

Mustard Gas-Induced Ocular Injuries: A Review of Manifestations and Managements

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Abstract

Purpose: To review ocular surface abnormalities caused by exposure to mustard gas and current approaches to manage its delayed-onset complications

Methods: A total of 198 medical articles related to mustard gas were reviewed using known international medical databases, 114 articles were more relevant to the main aim were selected.

Results: Mustard gas-related ocular injuries can be divided into immediate and late phases. Acute manifestations of varying degrees include eyelid erythema and edema, chemosis, subconjunctival hemorrhage, and epithelial edema, punctate erosions, and corneal epithelial defects. Late complications can cause progressive and permanent reduction in visual acuity (VA) and even blindness and occur in approximately 0.5% of those initially severely wounded. These complications consist of chronic blepharitis, decreased tear meniscus, conjunctival vessel tortuosity, limbal stem cell deficiency, corneal scarring and thinning, and lipid/amyloid deposits. Management of the late complications varies from symptomatic treatment to surgical interventions for dry eye, corneal epithelial instability, limbal stem cell deficiency, and corneal opacity.

Conclusion: Mustard gas-related ocular complications are progressive and some sort of surgical interventions may be ultimately required. A long-term and meticulous follow-up for these patients is warranted.

Keywords: Eye Injuries, Chemical Warfare, Mustard Gas

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Introduction

Iraqi army extensively used chemical weapons during the 8-years Iraq-Iran war (1980-1988). There were 398,587 veterans who needed long-term follow-up during the war. 52,195 of them (13%) were chemically injured.¹ Khateri reported 34,000 chemically injured Iranian victims with delayed complications who were exposed to sulfur mustard in 2003.² Mustard gas is named as king of the battle gases³ with cytotoxic, vesicant and blistering effects on exposed skin.⁴ It can cause both acute and delayed clinical manifestations and late complications even 40 years after the exposure as reported for victims of the first world war.⁵ People can be exposed to small or large amounts of mustard gas through terroristic actions, wars, leakage from the factories, and even activities like fishing.⁶ Mustard gas is a lipophilic, highly cytotoxic agent that rapidly penetrates the tissue and the eye is one of the organs mostly affected.⁷ Additionally, it can affect skin, respiratory, gastrointestinal, and renal systems as well as the bone marrow.⁸ The aim of our study was to review ocular surface abnormalities caused by exposure to mustard gas and current approaches to manage its delayed-onset complications.

Methods

During a systematic search, a total of 198 medical articles related to sulfur mustard were reviewed using known international medical databases such as Scopus, Medline, ISI, and Iranian medical databases such as Iranmedex, SID, and Irandoc. One hundred and fourteen articles were more relevant to the main aim. Eight articles were on general aspects of SM effects, 36 articles were related to respiratory effects, 16 articles were on dermatologic effects, 20 articles were on ophthalmologic effects, 11 articles on psychological effects, 10 articles on endocrinology and reproductive health effects, 4 articles related to quality of life and 9 articles were related to other items such as: neurologic, oncologic, hematologic, cardiologic, laboratory. No special evaluation was conducted on the quality of the reviewed manuscripts and the credit of journal was considered sufficient.

Results

Manifestations

Mustard gas-related ocular injuries can be divided into immediate and late phases. Acute manifestations of varying degrees including eyelid erythema and edema, chemosis, subconjunctival hemorrhage, and epithelial edema, punctate erosions, and corneal epithelial defects develop in 75-90% of exposed individuals and can follow three different courses including: complete resolution, persistent smoldering inflammation (chronic form), or reappearance of lesions after a latent period of quiescence (delayed form).^{5,9}

Late complications, developing after 1 to 40 years, can cause progressive and permanent reduction in visual acuity (VA) and even blindness and occur in approximately 0.5% of those initially severely wounded.^{5,8} A wide range of late ocular involvements have been reported which include chronic blepharitis, decreased tear meniscus, conjunctival vessel tortuosity, limbal ischemia and stem cell deficiency (LSCD), and corneal scarring, thinning, and lipid/amyloid deposits.^{5,8,10-14}

The pathogenesis of mustard gas keratitis (MGK) has not been elucidated but, it may involve an autoimmune reaction to corneal antigens altered by the mustard agent.⁸ A degenerative process resulting from initial damage to the limbus and cornea as well as toxic by-products leading to necrosis have also been postulated.^{15,16} It induces apoptosis at lower concentrations and both apoptosis and necrosis at higher concentrations.^{17,18}

Blepharitis and dry eye are similarly observed in all cases. Other distinctive features include perilimbal conjunctival ischemia, stem cell deficiency, epithelial irregularity, recurrent or persistent epithelial defects, corneal neovascularization and thinning, stromal scarring, and secondary degenerative changes including lipid and amyloid deposition.

Malignant transformation of conjunctival and corneal epithelia as well as intraocular involvements is not features of MGK. Meanwhile, the mutagenic effect of mustard gas has been known.¹⁷⁻²⁵ There is a significant increase in lung cancer among World War I veterans who are exposed to mustard gas compared with those who are not.²⁵ There is

also a higher incidence of oropharynx, respiratory tract, and skin cancers in those with occupational exposure to mustard.²⁵ The mutagenic effect is due to its ability to alkylate nucleic acids and proteins.²⁶ Interestingly, no cases of conjunctival or corneal intraepithelial neoplasia are encountered in a large series after a mean follow-up of 101 months and the incidence rate of pterygium is not greater than what expected in a normal population (1 in 175 eyes). Describing the conjunctival scrape cytology findings in 22 male war veterans exposed to mustard gas, Safaei et al observed dysplasia, mild inflammation and squamous metaplasia of conjunctiva in 9 cases. However, squamous cell carcinoma is not identified.^{27,28} It is possible that ischemic alterations in the conjunctiva accompanying MGK counter any tendency to autonomous and uncontrolled cell proliferation hence canceling its mutagenic effect on the eye.

Additionally, none of the participants had cataract and glaucoma at the first presentation nor developed corneal endothelial decompensation and chronic uveitis over the follow-up period. Cataract and glaucoma are observed among those who received topical and/or systemic steroids for any reasons. Performing a confocal study in a subgroup of these patients, we previously demonstrated that endothelial cell counts in these eyes did not differ from those in an age-matched normal group in spite of significant alterations in the anterior stromal matrix and keratocytes.²¹ These observations imply that the effects of the mustard gas are limited to the ocular surface and anterior stromal cornea and it does not penetrate into the anterior chamber at a sufficient concentration to damage intraocular structures.

Our experience shows that mustard gas has a progressive destructive effect on ocular surface and the majority of patients who initially had mild involvements ultimately developed significant conjunctival, limbal, and/or corneal abnormalities necessitating surgical interventions. In our previous report with a follow-up of between 13 and 168 months, 41.7% of the injured are managed conservatively and the remaining cases underwent more invasive procedures.⁵ However in the current report with a longer follow-up (between 36 and 198 months), only

36 (20.6%) out of 175 eyes remained untouched.

Management

The management of acute phase is relatively straightforward, chiefly consisting of symptomatic therapy to address patient's discomfort and ocular inflammation. It includes topical antibiotics, preservative-free lubricants, and anti-inflammatory agents. Topical steroid and non-steroidal anti-inflammatory drugs are found to be beneficial in ameliorating the initial inflammatory response and in postponing the development of corneal neovascularization, when given during the first week after exposure.¹⁹ Chronic administration (8 weeks) of the matrix metalloproteinase inhibitors such as doxycycline is also effective in attenuation of the acute and delayed injury.¹⁹ However, to this date, no definite treatment for delayed-onset MGK is available. Therapy which is tailored based on the type and severity of involvements, varies from symptomatic treatment to surgical interventions for dry eye, corneal epithelial instability, limbal stem cell deficiency, and corneal opacity.

Management of delayed complications of MGK is difficult and requires an overwhelming long-term follow-up. Therapy is initially symptomatic and includes measures to address tear deficiency and ocular surface instability (i.e., preservative-free artificial tears and lubricants, temporary or permanent punctal occlusion, blepharorrhaphy and tarsorrhaphy). A limited course of topical steroid may be used to control recurrent episodes of superficial inflammation, keratitis, or limbal inflammation.

The unique features of MGK are limbal and corneal involvements. Limbal abnormalities including vascular engorgement and tortuosity, ischemia, and LSCD can develop after exposure. Although LSCD has been reported in mustard gas-related ocular involvements, its clinical manifestations are completely different from those observed in other causes of LSCD such as acid or alkaline burns, thermal burns, Stevens-Johnson syndrome, ocular cicatricial pemphigoid, and multiple surgeries.²² For example, conjunctivalization of the corneal surface which is a striking feature in the latter conditions is hardly observed in MGK. Additionally, there is no correlation between

the severity of corneal involvements and LSCD in these eyes. Such differences can be explained by the presence of other concomitant abnormalities such as limbal ischemia and vascular abnormalities. Limbal ischemia may play a significant role in delayed MGK such as scleral and corneal thinning and the presence of leaking limbal vessels results in the accumulation of abnormal materials such as lipid and amyloid in the adjacent cornea. Therefore, the unique feature of limbal abnormalities observed in MGK is contributed by the combined effects of limbal stem cell deficiency, limbal ischemia, and abnormally leaking vessels. However, one mechanism can be more prominent than the others in certain cases.

According to our experience, when corneal involvements developed to a level resulting in decreased VA and/or discomfort, we initially performed only penetrating keratoplasty (PKP) and observed relatively acceptable outcomes, specially when corneal opacity is centrally located and there is no severe limbal involvement.²⁰ In cases demonstrating severe dry eye, limbal ischemia, or peripheral corneal involvements, however, a high rate of graft failure due to rejection reactions or opacity is noted. This observation led us to make efforts to address ocular surface abnormalities using punctal plaque, punctal occlusion, temporary or permanent tarsorrhaphy, and stem cell transplantations. Additionally, we have learned that the majority of corneal involvements are limited to the anterior stroma, leaving posterior stroma and endothelium relatively intact.²¹ Therefore, our techniques of corneal transplantation evolved from PKP to manual lamellar keratoplasty (LKP).

Surgical interventions

Stem cell transplantation

LSCD is diagnosed clinically as shown by late corneal staining with fluorescein, loss of limbal palisades of Vogt, superficial vascularization, and/or signs of conjunctivalization of the cornea and confirmed in some cases using impression cytology.²² Limbal stem cells can be harvested from two sources: first-degree relatives including parents, siblings, or children (living-related conjunctival-limbal allograft; IrCLAL) and cadaveric eyes (keratolimbal allograft; KLAL). Human

leukocyte antigen (HLA) matching is not performed for any kind of the donors.

The technique of IrCLAL has been described by us elsewhere.²³ KLAL is carried out very similarly. Briefly to prepare the recipient bed, limbal areas adjacent to the epithelial defects or thinned cornea are chosen and local peritomy, shaving, mild cauterization of the sclera, and superficial keratectomy are performed. It is followed by a half-thickness rectangular corneoscleral removal trying to dissect all ischemic limbal areas as well as peripheral thin and opaque corneas up to paracentral areas if seen necessary. A similar corneoscleral block exactly matching the shape of the recipient bed and containing conjunctiva is prepared from cadaveric eyes.

Stem cell rejection is classified as acute and chronic. Acute rejection is diagnosed in eyes with limbal and perilimbal vascular engorgement and conjunctival chemosis in the transplant areas. Chronic rejection is diagnosed in cases with progressive corneal vascularization with or without epithelial disintegrity manifesting as recurrent epithelial erosions adjacent to the limbal lenticules. Failure is considered when persistent epithelial defects (more than 2 weeks) occurred adjacent to the graft with or without progressive corneal vascularization and thinning. This type of failure is assumed to be the consequence of chronic stem cell rejection or dry eye.

IrCLAL and KLAL have been effectively used to treat LSCD in bilateral ocular surface disorders.²⁹⁻³¹ Both techniques of stem cell transplantation (IrCLAL and KLAL) can markedly decrease subjective complaints, heal persistent corneal epithelial defects, and lead to regression of peripheral corneal vascularization in the affected segments. The main objective of stem cell transplantation for other causes of LSCD is to continue the supply of new corneal epithelium for a prolonged, if not indefinite, period. However, we have realized that stem cell transplantation has more roles in MGK than only providing stem cells. Firstly, the sclera and cornea adjacent to abnormal limbal areas are thin and ischemic and demonstrate neovascularization and lipid and amyloid deposits which add to patient's discomfort. Additionally, corneal thinning is so severe in some cases that can

threaten the globe integrity. During stem cell transplantation, abnormal conjunctiva, sclera, and cornea are removed and replaced with matched blocks containing stem cells, and conjunctiva as well as partial thickness cornea and sclera. Therefore, several important abnormalities in MGK namely LSCD, conjunctival and limbal ischemia, scleral and corneal thinning, and deposits can be simultaneously addressed with stem cell transplantation.

Considering a lower chance for rejection and less need for intense immunosuppression, allogeneic limbal stem cells from living-related donors (lrCLAL) are initially performed and found effective in stabilizing the ocular surface in patients with delayed or chronic MGK.²³ In contrast to KLAL, however, lrCLAL cannot provide adequate corneal and scleral lamellae and cadaveric eyes should also be available if tectonic graft is needed. Additionally, the amount of stem cells which can be harvested from a living-related donor is limited (120 degrees of limbal area at maximum). Another advantage worth mentioning is KLAL makes it possible to harvest cornea and limbal blocks from the same donor if both transplantations are to be performed simultaneously, reducing the antigenic load to the recipient's immune system. Because of these reasons, the technique of transplantation has been changed into KLAL with capability of providing more stem cells and simultaneously addressing conjunctival, limbal, and corneal abnormalities

Corneal transplantation

Indications for corneal transplantation are corneal haziness due to scar and abnormal deposits and/or vascularization resulting in decreased VA and severe stromal thinning threatening globe integrity. Three techniques of corneal transplantation including PKP, LKP, and deep anterior lamellar keratoplasty (DALK) are tried in these patients. The technique of PKP for MGK has been previously explained.²⁰ For conventional LK, at least 50% of the corneal thickness is trephined and manual lamellar dissection performed using a crescent blade (Alcon Laboratories, Forth Worth, Texas, USA). During lamellar dissection, it is attempted to remove all scars and deposits chiefly confined

to the anterior and mid-stroma and create a single-plane, smooth, and clear recipient bed before a partial thickness corneal button is sutured. DALK is carried out using the Anwar big-bubble technique as described elsewhere in details.²⁴ In all three techniques, a Barron-Hessburg suction trephine with a diameter of between 7.0 and 8.0 mm is used, based on the vertical corneal diameter and the extent of corneal involvement, and a 0.5-mm oversize donor is sutured into the recipient bed using combined 8-bite interrupted accompanied by 16-bite single running 10-0 nylon sutures (Sharpoint, Angiotech, Vancouver, Canada). When indicated, both limbal stem cell and corneal transplantations are performed either simultaneously or sequentially.

An episode of graft rejection is defined as the presence of keratic precipitates in the PKP group and subepithelial infiltration in the PKP and LKP groups. Corneal graft failure is diagnosed when central portion of graft became significantly opaque due to either stromal edema (endothelial graft rejection) or scarring with or without vascularization (limbal stem cell deficiency or corneal ulcer. In the case of LKP, the presence of significant interface haziness involving the visual axis is also considered graft failure.

When corneal changes including scarring, thinning, and degenerative lipid/amyloid deposition preclude useful vision or threaten globe integrity, optical and tectonic corneal grafting becomes necessary.^{20,32} Reporting the outcomes of PKP in delayed-onset MGK in 22 eyes, our previous study indicates a clear graft is observed in 77.3% of cases but, it failed in 22.7% after 41 months and 50% developed subepithelial and/or endothelial graft rejection.²⁰ These observations as well as clinical and histopathological findings which indicate relatively intact posterior corneal stroma and endothelium in MGK cases led us to alter the technique of corneal transplantation into conventional LKP which is applicable in the vast majority of patients and yields acceptable visual outcomes.²¹ Recurrence of opacification and deposits in the graft is a frequent observation after keratoplasty. One advantage of LK is that it can be repeated with ease in the case of graft opacity. However, a full-thickness graft is still inevitable in certain conditions such as deep stromal scar, impending corneal perforation,

or when visually significant interface opacity develops.

Getting familiar with the technique of surgery and observing acceptable outcomes in keratoconic patients, we also attempted DALK using the Anwar big-bubble technique in a few cases.²⁴ But very soon, we realized that it is difficult to achieve a successful big bubble even after several intrastromal air injections and resumed conventional LKP. Failure to achieve a big bubble can be attributable to alterations of corneal stroma secondary to acute and chronic inflammation, stromal scar and fibrosis, and deposits noticed in histopathologic examinations, making stroma layers too rigid to be separated by air.²⁸

Combined approaches

A significant number of participants require both limbal stem cell and corneal transplantations which are performed either simultaneously or sequentially. The comparison of simultaneous versus sequential operation with respect to visual and refractive outcomes as well as graft rejection reactions is a subject of the study which is now underway in our center. However, there is a trend in our center to carry out both LKP and KLAL at the same session to reduce the number of operations and anesthesia which is a significant concern in such patients with respiratory problems and inherent anesthesia-induced risks. Additionally, during a simultaneous operation only one donor can be used to provide both cornea and stem cells hence reducing the load of antigens presented to the recipient's immune system. For this reason and as LKP eliminates the risk of graft failure secondary to endothelial rejection reactions, the outcomes of sequential and simultaneous LK and KLAL may not differ. This speculation will be examined in the future study.

Postoperative medical regimen

Topical eye drops including chloramphenicol 0.5% every 6 hours, betamethasone 0.1% every 6 hours, preservative-free artificial tears every 2 hours and lubricants every 8 hours as well as systemic prednisolone 1mg/kg/day are

started after both corneal and limbal stem cell transplantation of any kind. Topical antibiotic is discontinued after complete reepithelialization while, systemic and topical corticosteroids are tapered off over 2-4 weeks and 2-3 months, respectively, according to the severity of ocular inflammation.

For patients who underwent IrCLAL or KLAL, systemic cyclosporine A (Sandimmune; Novartis Pharma, Tokyo, Japan) 5 mg/kg/d is started at the time of surgery. The dose is reduced to 3 mg/kg/d after 6 months and discontinued after 1 year in the IrCLAL group and after 1.5-2 years in the KLAL group according to the condition. In addition to cyclosporine, patients in the KLAL group received 1 g of oral mycophenolate mofetil (CellCept, Hoffmann La Roche, Nutley, NJ) twice a day for at least 6 months. It is gradually tapered parallel to oral cyclosporine and discontinued after 1 year. Cell blood counts, blood pressure, and renal and liver function tests are monitored at appropriate intervals in collaboration with a kidney transplant expert to monitor for possible complications of immunosuppressive therapy.

Acute rejection reactions of corneal (subepithelial and endothelial) and stem cell transplants are treated by increasing the dose and frequency of topical and/or systemic steroids.

Conclusion

In conclusion, mustard gas-related ocular complications are progressive and some sort of surgical interventions may be ultimately required in the vast majority of victims to address dry eye, LSCD, and/or corneal opacity. According to our experience, the best approach for limbal and corneal involvements is KLAL and conventional LKP, respectively, which can be performed simultaneously when indicated. However, the results of this study should be interpreted in the context of its limitation. As a result of performing different techniques at different time, follow-up period is significantly longer in the IrCLAL and PKP groups than that in the KLAL and LKP groups, respectively. Therefore, it is advisable to design a randomized clinical trial to find the best management of MGK.

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