Chapter 1

Corneal Blindness Caused by Mustard Gas

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Additional information is available at the end of the chapter

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Abstract

Mustard gas is a lipophilic, highly cytotoxic agent that rapidly penetrates tissue, and the eye is one of the organs mostly affected. Mustard gas-related ocular injuries can be divided into immediate, chronic, and delayed-onset phases. Late complications, developing after 1–40 years, can cause progressive and permanent reduction in visual acuity and even blindness. A wide range of late ocular involvements have been reported, which include chronic blepharitis, limbal ischemia and stem cell deficiency, and corneal scarring and neovascularization. The majority of corneal involvements are limited to the anterior stroma, leaving the posterior stroma and endothelium relatively intact. Therefore, lamellar keratoplasty is appropriate for the management of corneal involvements in the majority of victims. This procedure can be performed alone or in combination with limbal stem cell transplantation.

Keywords: corneal blindness, mustard gas, corneal involvement, keratitis

1. Introduction

1.1. History

The exact date of the first sulfur mustard synthesis is somewhat unclear, but the first report by Despretz may have been in 1822. An 1860 report by Neimann described a delayed-effect vesicant oil as a reaction product of ethylene on a mixture of sulfur chlorides. In 1886, a process to produce significant quantities of pure sulfur mustard was described by Meyer using sodium sulfide, ethylene chlorohydrin, and hydrochloric gas [1, 2].

Mustard gas was used for the first time by German forces against Allied troops in July 12, 1917 that caused more than 2100 casualties. The Allies began using mustard gas against German troops in 1918. During 1935–1936, the Italian army dropped mustard-gas bombs in Ethiopia to destroy Emperor Haile Selassie's army. During 1963–1967, Egypt used mustard gas and a

nerve agent in Yemen to support a coup against the Yemeni monarchy. During the Iran-Iraq war (1980–1988), Iraq used chemical weapons, including tabun and mustard gas, against Iran and Iraq's Kurdish minority. Iraq's use of chemical weapons was confirmed by the United Nations experts [3].

1.2. Molecular formula of mustard gas and its biochemical mechanism of tissue injury

Sulfur mustard ($C_4H_8Cl_2S$) is one of a class of chemical warfare agents which are known as vesicants because they cause vesicles, or blisters, on exposed skin. Pure sulfur mustard is odorless, colorless, and viscous liquid at room temperature. It is usually yellow-brown in color and has an odor resembling garlic, horseradish, or mustard plants when used as warfare agents, which is how it got its name. However, this compound has absolutely no relation whatsoever to culinary mustard [4].

Mustard gas is a lipophilic, highly cytotoxic agent that rapidly penetrates tissue [5]. Exposed skin surfaces, eyes, the linings of both respiratory and gastrointestinal tracts, and renal systems as well as the bone marrow are all at risk. The risks increase dramatically under hot, humid conditions, and it can be lethal at sufficiently high doses [5, 6]. It has been demonstrated that 80% of sulfur mustard applied to the skin evaporates, 10% remains in the skin, and 10% gets absorbed systemically [7]. Susceptibility of the eyes to the toxic effects of mustard gas is due to moistness of the ocular surface, allowing activation of the agent. Additionally, corneal epithelial cells have a high turnover and metabolic rate that increase their vulnerability to the lipophilic sulfur mustard trapped into the oily tear layer [8].

Sulfur mustard is a cellular poison that triggers apoptosis as a cytotoxic mechanism. The acute toxic effects of mustard vesicants are usually attributed to the consequences of alkylation reactions with organic compounds including nucleoproteins such as DNA [9]. The ladder pattern of DNA fragmentation after cell exposure to mustard gas indicates internucleosomal cleavage of DNA. Alkylation reactions can result in genotoxic effects as well as physiological and metabolic disturbances that induce apoptosis [10]. In addition, mustard gas is a mutagen and is a known carcinogen that is associated with an increased risk of developing lung and other respiratory tract cancers [11].

2. Mustard gas-related ocular injuries

Mustard gas-related ocular injuries can be divided into immediate, chronic, and delayed-onset phases [12]. Acute manifestations of varying degrees, including eyelid erythema and edema, chemosis, subconjunctival hemorrhage, epithelial edema, punctate erosions, and corneal epithelial defects, develop in 75–90% of exposed individuals and can follow three different courses: complete resolution, persistent smoldering inflammation (chronic form), or reappearance of lesions after a latent period of quiescence (delayed form) [13, 14].

Late complications, developing after 1–40 years, can cause progressive and permanent reduction in visual acuity and even blindness, and they occur in approximately 0.5% of those initially

severely wounded [6, 13]. A wide range of late ocular involvements have been reported, which include chronic blepharitis, dry eye, conjunctival vessel tortuosity, limbal ischemia and stem cell deficiency, corneal scarring and neovascularization, corneal thinning and perforation, epithelial irregularity, recurrent or persistent epithelial defects, and secondary degenerative changes including lipid/amyloid deposits (**Figure 1**) [5, 6, 12–17].

Dry eye is a late ocular complication of exposure to mustard gas, the symptoms of which are often severe and persistent and can influence many aspects of intoxicated victims' lives [5, 6, 18, 19]. Although the exact pathophysiologic cause of dry eye syndrome after exposure to mustard gas is not known yet, most studies in this regard have revealed evidence for increased apoptosis in the conjunctival epithelium [20]. This apoptosis also occurs in goblet cells resulting in a significant decrease in goblet cell density thus reducing mucin production and tear film stability [20]. Additionally, dysfunction of lacrimal glands may occur secondary to lymphocytic infiltration of the glands [20].

Mustard gas-related corneal involvements are completely different from those observed in other causes of corneal opacities that develop after trauma, infection, and acid or alkaline burns [18]. For example, corneal thinning and fragility is a striking feature in mustard gas-induced ocular injuries [18]. Such differences can be explained by the presence of other concomitant abnormalities such as limbal ischemia and vascular abnormalities [18]. Limbal ischemia causes 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 [12]. Alterations of corneal stroma secondary to acute and chronic inflammation, stromal scar and fibrosis, and deposits make stromal layers too rigid to be separated by air. Therefore, deep anterior lamellar keratoplasty using the big-bubble technique is hard to perform in mustard gas-induced keratitis [12].

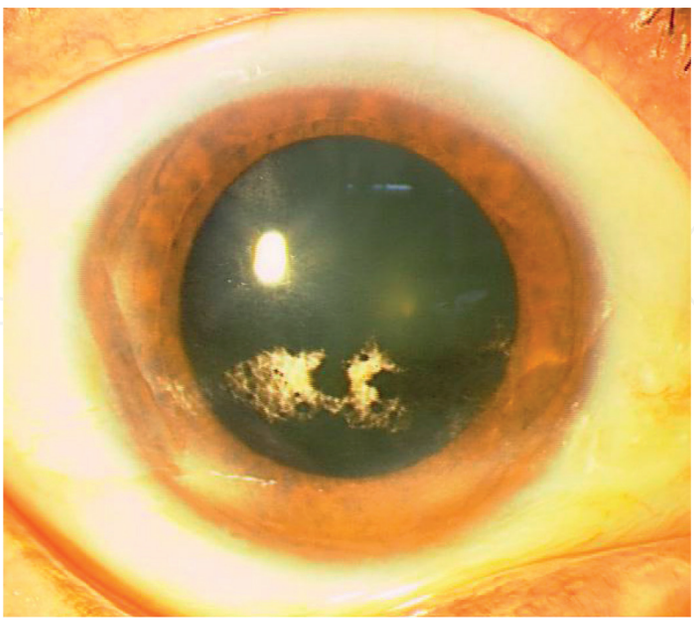

Figure 1. Abnormalities of the cornea, including surface irregularity, thinning, and intrastromal lipid and amyloid deposits, are evident in an eye suffering from mustard gas keratitis.

Although limbal stem cell deficiency has been reported in mustard gas-related ocular involvements, its clinical manifestations are completely different from those observed in other causes of stem cell deficiency such as acid or alkaline burns, thermal burns, Stevens–Johnson syndrome, ocular cicatricial pemphigoid, and multiple surgeries [18]. For example, conjunctivalization of the corneal surface, which is a striking feature in the latter conditions, is hardly observed in mustard gas-induced keratitis. Additionally, there is no correlation between the severity of corneal involvements and limbal stem cell deficiency in these eyes [12]. Limbal abnormalities observed in mustard gas-induced ocular involvements are 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 [12].

3. Management of mustard gas-induced ocular involvements

3.1. Management of acute phase

The management of the acute phase is relatively straightforward, chiefly consisting of symptomatic therapy to address the patient's discomfort and ocular inflammation. This approach includes copious irrigation with potable water at the time of exposure, topical antibiotics, preservative-free lubricants, and anti-inflammatory agents [21]. Artificial tears and lubricating ointments should be administered every 6 hours. Topical antibiotics (e.g., chloramphenicol or ciprofloxacin eye drops) should be prescribed every 6 hours for 7–10 days to prevent bacterial infection [21]. Topical steroids 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. Corticosteroid eye drops should be administered every 8–12 hours for a week and then gradually tapered over 2–3 weeks [21]. The prolonged use of topical corticosteroids (more than 3 weeks) should be avoided. Amniotic membrane transplantation can be considered for the management of acute phase because it suppresses inflammation and scarring and promotes healing [18]. Symblepharon formation is not the feature of mustard gas-induced ocular involvements. Therefore, the victims do not require symblepharolysis [12].

3.2. Management of chronic phase

To date, there is no definitive therapy for chronic and delayed-onset mustard gas-related keratitis. Therapy for delayed phase is tailored on the basis of the severity and type of involvements and can vary from symptomatic therapy to surgical interventions for ocular surface problems including dry eye and corneal epithelial instability, corneal opacity, and limbal stem cell deficiency [12].

3.2.1. Medical managements

Different medications have been used for the management of sulfur mustard-induced ocular injuries. They include preservative-free artificial tears, topical steroids and antibiotic, N-acetylcysteine, topical cyclosporine A, resolvin E1, topical form of essential fatty acids, thymosin β4, topical form of curcumin, newly formulated artificial tears, diquafosol, rebamipide, tretinoin, and oral uridine.

Preservative-free artificial tears and lubricants are one of the most prescribed drugs in the management of ocular symptoms in mustard gas-related corneal involvements. New formulas have been proposed for artificial tears, and can be used in the management of dry eye disease with any etiology. Recombinant human lubricin (proteoglycan 4), a natural substance [22], and hyaluronic acid with trehalose [23] are one of these new formulas, and have been found to be safe with a better patient satisfaction. Natural components of tear film such as anionic glycosaminoglycan polysaccharide in combination with polymers, hyaluronic acid, and carmellose sodium are quite effective in corneal epithelial staining [24]. Another new formula contains carmellose sodium, osmoprotectants, and hyaluronic acid and has been demonstrated to improve ocular symptoms in dry eye disease [25].

Curcumin is an anti-inflammatory agent with anti-cancer and anti-apoptotic properties [26, 27]. Dietary curcumin is found to decrease lens opacification in a rat model of naphthalene-induced cataract [28]. Curcumin is effective in the management of different respiratory and cutaneous symptoms in sulfur mustard-exposed casualties [29, 30]. This natural hydrophobic polyphenol is proposed as an alternative treatment for dry eye disease [31]. Maria et al. [32] have developed a formulated eye drop for curcumin with more aqueous solubility properties. This sustained-release drop may be appropriate for the management of different inflammatory ocular surface disorders encountered in sulfur mustard-exposed patients [32]. However, further animal studies and clinical trials are required to approve the efficacy of this formulation.

Resolvin E1 (RvE1), a derivative of eicosapentaenoic acid, is an endogenous lipid mediator and can inhibit pro-inflammatory responses [33]. This drug has been used for the management of periodontitis, inflammatory bowel disease, and prevention of vascular inflammation [33, 34]. It has been shown that the topical administration of RvE1 significantly down regulates cyclooxygenase-2 (COX-2) expression and increases tear production, resulting in an increase in the density of superficial epithelial cells in a dry-eyed mouse model [35]. These features make RvE1 a potential therapeutic option in delayed ocular lesions induced by sulfur mustard. Similarly, thymosin β4 eye drops have been found to be effective in the treatment of dry eye disease and corneal vascularization and thus may have a role in the management of delayed ocular lesion in sulfur mustard-exposed victims [36]. There is no report of ocular toxicity associated with the topical form of thymosin β4 [36].

Diquafosol is a P2Y2 purinergic receptor agonist that stimulates the receptors in ocular tissues and thus increases mucin (conjunctival goblet cells stimulation) and the aqueous portion of tear film (conjunctival epithelial cells stimulation) [37]. Three percent diquafosol ophthalmic solution is effective for the treatment of dry eye disease through tear film stabilization and repair of corneal epithelial damages [38, 39]. Another P2Y2 receptor agonist is uridine. Oral uridine is reported to be beneficial for increasing mucin secretion and tear production [40].

Rebamipide is a mucosal protective agent with anti-inflammatory, immunosuppressive, and anti-apoptotic activities [41]. Corneal and conjunctival mucin can be effectively and safely increased by 2% rebamipide ophthalmic suspension [42]. The efficacy of diquafosol, rebamipide, and oral uridine in sulfur mustard-exposed patients should be investigated in clinical trials.

Tretinoin (0.01% all-trans-retinoic acid) is effective in the treatment of dry eye disease [43]. Tretinoin improves tear film break-up time and Schirmer tear test results [43]. However, tretinoin cannot

improve ocular symptoms such as foreign body sensation and photophobia [43]. Therefore, it can be considered a secondary option for the treatment of mustard gas-induced dry eye. Tretinoin in combination with topical interferon α-2b is an option in the management of partial limbal stem cell deficiency [44].

Cyclosporine A is an approved immunomodulatory ophthalmic product with different concentrations (0.05, 0.1, 1, and 2%) and has been used to increase tear production in dry eye patients [45]. Cyclosporine blocks the IL-2 signaling pathway and then inhibits T cell-mediated immune response [46]. Recently, Jadidi et al. [20] demonstrated that the treatment with topical cyclosporine A 0.05% in patients with severe dry eye due to mustard gas injury increased goblet cell density in the bulbar conjunctiva and improved symptoms of the disease.

Omega-3 plays important roles in human biology through decreasing cytokines and inhibiting oxidative stress [47]. It is an anti-inflammatory agent that prevents apoptosis in ocular tissues and can reduce tear osmolality and increase tear production in patients with dry eye disease [48–50]. However, there is no evidence of its significant effectiveness in meibum lipid composition [50]. A topical form of omega-3 fatty acid in combination with hyaluronic acid could successfully treat dry eye in a mouse model [47].

N-acetylcysteine, a mucolytic agent, has been used in ophthalmology to prevent corneal melting and perforation in different corneal diseases, including alkali-burned corneal ulcers [51] and filamentous keratitis [52]. N-acetylcysteine is a derivative of cysteine, which inhibits collagenase irreversibly by reducing disulphide bonds and by chelating calcium or zinc. It also inhibits matrix metalloproteinase-9 (MMP-9), potentially by similar mechanisms. N-acetylcysteine may be useful clinically to treat corneal destruction in mustard gas-induced keratitis in which MMP-9 activity and inflammatory cytokines are upregulated [53]. Although the exact mechanism of inhibition of MMP-9 secretion by N-acetylcysteine is currently unknown, the inhibitory properties of N-acetylcysteine on inflammation has been shown to act through nuclear factor-kB, which has a pivotal role in inducing the expression of multiple genes in immune and inflammatory responses [54, 55]. Topical applications of 5 and 20% N-acetylcysteine have been shown to be effective in the treatment of ocular surface disorders without toxic effects. However, prolonged treatment of N-acetylcysteine has adverse effects on the cornea.

3.2.2. Surgical managements

Dry eye can be addressed surgically using punctal plug, punctal occlusion, and temporary or permanent tarsorrhaphy [12]. Amniotic membrane transplantation is an effective approach for the management of persistent epithelial defects when limbal stem cell deficiency is partial because it suppresses inflammation and scarring and promotes healing [18]. Amniotic membrane transplantation is beneficial with keratectomy in the case of lipid deposition, and it has been used as a graft in limbal stem cell transplantation [18]. However, transplanted amniotic membrane can integrate into the corneal stroma, resulting in a reduction in visual acuity (**Figure 2**).

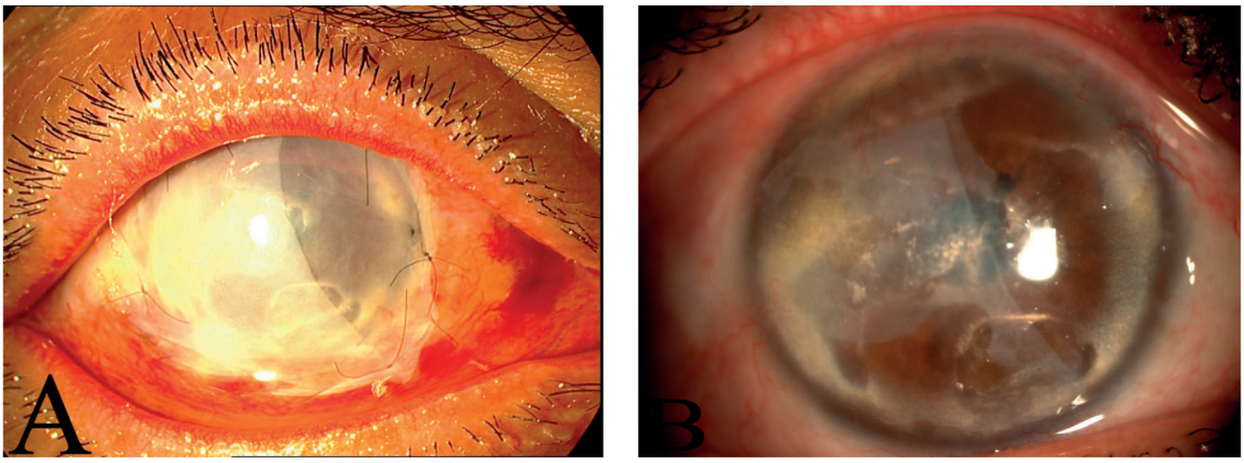

Figure 2. (A) Amniotic membrane transplantation was performed for the management of persistent epithelial defects in victim of mustard gas. (B) Please, note transplanted amniotic membrane has integrated into the corneal stroma, resulting in a reduction in visual acuity.

When significant limbal ischemia and/or stem cell deficiency develop, stem cell transplantation is required to provide a viable source of corneal epithelial cells as well as address conjunctival ischemia and scleral and peripheral corneal thinning [56, 57]. Limbal stem cells can be harvested from first-degree relatives, including parents or siblings (living-related conjunctival-limbal allograft) [56]. However, we noticed that living-related conjunctival-limbal allograft cannot provide adequate corneal and scleral lamellae, and cadaveric eyes should also be available [56]. Therefore, the technique of limbal stem cell transplantation was changed to keratolimbal allograft, which is harvested from cadavers and can provide more stem cells [57]. Another advantage worth mentioning is that keratolimbal allograft makes it possible to harvest corneal and limbal blocks from the same donor, if both transplantations are to be performed simultaneously [57]. This approach can reduce the antigenic load to the recipient's immune system [57].

3.2.2.1. Corneal transplantation for the management of mustard gas-induced keratitis

Traditionally, penetrating keratoplasty has been commonly performed as an ultimate treatment of different corneal pathologies, and numerous studies have reported good visual results after surgery [58]. We performed penetrating keratoplasty in 27 eyes of 27 victims of mustard gas and followed the patients for 15–96 months [58]. We reported a graft survival rate of 77.3%, indicating relatively acceptable outcomes, especially when corneal opacity is centrally located, and there is no severe limbal involvement (**Figure 3**) [58]. However, in cases demonstrating severe dry eye, limbal ischemia, or peripheral corneal involvements, a high rate of graft failure due to rejection reactions or recurrence of opacity was noted (**Figure 4**) [58]. Additionally, most corneal involvements are limited to the anterior stroma, leaving posterior stroma and endothelium relatively intact [59–61]. Therefore, the technique of corneal transplantation has evolved from penetrating keratoplasty to lamellar keratoplasty.

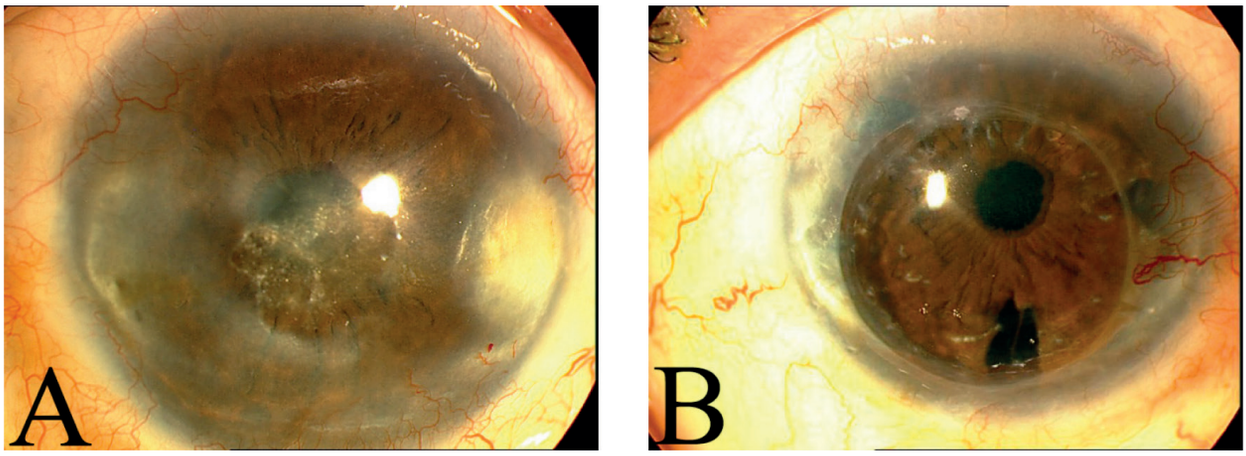

Figure 3. (A) Signs of mustard gas-induced keratitis, including surface irregularity, thinning, and intrastromal lipid and amyloid deposits, are evident. (B) Penetrating keratoplasty was performed in the same eye and yielded a clear graft 16 months postoperatively in an eye with mustard gas keratitis.

3.2.2.1.1. Indications for conventional lamellar keratoplasty

Indications for optical or tectonic lamellar keratoplasty in mustard gas-induced corneal involvements are corneal haziness leading to decreased visual acuity, photophobia, discomfort caused by corneal surface irregularity, abnormal deposits or severe corneal thinning threatening globe integrity, or a combination thereof [12]. A full-thickness graft is still inevitable in certain conditions such as significant interface opacity, deep stromal scar, and corneal perforation [12].

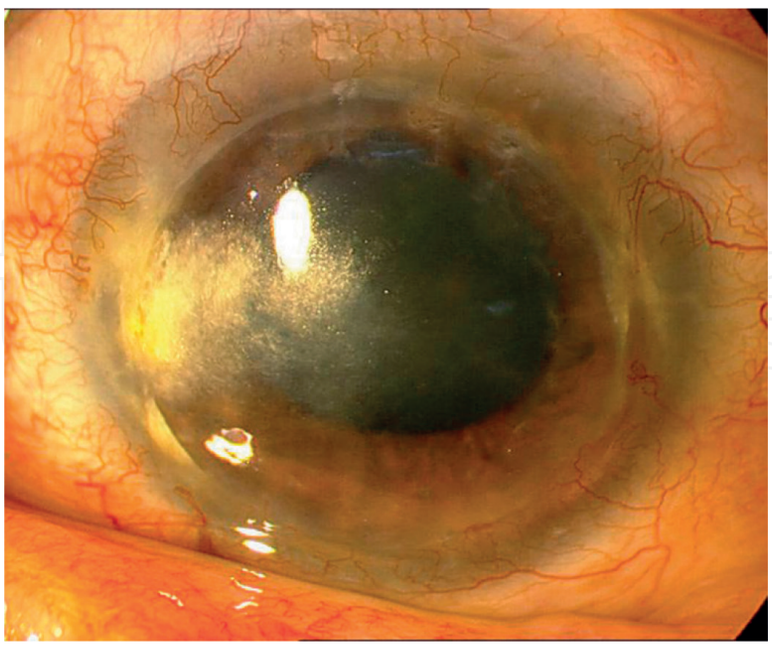

Figure 4. A penetrating keratoplasty graft opacity results from limbal stem cell deficiency and ocular surface abnormalities in a victim of chemical warfare.

3.2.2.1.2. Surgical technique

Manual lamellar dissection technique is used to perform conventional lamellar keratoplasty. The size of recipient trephine is selected on the basis of the vertical corneal diameter and the extent of corneal involvements. Based on the corneal thickness and the depth of opacities, at least 70% of the corneal thickness is trephined and manual lamellar dissection is performed using a crescent blade. During lamellar dissection, it is attempted to remove all deposits and opacities, mainly confined to the anterior- and mid-stroma, and to create a smooth, clear, and single-plane recipient bed. A partial-thickness donor corneal graft, prepared from a fresh whole globe with an intact epithelium, oversized by 0.5 mm, and matching the depth of the recipient bed is sutured using combined 8-bite interrupted sutures accompanied by 16-bite single running 10-0 nylon sutures (**Figure 5**). The suture tension should be moderate because very tight sutures prevent the appropriate spreading of tear film over the cornea, retarding reepithelialization of the graft in such compromised eyes.

We performed conventional lamellar keratoplasty in 51 eyes with mustard gas-induced corneal involvements and followed up the patients for 19–107 months. Best-corrected visual acuity was 0.35 ± 0.16 (0.0–0.48) logMAR at the final follow-up and graft survival rate was 91.7% in this series [58]. Postoperative complications included epithelial rejection (two eyes), persistent epithelial defects (four eyes), graft opacity (three eyes), and significant interface haziness (three eyes) [58].

3.2.2.1.3. Concomitant procedures

The unique features of mustard gas-induced ocular injuries are limbal and corneal involvements [12]. Based on the severity of dry eye, corneal epithelial instability, and

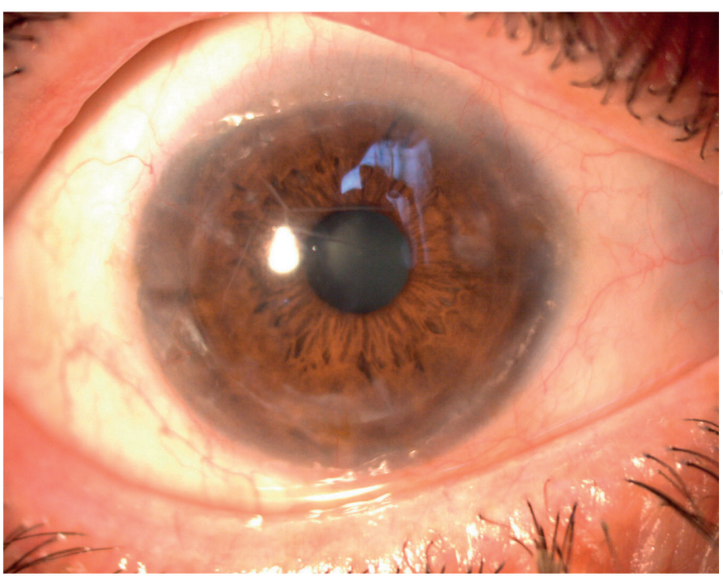

Figure 5. Lamellar keratoplasty was performed for mustard gas-induced keratitis. Despite the presence of Descemet's membrane wrinkling, the patient has acceptable visual acuity.

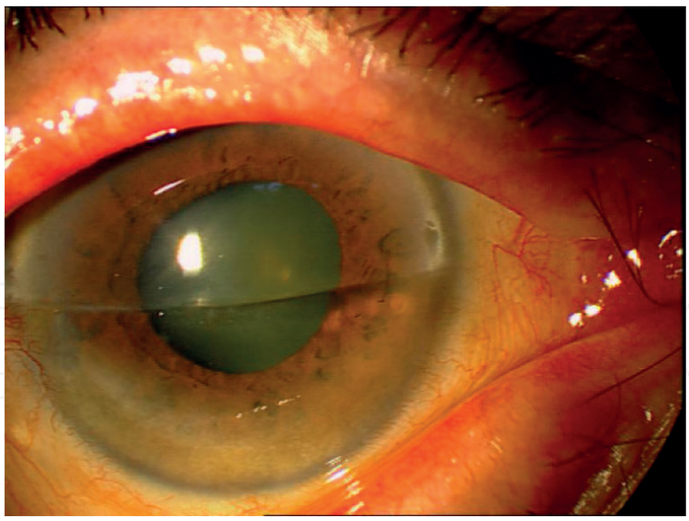

Figure 6. Simultaneous en bloc keratolimbal allograft and lamellar keratoplasty were performed to address coexisting mustard gas-induced limbal stem cell deficiency and corneal involvements in the same patient.

limbal stem cell deficiency, other interventions including punctal occlusion, temporary or permanent tarsorrhaphy, and limbal stem cell transplantations may be required to address these late complications at the time of corneal transplantation. A significant number of participants require both limbal stem cell and corneal transplantations. There is a trend to carry out both lamellar keratoplasty and limbal stem cell transplantation at a single session (**Figure 6**) to decrease the number of surgeries and anesthesia administrations [57]. In addition, only one donor can be used to provide both stem cells and cornea during a simultaneous operation, which can decrease the antigenic load presented to the recipient's immune system [57]. Furthermore, the total duration of oral corticosteroid and immunosuppressive treatment is shorter in the simultaneous approach than in the sequential approach, which require oral corticosteroid and immunosuppression after each surgical intervention [57].

3.2.2.1.4. Postoperative medical regimens

Postoperatively, the patients are medicated with 0.5% chloramphenicol eye drops every 6 hours, 0.1% betamethasone eye drops every 6 hours, preservative-free artificial tears every 2 hours, lubricating ointments every 8 hours, and systemic prednisolone 1 mg/kg daily [12]. Topical antibiotics are discontinued after complete epithelial healing, whereas oral and topical corticosteroids are tapered off over 2–4 weeks and 2–3 months, respectively, based on the severity of ocular inflammation [12].

For patients who undergo limbal stem cell transplantation concomitantly, systemic tacrolimus 1 mg twice a day is started at the time of surgery and continued for 1.5 years. Additionally, 1 g oral mycophenolate mofetil is prescribed twice daily for at least 6 months. It is then tapered gradually and discontinued after 1 year [12]. Cell blood counts, blood pressure, and renal and liver function test results should be monitored at appropriate intervals in collaboration with a kidney transplantation expert to monitor for possible complications of immunosuppressive therapy.

3.2.3. Complications of lamellar keratoplasty

3.2.3.1. Intraoperative complications

3.2.3.1.1. Descemet's membrane perforation

Perforation in Descemet's membrane during lamellar keratoplasty which is reported to be as high as 26.3% [62] can occur during any step of surgery including trephination, stromal excision, and donor suturing. The moment of perforation is crucial for the completion and the success of lamellar keratoplasty. Early perforations make stromal dissection more difficult and result in a greater residual stroma and hence slower visual recovery because of interface opacification [63]. Additionally, the size of perforation determines the severity of endothelial damage; a large hole within Descemet's membrane leads to a flat anterior chamber necessitating multiple air injections which is associated with more severe endothelial damage [63].

Management of Descemet's membrane perforation depends upon the location and size of the hole and the step of surgery at which this complication takes place. Perforations that occur during trephination can be managed by tight sutures at the site of perforation before lamellar dissection. Finally, sutures which fix donor tissue to the recipient bed in the site of perforation should be full thickness including recipient Descemet's membrane. If perforation occurs during stromal dissection, the site of perforation should be dissected last at a different plane to leave some stroma over this area to seal the perforation. At the end of operation, the anterior chamber is partially filled with an air bubble. If anterior chamber is completely filled with air, pupillary block may develop postoperatively. For perforation occurring during suturing, injection of air into the anterior chamber at the conclusion of surgery usually suffices.

3.2.3.2. Postoperative complications

3.2.3.2.1. Persistent epithelial defects

Because of ocular surface abnormalities including severe blepharitis and dry eye as well as limbal stem cell deficiency, victims of mustard gas are susceptible to develop persistent epithelial defects after keratoplasty [12]. Persistent epithelial defects can lead to postoperative complications such as subepithelial scarring or infectious keratitis. Therefore, it should appropriately be managed. Intraoperative measures include the use of good donor quality grafts with intact epithelium and the avoidance of damage to the corneal epithelium during the preparation of the donor tissue. Additionally, appropriate suture tension and surgical wound apposition, punctal occlusion, and tarsorrhaphy encourage the epithelialization of donor grafts [21]. Postoperatively, control of inflammation with topical steroids, deliberate use of preservative-free artificial tears and lubricating ointments as well as treatment of blepharitis are advisable [21]. Sometimes, it is necessary to prescribe autologous serum 20% and/or fit a bandage contact lens in intractable cases [21].

3.2.3.2.2. Suture-related complications

Suture-related complications such as sterile reactions, early suture loosening, cheese-wiring, and suture-related scarring and vascularization can develop after lamellar keratoplasty when

suture are in place. These complications can be reduced or even prevented by appropriate suture depth, length, and tension. Additionally, the administration of topical corticosteroid for an adequate period after surgery can significantly reduce suture-related complications. However, the long-term use of corticosteroid eye drops may increase the risk of cataract, glaucoma, graft ulcer, and endophthalmitis from micro-defects or microperforation near the suture.

3.2.3.2.3. Refractive error and astigmatism

Similar to penetrating keratoplasty, postoperative myopic and astigmatic refractive errors remain the main reason for patient's dissatisfaction after lamellar keratoplasty. A wide range of postoperative refractive error from −13.0 D to +7.0 D is reported after lamellar keratoplasty [64, 65]. Topographic astigmatism of greater than 4 D has been reported in 16–34.4% of the patients [64, 65].

There are several options to treat astigmatism following lamellar keratoplasty that vary from optical correction using glasses or rigid gas-permeable contact lenses to surgical interventions including relaxing incisions, femtosecond laser arcuate keratotomy, wedge resection, photorefractive keratectomy, laser in situ keratomileusis, and toric phakic intraocular lens implantation [66]. Spectacles may be insufficient when a significant amount of astigmatic anisometropia is present, and rigid gas-permeable contact lenses may be an option only if they are well tolerated by the patient [66]. Astigmatic keratotomies can be precisely performed by using a femtosecond laser. However, this technology is not widely available, and its cost-effectiveness needs to be taken into account [66]. Excimer laser photoablation techniques are capable of treating coexisting spherical refractive error, but their efficacy is limited in the correction of high degrees of astigmatism. Manual relaxing incision, performed on the steep meridian, is widely used for high astigmatism after keratoplasty because it is a safe and simple procedure with no risk of postoperative haze and minor manipulation to the allograft. This technique, however, has some disadvantages including unpredictable results and risk of corneal perforation [66]. Corneal perforation can occur during manual relaxing incision because it is difficult to evaluate precisely the depth of the blade by conventional en face microscopy. Microperforations that present a slight leak without the development of a shallow anterior chamber usually self-seal and require no further interventions. A bandage contact lens and systemic carbonic anhydrase inhibitor can be used to manage such microperforations. If a shallow anterior chamber develops, however, the site of perforation should be sutured using 10-0 nylon suture material.

3.2.3.2.4. Graft immune rejection

Although lamellar keratoplasty eliminates the risk of endothelial rejection, other types of graft rejection (epithelial and stromal) may still develop with an incidence between 3 and 14.3% [67, 68]. Epithelial and stromal graft rejections after lamellar keratoplasty are very similar to those following penetrating keratoplasty and can be reversed by frequent topical steroid [68]. Epithelial and stromal graft rejections after lamellar keratoplasty must be treated appropriately to prevent less severe but still important complications including graft vascularization and suture abscess which can result in graft opacification and even failure [69]. Each episode

of graft rejection is treated with 0.1% topical betamethasone every 1–4 hours, based on the severity of rejection. The topical corticosteroid dose is gradually tapered over 2 weeks after resolution of the rejection episode [21].

3.2.3.2.5. Graft opacification and interface vascularization

Recurrence of opacification (scars and deposits) can occur at two sites: the graft itself and donor-recipient interface. Recurrence of opacification and deposits in the graft are frequent observations after keratoplasty in mustard gas-induced corneal involvements as a consequence of dry eye, limbal ischemia, limbal stem cell deficiency, and the presence of leaking vessels [57]. The advantage of lamellar keratoplasty is that it can be repeated with ease when recurrent graft opacity precludes useful vision or causes ocular irritation.

Donor-recipient interface opacification is a unique complication following conventional lamellar keratoplasty that develops due to recipient bed roughness, inadequate tissue removal, inadequate donor-recipient adhesion, or postoperative vascular invasion. Surface and suture complications may stimulate vascularization of the graft and interface. Extensive vascularization may result in lipid and protein extravasations leading to interface opacification (**Figure 7**) and hence visual acuity reduction. A full-thickness graft is still inevitable when deep stromal scar or visually significant interface opacity develops [58].

3.2.3.2.6. Interface keratitis

The interface left during lamellar keratoplasty is a potential dead space and microorganisms inoculated intraoperatively have a chance to proliferate within this space away from recipient immune response. Candida species is the most common microorganism obtained

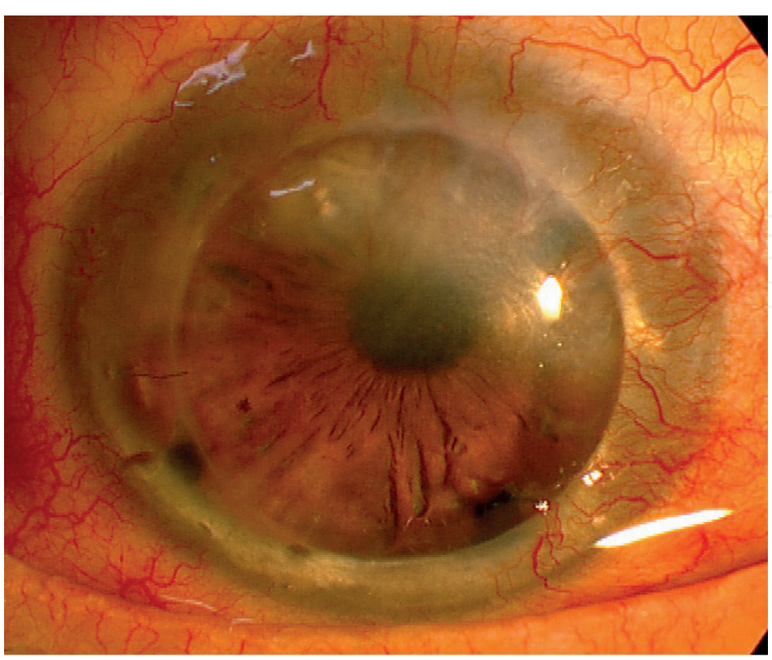

Figure 7. A lamellar corneal graft complicated with dense interface haziness and vascularization 4 years after transplantation in a mustard gas victim necessitating penetrating keratoplasty.

from interface keratitis [70]. Infection with this microorganism occurs because of donor corneal contamination or by the indigenous microflora of the conjunctiva and ocular adnexa. Recipient Descemet's membrane separates the site of infection from the intraocular structures after transplanting a contaminated donor cornea to the recipient bed. However, the location of infection may make it more difficult to obtain specimens for culture. Furthermore, it may prevent adequate penetration of topical, intraocular, and systemic antibiotics, making conservative treatment more likely to fail. Given that, both topical and systemic antibiotics should be prescribed, but penetrating keratoplasty may be needed to eradicate the infection [70].

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