Mustard Gas Induced Ocular Surface Disorders

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Sulfur mustard is a vesicant agent with severe irritating effects on living tissues, including skin, mucous membranes, eyes, and the 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 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 and 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.

Herein, we will discuss medical and surgical management for a number of patients with chronic or delayed mustard gas induced ocular surface disorders.

CASE PRESENTATION

What is your general management strategy for patients with mustard gas induced ocular surface disorders?

Mohammad-Ali Javadi, MD

Management depends on the stage of the disorder, namely acute, chronic, or delayed onset. At the present time, we are encountering more chronic and delayed-onset types of injury. Our approach also depends on the severity of the disease. In mild cases with only dry eye syndrome and symptoms such as foreign body sensation and photophobia without any corneal vascularization or lipid deposition, the first step is preservative-free lubricants accompanied by lower punctal occlusion and close follow up. Cases with moderate blepharitis resistant to conventional therapy require chronic management. Sunglasses are also sometimes helpful.

Farid Karimian, MD

Delayed-onset mustard gas induced ocular surface disorders may present years, even 30 years, after exposure to this chemical warfare agent. Many patients suffering from the delayed-onset type have well-documented normal eye examinations years before. Those cases with definite exposure to mustard gas must be visited and examined periodically to detect its deleterious effects in early stages. Our hospital is a unique tertiary center with referral cases from all over the country. Tortuosity and segmentation of perilimbal vessels as well as appearance of avascular and ischemia areas may be the earliest detectable signs of the disorder. There may be some areas of shiny brown deposition in the epithelium (similar to iron) in the palpebral fissure. Telangiectasia of the lid margin as well as meibomian gland dysfunction must be detected and treated appropriately. Associated dry eye conditions must be treated and punctal occlusion should be considered and performed accordingly.

Sepehr Feizi, MD

Management of the acute phase is relatively straightforward, chiefly consisting of symptomatic therapy to address patient
discomfort and ocular inflammation. This includes topical antibiotics, preservative-free lubricants, and anti-inflammatory agents. Topical steroids and non-steroidal anti-inflammatory drugs are used to ameliorate the initial inflammatory response and to postpone the development of corneal neovascularization if given within the first week after exposure. Chronic administration (8 weeks) of matrix metalloproteinase inhibitors such as doxycycline is also effective in attenuating acute and delayed injury. However, to date, no definite treatment for delayed-onset mustard gas induced ocular surface disorders is available. Therapy is tailored based on the type and severity of involvement and varies from symptomatic treatment to surgical intervention for dry eye, corneal epithelial instability, limbal stem cell deficiency, and corneal opacity.

What is your treatment plan in case #1 with a centrally clear cornea, mild peripheral opacification and thinning, and perilimbal conjunctival ischemia? (Figure 1)

Mohammad-Ali Javadi, MD

On the basis of our experience, surgical intervention is advisable in cases with early stages of mustard gas keratitis (MGK). Therefore, the first step would be lower punctal occlusion, followed by sectoral keratolimbal allograft (KLAL) surgery on the temporal side. Since the limbal regions in the palpebral fissure are usually involved, the nasal side may also require KLAL surgery. Immunosuppressive agents are administered after KLAL according to our protocol.³

Farid Karimian, MD

This case which is a mild form of MGK can be managed with conservative and supportive treatment. As visible, the lacrimal puncta are patent which must be occluded at this stage. Telangiectatic vessels in the lid margin and meibomianitis are indicative of blepharitis in this case. Treatment must be directed toward controlling this condition. Treatment of blepharitis in these patients is generally complicated. They must become aware of the importance of proper control of blepharitis, and how this can affect the natural course of MGK. Lid margin hygiene and scrub, as well as low potency, low dose steroids (with close observation of their side effects) are prescribed. If there is tear film deficiency, preservative-free tear substitutes are given. This patient must be followed every six months for possible progression of MGK.

Sepehr Feizi, MD

Low-grade smoldering acute and chronic inflammatory response is a prominent feature in MGK. The ongoing inflammatory reaction can be evoked by either the direct toxic effects of mustard gas itself, inducing the release of inflammatory mediators, or alteration in the ocular surface structures, resulting in meibomian gland dysfunction, tear film deficiency, and conjunctival and limbal ischemia. This lingering inflammation leads to ocular surface destruction and explains the eventual requirement of surgical intervention in the majority of chemical warfare victims. Therefore, I would prefer to perform sectoral KLAL and punctal occlusion as well as prescribe lubricants in this early stage to remove abnormal conjunctiva, sclera and peripheral cornea and to halt the progressive course of the disease.

How about case #2 with mild inferior corneal thinning and central superficial corneal irregularity
and opacity? Would you use rigid gas permeable (RGP) contact lenses in this case? What is your opinion about superficial keratectomy? (Figure 2)

Mohammad-Ali Javadi, MD

Based on my experience, the procedure of choice in this case is sectoral KLAL on both temporal and nasal sides (between 100 and 120 degrees on each side) with simultaneous conventional lamellar keratoplasty (LKP). Since endothelial function is nearly normal in these cases and the chance of recurrence of opacity in the graft is higher than other indications for corneal transplantation, LKP is preferable to full-thickness penetrating keratoplasty (PKP). Superficial keratectomy is not recommended and may even lead to persistent epithelial defects due to the loose epithelium caused by partial limbal stem cell deficiency (LSCD). RGP contact lenses are not tolerable in most of these patients and I do not recommend using them.

Farid Karimian, MD

There is usually some degree of LSCD in these patients, thus the epithelial cells are not normal. Central corneal irregularity and opacity are indicators of progression of LSCD. Unfortunately, this condition is not stable and will progress. Application of RGP contact lenses in these cases will aggravate LSCD, and further compromise epithelial integrity and health. Furthermore, superficial keratectomy may lead to persistent epithelial defects which are difficult to manage. When needed and indicated, bandage soft contact lenses can be used for their protective effect over the limbal stem cells and the vulnerable epithelium.

Sepehr Feizi, MD

For the reasons mentioned earlier, again I would prefer to perform sectoral KLAL to replace the abnormal inferior limbus accompanied by superficial keratectomy to remove abnormal epithelium from the corneal center. Superficial keratectomy alone is not appropriate as can lead to persistent epithelial defects.

What is your preferred treatment plan in case #3 with diffuse and deep corneal opacity without persistent epithelial defect and no invading telangiectatic vessels? Do you think he needs corneal transplantation only or stem cell transplantation is necessary as well? Which type of corneal graft do you prefer and why? (Figure 3)

Mohammad-Ali Javadi, MD

Without a slit lamp photo, it is not possible to estimate the depth of corneal involvement. We have had some experience with both LKP and PKP in such cases. We have noted that...
opacities can recur after corneal transplantation which can be more severe as compared to before intervention, necessitating regrafting. Therefore, I have changed my initial approach and perform lamellar or penetrating keratoplasty in combination with KLAL.  

Farid Karimian, MD

In this case, LSCD is severe and any corneal transplantation, lamellar or penetrating, has only a short life span. Moreover, complications such as persistent corneal epithelial defects, infectious ulceration, suture related complications, rejection episodes and finally failure are inevitable. The procedure of choice in this case with severe MGK is segmental KLAL with at least two 120 degrees (nasal and temporal) segments. As usually evident in these cases, the superior and inferior limbal stem cells seem to be relatively spared, which could be due to coverage of the superior and inferior limbal areas by the upper and lower lids during mustard gas exposure. The central scar seems to be deep and the procedure of choice is LKP, if possible, with removal of scarified corneal stroma as much as possible. At the conclusion of surgery, punctal occlusion as well as lateral tarsorrhaphy is of utmost importance. The postoperative treatment regimen will include immunosuppressive medications (tacrolimus or cyclosporine-A with mycophenolate mofetil) which are started and continued at a lower maintenance dose for 12 to 24 months. Tapering depends on the postoperative course and episodes of rejection. Oral steroids (usually prednisolone) are started, tapered and continued on a lower maintenance dose. Monitoring liver and renal function, and blood pressure while receiving these immunosuppressive medications is of great importance in these patients who usually suffer from systemic involvements (mostly pulmonary).

Sepehr Feizi, MD

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 of time. However, stem cell transplantation serves further purposes in MGK than simply providing stem cells. First, the sclera and cornea adjacent to abnormal limbal areas are thin and ischemic, and demonstrate neovascularization, lipid and amyloid deposits, adding to patient discomfort. Additionally, corneal thinning is severe in some cases which can threaten globe integrity. With stem cell transplantation, the abnormal conjunctiva, sclera, and cornea are removed and replaced with matched blocks containing stem cells, conjunctiva, and partial thickness cornea and sclera. Therefore, several important abnormalities in MGK including LSCD, conjunctival and limbal ischemia, scleral/corneal thinning and deposits, can be addressed simultaneously with stem cell transplantation.

When corneal changes including scarring, thinning, and degenerative lipid or amyloid deposition preclude useful vision or threaten globe integrity, optical and tectonic corneal grafting becomes necessary. Reporting on the outcomes of PKP in delayed onset MGK in 22 eyes, a previous study indicated that a clear graft was observed in 77.3% of cases, but the procedure failed in 22.7% of eyes after 41 months and that subepithelial or endothelial graft rejection, or both, developed in 50% of cases.  

What is your treatment plan for case #4 with severe inferior temporal corneal thinning and opacity? (Figure 4A) What are the criteria for surgical intervention in this group of cases? Sectoral cadaveric KLAL surgery has been performed for
him (Figure 4B). Do you agree with this surgery in this case? What is your idea about living-related conjunctival-limbal allograft (lr-CLAL) surgery?

Mohammad-Ali Javadi, MD
Initially, we performed lr-CLAL to manage LSCD in these cases. However, we soon found that there were some problems with donors and outcomes. At present, my preferred approach is sectoral KLAL. According to my earlier experience, amniotic membrane transplantation with limited superficial keratectomy would do well in few cases with mild involvement.

Farid Karimian, MD
Considering the destructive effect of mustard gas in the inferotemporal limbal area, as well as complicated thinning of the adjacent cornea, reconstructive procedure only in the same area is indicated. Most of the cornea is clear in this case, and only one quadrant of LSCD is present. I agree with the performed procedure. The nasal limbal area in this case also seems to be ischemic and the patient should be monitored for delayed-onset complications of mustard gas exposure. This means that a “healthy-looking” cornea in a mustard gas exposed case does not guarantee lifelong health of LSCs and cornea. Progressive corneal thinning, extending vascularization and deposition toward the visual axis can be considered as main indications for surgical intervention in these cases. The area of involvement is extensive which may necessitate further surgery in future. Living-related conjunctival-limbal allograft surgery seems not to be a proper option.

Sepehr Feizi, MD
Living-related conjunctival-limbal allograft (lr-CLAL) and KLAL surgery have been used effectively to treat LSCD in bilateral ocular surface disorders. Both techniques of stem cell transplantation can markedly decrease subjective symptoms, heal persistent corneal epithelial defects, and lead to regression of peripheral corneal vascularization in the affected segments. Considering a lower chance for rejection and less need for intense immunosuppression, lr-CLAL initially was considered and found to be effective in stabilizing the ocular surface in patients with delayed or chronic MGK. In contrast to KLAL, lr-CLAL cannot provide adequate corneal and scleral lamellae, and cadaveric eyes also should be available if a tectonic graft is needed. In addition, the amount of stem cells that can be harvested from a living-related donor is limited (120 degrees of limbal area at most). Another advantage worth mentioning is that 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. For these reasons, I prefer KLAL with the capability of providing more stem cells and

Figure 4. (A) Severe peripheral corneal thinning and opacity with perilimbal conjunctival ischemia. (B) The same case after sectoral cadaveric keratolimbal allograft transplantation.
simultaneously addressing conjunctival, limbal, and corneal abnormalities.

What is your treatment plan in cases #5 (Figure 5) and #6 (Figure 6) with extensive corneal opacification, lipid and amyloid deposition, thinning, and invading tortuous telangiectatic vessels?

Mohammad-Ali Javadi, MD

As previously mentioned, the first step is punctal occlusion followed by sectoral KLAL to remove the abnormal limbus and lipid depositions in the peripheral cornea with concomitant LKP or PKP. Another option for case #6 is hemi-corneoscleral transplantation using a fresh globe. In this approach, the superior uninvolved cornea is left untouched and about three-fourths of the inferior cornea and the abnormal inferior limbus are replaced with a hemi-sclerocorneal graft.

Farid Karimian, MD

LSCD seems to be the basic pathogenetic mechanism leading to corneal thinning, vascular invasion and subsequent lipid and amyloid deposition. This mechanism has already been reported from our center. Management of such severe corneal scarring with LKP or PKP alone will not be a long-lasting procedure and graft survival will be of short duration. These 2 cases have extensive areas of limbal ischemia and are affected with tortuous vessels invading the cornea. My suggestion is at least 270 degrees of segmental KLAL (excluding the superior quadrant which seems to be less affected) followed by immunosuppressive therapy. In comparison to PKP, LKP is the preferred procedure. In case of significant visual axis involvement or full-thickness corneal involvement, PKP, albeit with high risk, can be considered. It has been shown that performing subsequent LKP or PKP months after KLAL, or simultaneous surgery in the same session have equal success rates in these cases.

Sepehr Feizi, MD

There is significant opacification of the corneal stroma accompanied by limbal ischemia as well as LSCD necessitating both stem cell and corneal transplantations in these two cases. A considerable number of patients require both limbal and corneal transplantations which can be performed either simultaneously or sequentially. I have a tendency toward performing 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 the cornea and stem cells potentially reducing the load of antigens presented to the recipient’s immune system. For this reason and since LKP eliminates the risk of graft failure due to endothelial rejection reactions,
the outcomes of sequential and simultaneous LKP and KLAL may not differ. Furthermore, the total duration of oral corticosteroid treatment is shorter in the simultaneous group than in the sequential group. Therefore, I would perform simultaneous LKP and KLAL in addition to punctal occlusion and lateral tarsorrhaphy for these two cases.

What is your idea about amniotic membrane transplantation (AMT) in cases with MGK? What are the indications for its use?

Mohammad-Ali Javadi, MD
Previously, I used to perform AMT for cases with persistent CED or when it was not possible to do major surgery due to severe respiratory distress.

Farid Karimian, MD
There is no widespread and specific indication for AMT in these cases. Amniotic membrane can be used as a graft, when extreme thinning and general condition do not allow for a keratoplasty procedure. Furthermore, at the conclusion of limbal stem cell transplantation with or without keratoplasty, amniotic membrane can be used as bandage, covering the transplanted area. It can also be used in a limited number of cases with partial LSCD associated with persistent corneal epithelial defects. Further applications of AMT, for example, in ex vivo expansion of limbal stem cells have to be elucidated in future studies.

Sepehr Feizi, MD
Generally speaking, AMT alone has no role in the management of MGK as it cannot reverse the underlying abnormalities leading to different manifestations including LSCD, limbal ischemia, corneal vascularization or thinning, and abnormal deposits in the stroma. It can be used in conjunction with other interventions such as KLAL to provide an appropriate environment for the transplanted limbal stem cells to migrate over the cornea.

Conflicts of Interest
None.

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