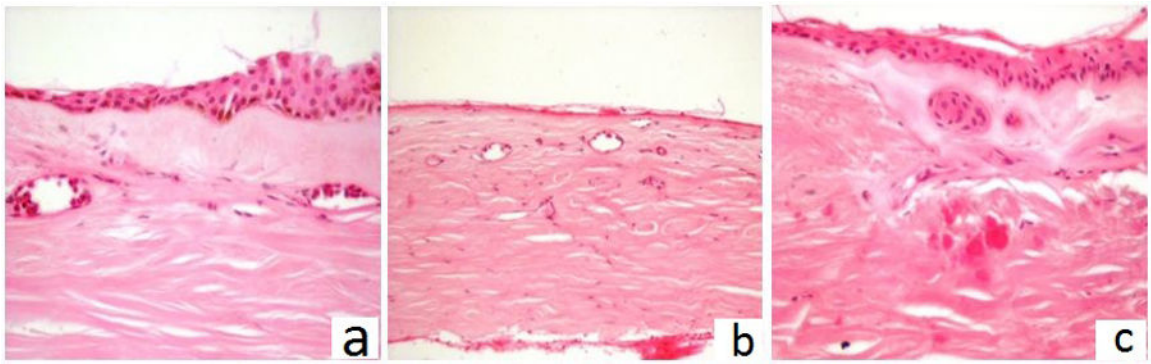

Figure 4.

Histopathological findings of MGK. **a.** H&E staining x 400, irregular attenuated epithelium, disruption of Bowman's membrane, subepithelial amorphous hyalinized material, intrastromal vascular channels, paucity of keratocytes. **b.** H&E staining x 200, denuded epithelium, multiple vascular channels, degenerated collagen fibers. **c.** H&E staining x 400, amorphous subepithelial hyalinized material with epithelial islands, disruption of Bowman's membrane, spheroidal degeneration, paucity of keratocytes.

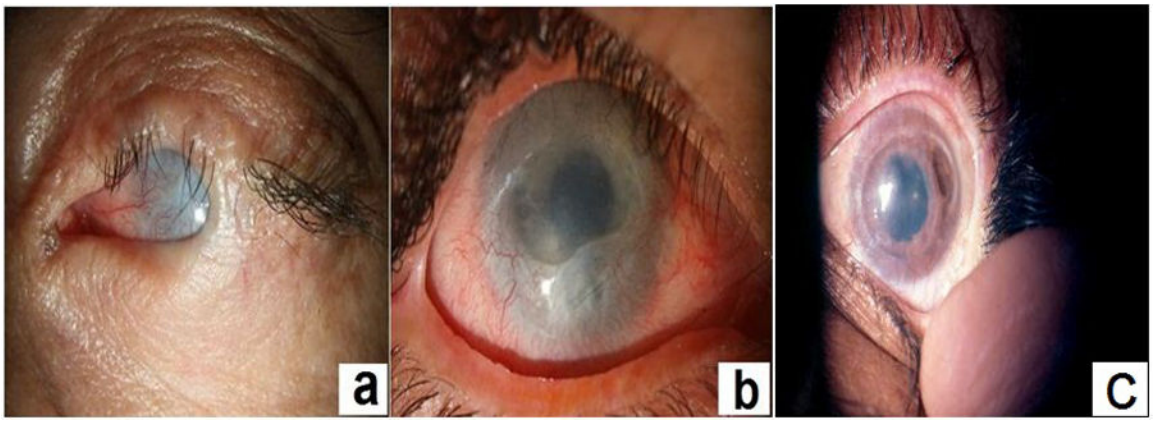

Figure 5.

Advanced cases of MGK. **a.** Tarsorrhaphy in a 55-year-old man who was suffering from chronic MGK with severe corneal opacity and conjunctivalization. **b.** Amniotic membrane transplantation in a 61-year-old man with persistent epithelial defect and peripheral thinning. **c.** Recurrence of MGK after penetrating keratoplasty showing peripheral corneal thinning.

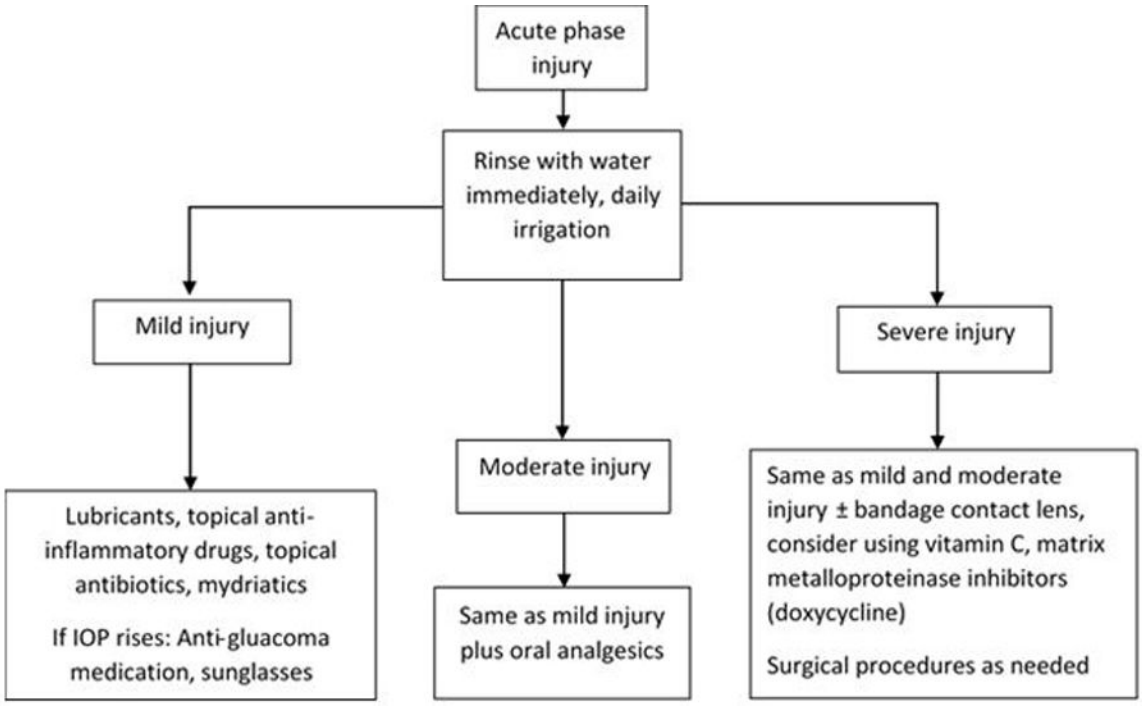

Figure 6.
Summary of the management of acute ocular injury by mustard gas.

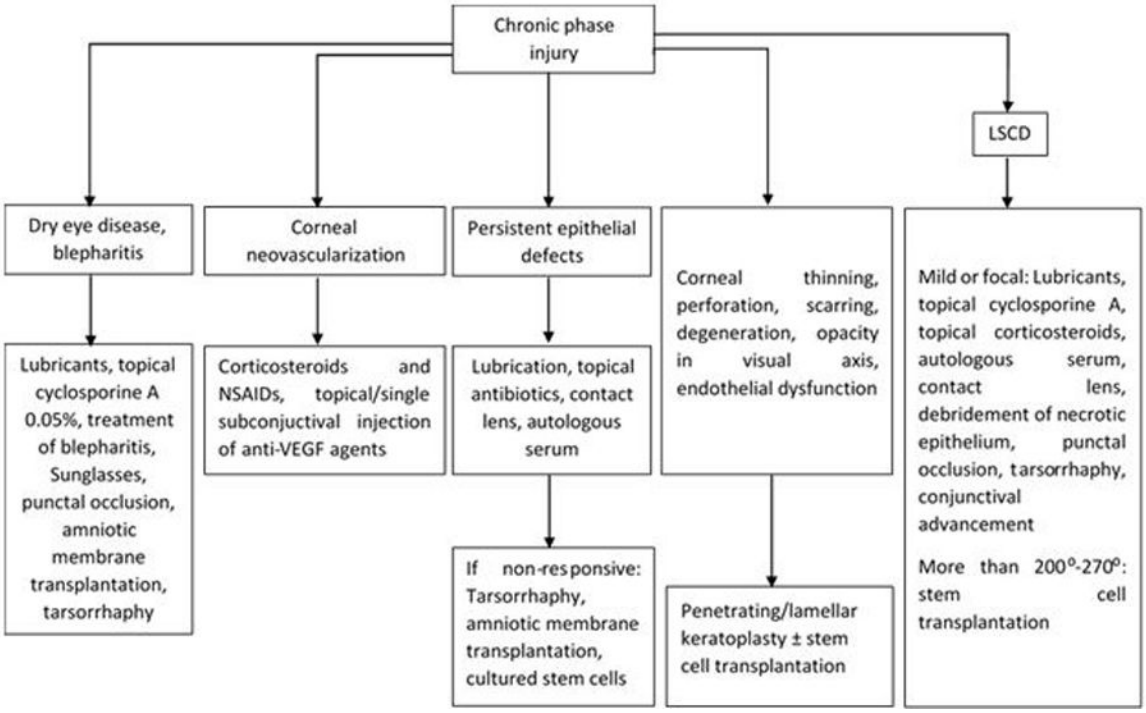

Figure 7.

Summary of the management of chronic ocular injury by mustard gas (NSAID: Non-steroidal anti-inflammatory drugs; VEGF: vascular endothelial growth factor; LSCD: limbal stem cell deficiency).

Table 1.

Summary of dose-related acute eye injuries following mustard gas exposure.

Severity of injury	Dosage	Signs and symptoms	Time of onset of symptoms after exposure	Resolution
Mild	<80 mg/min/m^3	• Eyelid swelling • Eye redness • Ocular discomfort	4–24 hours	Few days to couple of weeks
Moderate	100–200 mg/min/m^3	• Pain • Blepharospasm • Edematous cornea • Corneal bullae formation • Transient loss of vision • Photophobia • Chemosis • Blepharitis	3–6 hours	2–6 weeks
Severe	>200 mg/min/m^3	• Uveitis • Iris vasodilation • Miosis • Conjunctival and limbal necrosis • Eyelid necrosis • Adhesion between eyelids and globe • Corneal ulceration • Corneal neovascularization • Cataract • Permanent blindness	Rapid onset	Several weeks

Table 2.

Summary of signs and symptoms of chronic and delayed eye damages following mustard gas exposure.

Severity of injury	Signs	Symptoms
Mild	• MGD • Blepharitis • Shortened tear meniscus • Telangiectatic conjunctival vessels • Comma-shaped vascular tortuosity in the palpebral fissure area • Subconjunctival fibrosis, hemorrhage and scarring • Punctate epithelial erosions	• Photophobia • Foreign body sensation • Dry eye • Lacrimation • Mild eye redness
Moderate	Similar to mild injury plus any of: • Corneal irregular astigmatism • Mild to moderate limbal ischemia • Corneal irregularity • Peripheral corneal thinning • Lipoid and amyloid deposits in the corneal periphery • Neovascularization of peripheral cornea • Peripheral stromal scars and corneal opacity • Peripheral intra-stromal hemorrhage • Decreased corneal sensation	Similar to mild injury plus any of: • Decreased visual acuity • Remarkable redness • Itching • Pain
Severe	Similar to mild and moderate injury plus any of: • Severe limbal ischemia and limbal stem cell deficiency • Corneal thinning and opacity • Central and peripheral corneal vascularization and conjunctivalization • Central and peripheral stromal band keratopathy and scars • Central and peripheral intra-stromal hemorrhage • Descemetocele • Corneal ulcer • Corneal melting/perforation • History of previous corneal and limbal interventions	Similar to mild and moderate injury plus any of: • Severe photophobia • Severe vision loss • Severe pain

Table 3.

Comparison between disorders secondary to mustard gas and chemical agents.

	Mustard gas	Chemical injury
Limbal stem cell deficiency	Gradual and progressive; mostly, at nasal and temporal cornea followed by an extension to the other healthy sections	Dependent on the severity and extension of the primary insult
Corneal involvement	Peripheral involvement may be more common than central part	Dependent on the severity and extension of the primary insult
Corneal neovascularization	Leakage and tortuosity of aberrant vessels are usually present.	Leakage and tortuosity of aberrant vessels are less common.
Systemic involvement	Usually present such as dermatologic, gastrointestinal, respiratory, nephrologic, and hematologic disorders	Uncommon
Peri-ocular disorders	Uncommon	Usually present such as distichiasis, trichiasis, entropion, ectropion, symblepharon, and forniceal scars and shortening
Dry eye disease	Common	Common
Recurrence	Common	Uncommon
Management	* Conjunctival advancement to address limbal ischemia and peripheral involvement *It needs careful follow up for any recurrence. *Benign course of glaucoma usually controlled via topical drops	*Performing adnexal reconstruction before ocular surface reconstruction and limbal stem cell transplantation *Tenonplasty to address limbal ischemia * More aggressive and progressive course of glaucoma requiring surgical procedures