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Superficial Keratectomy in a Standing Horse with Advanced Corneolimbal Squamous Cell Carcinoma

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Abstract : A 12-year-old gelding Warmblood Horse was presented with a corneolimbal mass in the right eye (OD) of 6 months duration. Clinical signs included ocular discomfort, persistent mucoid ocular discharge, and conjunctival hyperemia. The mass was excised by superficial keratectomy under sedation in a standing position, followed by a topical application of 0.04% mitomycin C (MMC), and a placement of a conjunctival advancement graft. The histopathological diagnosis was squamous cell carcinoma. One month after surgery, recurrence of the mass was suspected upon examination of the eye. Topical MMC and 5-fluorouracil followed by cryotherapy were applied as adjunctive therapies after debulking of the mass. The surgical site healed without complications and with a cosmetically acceptable result. No recurrence of the mass was noted four years following the second procedure.

Key Words **:** chemotherapy, equine, squamous cell carcinoma, standing surgery, superficial keratectomy.

Introduction

Squamous cell carcinoma (SCC) is the most common ocular neoplasm in the horse and is frequently associated with the cornea, corneolimbal junction, third eyelid and eyelids (7). Approximately 30% of ocular SCC originates from the corneolimbal region, most commonly from the temporal limbus.

A wide range of treatment modalities have been used for equine ocular SCC. The primary treatments are enucleation and superficial keratectomy (SK) with adjunctive therapies including cryotherapy, radiofrequency hyperthermia, radiation, laser ablation, or topical chemotherapy (15). Enucleation remains the most conclusive treatment for advanced SCC. However, combined SK and adjunctive therapies offers an alternative to enucleation, allowing preservation of the eye and vision. However, general anesthesia presents a greater risk for mortality, morbidity and complications in the horse compared to other animals (8). Horses receiving general anesthesia for ocular surgery are at a significantly greater risk for unsatisfactory recovery than horses anesthetized for other types of surgery (16). Since standing surgeries under sedation are safer and more economical than surgeries under general anesthesia. In this case report, we describe the long-term successful outcome of a superficial keratectomy combined with adjunctive therapies for an advanced corneolimbal SCC carried out in a standing sedated horse.

Case

A 12-year-old gelding Warmblood Horse was presented with a 6-month history of ocular discomfort, persistent mucoid ocular discharge, conjunctival hyperemia, and a red nodular mass on the cornea, limbus and bulbar conjunctiva OD.

Neuro-ophthalmic examinations including menace response, pupillary light reflex (PLR) and dazzle reflex were normal in both eyes. The horse was sedated with a combination of detomidine hydrochloride (0.01 mg/kg, IV; Dormosedan, Orion Pharma, Orion Corporation, Espoo, Finland) and butorphanol tartrate (0.05 mg/kg, IV; Butophan, Myungmoon pharm., Seoul, Korea). Auriculopalpebral and frontal nerve blocks were performed using 2 ml of 2% mepivacaine (Emcaine 2%, Reyon Pharm., Seoul, Korea) to facilitate ocular examination. Slit-lamp biomicroscopy (Keeler PSL one, Keeler instruments Inc, Broomall, PA, USA) revealed an irregularly rounded and diffusely raised red mass which was approximately a 0.5 mm in thickness and 3.5 cm in diameter with corneal edema and neovascularization around the edge of the mass. It appeared to originate from the temporal limbus and conjunctiva and extended onto the central cornea (Fig 1A). Ninety percent of the entire cornea was affected

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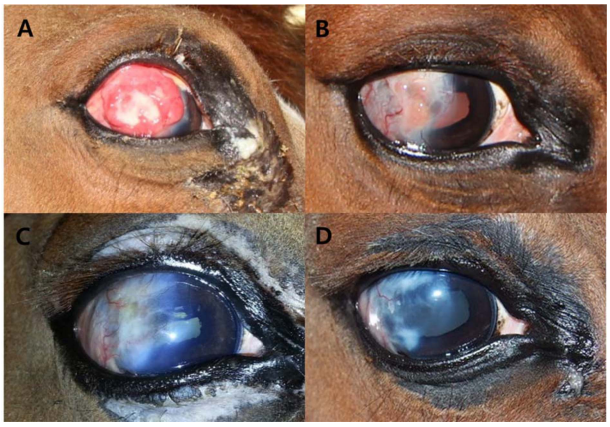

Fig 1. (A) Preoperative clinical photograph of a 12-year-old gelding Warmblood with a 0.5 mm thick and 3.5 cm in diameter large proliferative mass in lateral limbus and severe mucopurulent discharges around medial canthus. (B) Four-week postoperative appearance with a smooth, slightly raised, pink mass, indicating recurrence of SCC. (C) Four-month and three-month postoperative appearance after the first surgery and after the second procedure, respectively, showing mild granulation tissue surrounding with neovascularization and conjunctival graft. (D) One-year postoperative appearance after the first surgery showing only mild subepithelial fibrosis axially and corneal scar by conjunctival graft laterally.

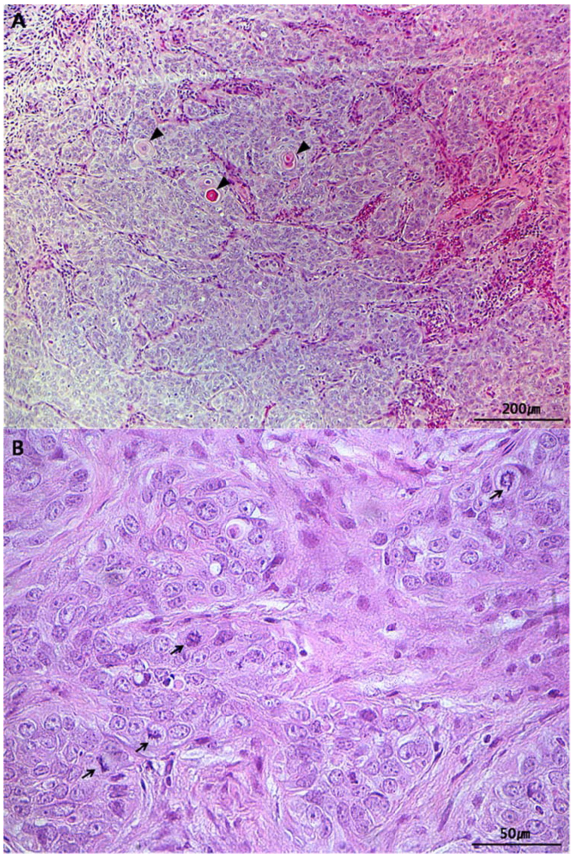

Fig 2. Histological features of the excised tissue. (A) Neoplastic basal cells were arranged in ribbon type or acinar type. Squamous differentiation and the formation of keratin pearls (arrowheads) were also observed in some part of the mass. Original magnification ×100, H&E. (B) Tumoral cells exhibited moderate degree of pleomorphism. Several mitotic figures (arrows) were observed in a high-power field. Original magnification ×400, H&E.

with the only clear window being nasally. There was severe mucopurulent discharge on the mass and conjunctiva, leading to remarkable black crust at the medial periocular area OD. Fluorescein stain was negative and the patency of the nasolacrimal system was confirmed by a positive Jone's test in both eyes. Intraocular pressures measured by a rebound tonometer (TonoVet, Tiolat, Helsinki, Finland) were 17 and 20 mmHg OD and OS, respectively. The presumptive diagnosis was SCC based on clinical appearance of the mass. Given the mass size, recent rapid progression, the degree of corneal invasion, potential recurrence, and potential complications of the surgery, vision loss was considered a potential sequelae following surgery. Therefore, enucleation was offered to minimize postoperative complications and to guarantee complete removal of the mass. Nevertheless, the owner elected to attempt to save the globe and vision through surgical removal of the mass under standing sedation rather than general anesthesia. Routine blood work (CBC and biochemistry profile) prior to surgery was unremarkable.

The horse was placed in stocks and the head was supported by head stands. Preoperative medications included flunixin meglumine (Banamine, Schering- Plough Animal Health, Union NJ, USA) 1.1 mg/kg, IV and procaine penicillin (Aquacillin, Anthony Products Production Co, Irwindale CA, USA) 20 000 U/kg, IM. The horse was sedated with a combination of detomidine hydrochloride (0.02 mg/kg, IV) and butorphanol (0.05 mg/kg, IV). One-third of initial volume of each agent was administrated 5 times based on the movement of the horse and duration of both agents until completion of the procedure. The auriculopalpebral and frontal nerves were blocked by injection of 0.3 ml of 2% mepivacaine to minimize eyelid movement and sensation of the upper eyelid. Topical 0.5% proparacaine hydrochloride (0.3 ml, Alcaine, Alcon Korea, Seoul, Korea) and 2.5% phenylephrine hydrochloride (0.3 ml, Mydfrin, Alcon Korea, Seoul, Korea), for corneal anesthesia and decrease hemorrhage, respectively, were applied onto the corneal surface and repeated every 15 min to maintain effect during surgery as needed.

The periocular area was clipped and aseptically disinfected using a 0.5% povidone iodine solution. The eye was draped for aseptic ocular surgery and an eyelid speculum was placed. Superficial keratectomy was performed in a standing position with 2.5X Heine HR-C Binocular Loupes (Heine USA, Dover, NH, USA). A curvilinear incision was made 2 mm around the margin of the corneal tumor with a microsurgical blade # 367 R (Aesculap AG & Co, Tuttlingen, Germany). The anterior corneal stroma with the tumor was lifted with a Martinez corneal dissector to the limbus, and was excised at the limbus using the tenotomy scissors. Corneal excisions were made to approximately one-half and one-fifth thickness at the limbus and in the center of cornea, respectively. The resected cornea and mass were fixed in 10% buffered formalin and submitted for routine histopathology

evaluation.

A 0.04% MMC (Mitomycin-C injection 10 mg, Kyowa Hakko Kirin Co., Ltd. Shizuoka, Japan) solution was applied to the surgical wound twice for 5 min at an interval of 1 min on the area of corneal defects using saturated cellulose sponges immediately after SK. A conjunctival hood graft was performed to protect one-third of the corneal defect using 7-0 absorbable suture (Polyglactin 910, Coated-Vicryl, Ethicon, NJ, USA) in a simple interrupted pattern. A subpalpebral lavage (SPL) system (Eye Lavage kit-Subpalpebral; Mila International, Inc., Erlanger, KY, USA) was placed through the upper eyelid.

Postoperative topical medications included (i) 1% atropine sulfate (Ocutropin, Samil Pharm., Seoul, Korea), q24h; (ii) autologous serum, q3h; (iii) 1% EDTA, q3h; (vi) gatifloxacin (Gatiflo, Taejoon Pharm., Seoul, Korea), q4h for 2 weeks through SPL. Systemic medication consisted of procaine (20 000 U/kg, IM) and flunixin meglumine (1.1 mg/kg, IV) q12h for 7 days. The latter was continued q24h for another 7 days to control the postoperative pain and uveitis. The diagnosis of squamous cell carcinoma was confirmed by histopathologic examination (Fig 2).

A 0.04% MMC was applied to the area uncovered by conjunctival graft 4 times a day for 2 weeks with same procedure mentioned above. At the 4-week recheck, a smooth, slightly raised pink mass was observed on the edge of the keratectomy site that was uncovered by conjunctival graft (Fig 1B). Adjuvant therapy using cryotherapy was settled on for the second procedure.

Sedation was achieved with detomidine hydrochloride (0.01 mg/kg, IV). Topical 0.5% proparacaine hydrochloride was administrated and repeatedly applied as needed. The mass was debrided thoroughly with a #15 sterile surgical blade until there was a clear corneal stroma. Cryotherapy was performed using a 3 mm tip probe of Histofreezer® (Solar-Care Technologies, Bethlehem, PA, USA). The freezing was stopped when the ice ball exceeded 3–5 mm beyond the visible tumor margins.

Since the size of tumor was larger than the probe of the instrument, multiple areas were frozen with an overlap of 2-3 mm and double freeze/thaw cycle with rapid freeze and slow thaw. Immediately after cryotherapy, a 0.04% MMC was applied as described above for intraoperative application for 5 min and the surgical wound was left to heal by second intention. The same postoperative topical medications as for the first procedures were administrated. The chemotherapy with 0.04% MMC and 1% 5-fluorouracil (5-FU) was topically applied 4 times a day on a weekly basis alternately for a total of 6 weeks to prevent a tumor recurrence.

The horse was reevaluated 4 months after the first surgery and 3 months after the second procedure (Fig 1C). The menace responses were normal and both PLR and dazzle reflexes were present. The eye remained comfortable and there was mild granulation tissue with neovascularization on the central cornea. The conjunctival graft on the temporal cornea was intact and well vascularized. Topical neomycin-polymyxin B- dexamethasone hydrochloride (Maxitrol eyedrop, Alcon Laboratories Inc., Fort Worth, Texas, USA, q8h) was added for 3 weeks to further suppress the granulation tissue and reduce corneal scar. After that, all medications were discontinued.

The horse was reexamined 1 year after the first surgery (Fig 1D). The owner reported that the horse returned to his work without any clinical problems nor tumor recurrence. The second surgical site remained epithelialized and had only mild subepithelial fibrosis, leading to improvement of the axial vision. The corneal scar by the conjunctival graft accounted for nearly 30% of the temporal cornea. The non-ulcerative blepharitis has completely healed. The owner was satisfied with the cosmetic outcome and visual function. There was no recurrence of the tumor in the following 3 years without any medications.

Discussion

This report described successful removal of advanced corneolimbal SCC in a standing horse by combined SK with adjunctive therapies including MMC, 5-FU, and cryotherapy.

Several factors should be considered to elect treatment of ocular SCC: tumor location, tumor size, extent of invasion, vision status, the horse's purpose, available equipment, and the owner's financial constraints (7). General anesthesia presents a greater risk for mortality, morbidity and complications in the horse compared to other animals (8). Therefore, appropriate facilities and expertise are required for general anesthesia, which in turn, leads to increased costs (20). The perianesthetic mortality rate from non-colic-related anesthetics in horses is 120 times higher and 10 times higher than that of humans and dogs, respectively. Moreover, general anesthesia may be associated with perianesthetic or recovery-related complications such as hemorrhage, extreme increases in heart rate or blood pressure, postanesthetic myopathy or neuropathy, trauma, breakdown of surgical incisions, or destruction of bandages or casts (20). Therefore, standing ocular surgery should be considered in the horse as a safe and cost-effective alternative to surgery under general anesthesia, especially for high-risk patients.

Recently, the primary procedure, SK, has been performed primarily on small sizes of ocular SCC in standing horses to decrease the expense and risk of general anesthesia. In addition, both chemical restraint and ocular nerve block have been reported to facilitate standing ocular surgery in horses (5). The advantages and success of ocular surgeries in the standing horse have been recently reported (12). The most important benefit for standing surgical procedures is to lower anesthesia-related complications described above. Other advantages include decreased hospitalization time and cost incurred as well as less need for surgical and anesthetic equipment and facilities. Therefore, many ocular procedures involving the adnexa, conjunctiva, and cornea, as well as enucleation, can be successfully executed in properly restrained and sedated standing horses for diagnostic and therapeutic purposes (5,17).

A good sedation is required for successful standing ocular surgery, in addition to periocular nerve block to reduce pain and induce eyelid akinesia. Drugs from the α_2-agonists class, such as xylazine, romifidine, and detomidine, are the most

commonly used sedative agent in horses due to their rapid onset and duration of action with a single bolus injection (12). Of the aforementioned drugs, it is well known that detomidine is the best sedative for ophthalmic procedures in the standing horse (5,6). The addition of an α_2-agonist drug such as dexmedetomidine or detomidine can enhance the duration of action of local anesthetics through vasoconstriction (12). Use of xylazine should be avoided because it can cause head movement and exaggerated response to stimuli (6).

The use of opioids, such as butorphanol, in horses is somewhat controversial for standing ocular surgery because of potential adverse effects, excitement, increased motor activity, restlessness, and shivering after a bolus injection when used alone (6,9,10). Abrupt head movement and startle response may remain even if α_2-agonists were used in conjunction with butorphanol. However, when used clinically, these complications are rare at lower analgesic doses (1). In addition, opioids have been used routinely to reduce the effective dose of α_2-agonists in horses in conjunction with analgesic purposes (2). Butorphanol was elected to be used in this case to reduce the severe pain associated with SK. The dense sensory innervation of the superficial cornea can produce severe pain, leading to induction of axonal reflex anterior uveitis. In addition, it is well recognized that adding opioid sedatives enhances the effects of acepromazine and α_2-adrenoceptor agonists without seriously compromising vital function (3). In the UK, detomidine combined with butorphanol are most commonly used for sedation by a simple bolus IV injection (19).

It is well known that medical therapy alone is usually ineffective in the treatment of corneal SCC (15). In general, combined surgical removal and some type of adjunctive therapy are considered as best effective therapy to lower recurrence rate (11). Therefore, intraoperative ß-irradiation, cryotherapy, radiofrequency hyperthermia, carbon dioxide (CO_2) photoablation, topical application of MMC, 5-FU, amniotic membrane transplantation, and permanent bulbar conjunctival graft have been recommended as adjunctive therapy (14). Therefore, conjunctival hood graft, MMC, 5-FU, and cryotherapy were carried out to alleviate the recurrence rate of SCC combined with SK in this report.

Recently, the effectiveness of MMC as an adjunctive therapy following surgical excision of ocular SCC was demonstrated in horses (4,13,18). The antineoplastic and antifibrotic efficacy of MMC led to a low recurrence rate of SCC and decline of scarring formation postoperatively, respectively. In addition, the MMC is cost effective and readily available with no need for specialized or expensive equipment. Horses receiving adjunctive topical MMC therapy were no more likely to experience tumor recurrence than horses that underwent CO_2 laser ablation (4). In addition, multiple treatments of MMC were reported to be a better option than a single intraoperative application of MMC to delay recurrence of SCC (18).

Conclusions

This case report describes the successful outcome of SK and various adjuvant therapies for the treatment of advanced corneolimbal SCC in a standing horse without intraoperative complications, with only mild corneal scarring long term, and no recurrence of the tumor over a 4-year follow-up period. A standing SK for SCC removal may minimize the risks and costs associated with general anesthesia in horses. Therefore, standing ocular surgery in the appropriately restrained and sedated horse could be an alternative to general anesthesia for the surgical removal of an extensive corneal tumor.

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