pISSN 1598-298X / eISSN 2384-0749
J Vet Clin 35(6) : 311-314 (2018)
http://dx.doi.org/10.17555/jvc.2018.12.35.6.311

Journal of Veterinary Clinics
www.ksvc.or.kr

Corneal Squamous Cell Carcinoma Presumed to Arise from Corneal Fibrosis in a Shih-Tzu Dog

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(Received: January 22, 2018 / Accepted: August 20, 2018)

Abstract : Squamous cell carcinoma (SCC) is a form of neoplasm that origins from the epithelial surface of many organs. Ocular occurrence in small animals is rare, especially in the central cornea without the involvement of limbus or conjunctiva. In the current case, a 10-year-old, spayed female Shih-Tzu was presented with a central corneal mass. Through an ophthalmic examination the sign of corneal scarring around the mass was found. Pink fleshy lesion that protruded outward was removed through superficial keratectomy. The mass with the size of 8.5 × 6.5 millimeter was histopathologically diagnosed as corneal SCC infiltrating not only the epithelium, but also the superficial corneal stroma with surrounding superficial lymphoplasmacytic and neutrophilic chronic keratitis. Also, the adjacent, non-affected corneal epithelium was markedly hyperplastic and keratinized; the adjacent stroma was moderately vascularized and fibrotic. The pulse-dose therapy using 1% topical 5-flourouracil were applied for five cycles. The tumor has not recurred through nine months of follow-up time.

Key words **:** 5-fluorouracil, corneal scarring, corneal squamous cell carcinoma, Shih-Tzu.

Introduction

Squamous cell carcinoma (SCC) is a form of neoplasm that origins from the epithelial surfaces of any organs. The most commonly affected site is skin (20). However, a rare form of ocular SCC also affects central cornea without the involvement of limbus or conjunctiva; such form of SCC has not been readily studied yet, only reported in less than thirty cases; but is increasing in number in recent years (9). The suggested predisposing factors of such tumor include the history of previous trauma, chronic irritants, and the prolonged use of topical immunosuppressants (9).

In the current case, a Shih-Tzu with the squamous cell carcinoma on the central cornea and the suspected history of previous corneal trauma would be presented. The exophytic and invasive corneal lesion was removed surgically, and medically managed consecutively with topical 5-flourouracil (5-FU).

Case

A ten-year-old spayed female Shih-Tzu was referred to Daegu Animal Medical Center for a prominent pink mass on the central cornea. The lesion was first noticed by the owner three months before the visit to the clinic, which increased in size since.

The thorough ophthalmic examination was performed. The result of Schirmer tear test-1 for both eyes (OU) was 21 mm/min. The intraocular pressure measured with a rebound tonometer (TonoVet®, Tiolat Ltd, Finland) was 19 mmHg for the right eye (OD) and 21 mmHg for the left eye (OS). The neuro-ophthalmic examination including direct and consensual pupillary light reflex, dazzle reflex, and menace response was normal in OU. Via slit lamp biomicroscopy, the exophytic mass and the focal increase in corneal opacity, indicating corneal fibrosis and edema, surrounding the mass were observed in OS (Fig 1A). The mass was oval with the size of 8.5 × 6.5 millimeter. The cornea was negative for fluorescein staining (Fig 1B). Other than the corneal lesion, there was no significant change except for a few geriatric changes such as iris atrophy and nuclear sclerosis.

For the removal and histopathologic assessment of the lesion, superficial keratectomy and temporary tarsorrhaphy were performed (Fig 2). Pre-anesthetic medication includes midazolam (Midacum®, 0.15 mg/kg, IV; Myungmoon Pharmaceutical Co., LTD, Korea), butorphanol (Butophan®, 0.15 mg/kg, IV; Myungmoon Pharmaceutical Co., LTD, Korea). Propofol (Provive™ 1%, IV; Claris Injectable Ltd., India) was used as an induction agent injected until the loss of consciousness and absence of reflexes. Then, under the general anesthesia with isoflurane inhalation, the surgical area was aseptically prepared using 0.2% povidone iodine solution. Using No. 6400 beaver blade (ACE Surgical Supply Co., Inc., US), the incision was made on the normal cornea 2 mm apart from the mass. With a corneal dissector, lamellar keratectomy was performed to remove the mass. However, because the neoplasm had invaded deep into stroma, it was impossible to remove the confirmed mass completely. The excised mass was fixed in 10% neutral buffered formalin and sent for the histopathological evaluation. Post-surgical management included topical antibiotics including levofloxacin

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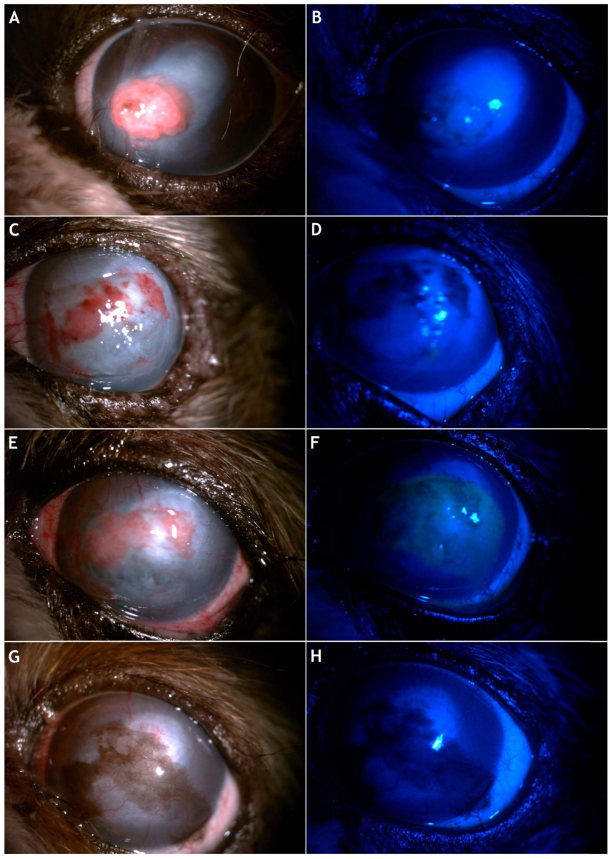

Fig 1. The gross examination of the patient's left eye. A and B shows the affected eye before the surgery. Two weeks after the superficial keratectomy, the epithelium fully healed, showing no sign of fluorescein staining (C and D). However, while using 5-FU as topical chemotherapy, the complications including increased discomfort, neo-vascularization of the cornea and conjunctival hyperemia had developed (E and F). G and H shows the comfortable eye after two weeks from the end of chemotherapy.

(Cravit®, q4h; Santen Pharmaceutical Co., LTD, Japan), tobramycin (Tobran®, q4h; YoungIl Pharmaceutical Co., LTD, Korea), and cyclopentolate (Ocucylo®, q12h; SamIl Pharmaceutical Co., LTD, Korea). For systemic medication, oral carprofen (Rimadyl®, 2.2 mg/kg, q12h; Zoetis, US), amoxicillin-clavulinic acid (Amo-Cla®, 12.5 mg/kg, q12h; GunIl Pharmaceutical Co., LTD, Korea), and doxycycline (Doxycycline Tab., 5 mg/kg, q12h; Young Poong Pharmaceutical Co., LTD, Korea) were prescribed for two weeks.

Histologically, there is a well-delineated and exophytic neoplastic mass infiltrating, replacing and expanding through the corneal epithelium and superficial corneal stroma (Fig 3A, 3B). Neoplastic cells have variably distinct cell borders with abundant amphophilic to eosinophilic cytoplasm and prominent intercellular bridges. Nuclei are irregularly round to oval with finely stippled chromatin and multiple distinct magenta nucleoli. There are four mitotic figures per high power field with occasional bizarre mitotic figures. There is moderate anisokaryosis and anisocytosis. Cords and islands often contain central, compact eosinophilic lamella of keratin, or keratin pearls (Fig 3D); there is frequent desmoplasia. Neoplastic cells extend into deep surgical margins. There is a marked neutrophilic and lymphoplasmacytic inflammatory infiltrate throughout the neoplastic mass (Fig 3C). The deep margin of the tissue sample included neoplastic cells. The adjacent corneal epithelium is markedly hyperplastic and keratinized. There is moderate vascularization and fibrosis of the adjacent corneal stroma. As a result, the lesion was proven to be squamous cell carcinoma with surrounding superficial lymphoplasmacytic and neutrophilic chronic keratitis.

Two weeks after the surgery, it was confirmed through the fluorescein staining that the corneal epithelium had healed completely (Fig 1C, 1D); thus, the topical chemotherapy was started. The commercial 5-FU (5-FU Inj., 250 mg; Choong Wae Pharmaceutical Co., LTD, Korea) was diluted with normal saline into the concentration of 1% as described in the previous literature (10). The regimen was to use the 1% 5-FU four times per day for seven consecutive days once a month for six cycles. The owner was instructed to use latex gloves when applying the compounded 5-FU solution. Along with the 5-FU, tobramycin was prescribed to be used twice a day-for the prophylactic purpose for possible infection. However, while the application of topical 5-FU, through the regular ophthalmic examination, the patchy fluorescein staining indicating the epithelial erosion of the cornea, increased discomfort, neo-vascularization of the cornea and conjunctival hyperemia of the treated eye was confirmed (Fig 1E, 1F). Thus, the dose of 5-FU was decreased to applying for four times per day for four consecutive days in a month from the third cycle. The owner had declined the sixth cycle, but no metastasis nor recurrence is seen thereafter for nine months (Fig 1G, 1H).

Discussion

Squamous cell carcinoma, a neoplasm that arises from any epithelial surface, most commonly affects skin, accounting

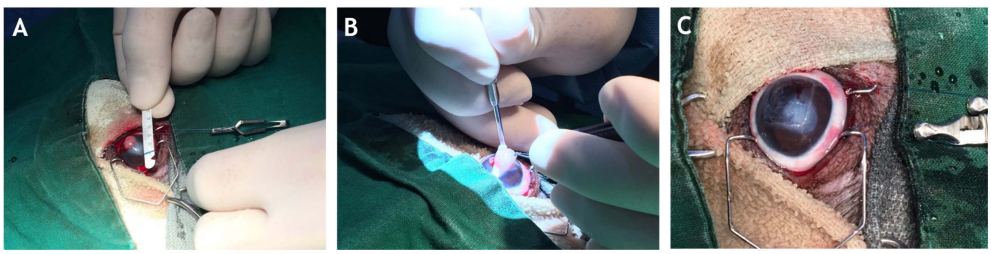

Fig 2. The picture of performing surgery on the patient. For the removal and histopathologic assessment of the lesion, the size of the lesion was first measured (A). Then, superficial keratectomy was performed (B). The C is the post-operative eye of the patient.

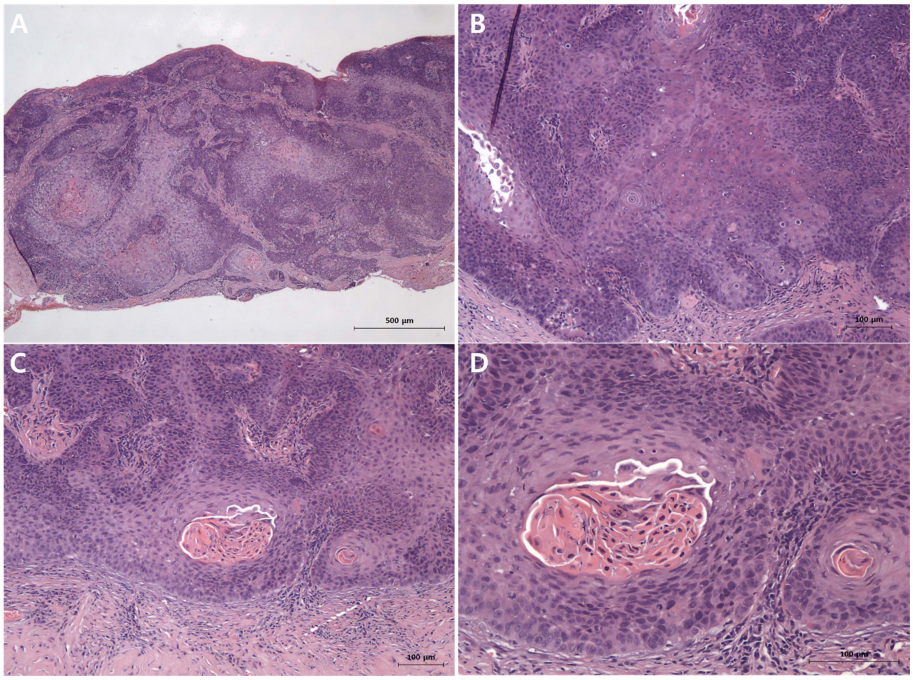

Fig 3. The histopathological examination of the mass in magnification of × 40 (A), × 100 (B), × 200 (C) and × 400 (D). The C and D shows the cords and islands containing central, compact eosinophilic lamella or keratin, or keratin pearls; also, the surrounding tissue shows the nests of tumor cells.

for 6.2% of nonhematologic cutaneous neoplasms of dogs (20), but this type of tumor can also appear on oral epithelium, mammary gland, ocular adnexa, and lung. The common sites of squamous cell carcinoma in relation to the eye are conjunctiva, eyelid and corneoconjunctival junction, or limbus, mostly affecting larger domestic animals. Since the occurrence of SCC in central cornea is so rare, the differential diagnosis should be carefully made. The list includes benign lesions such as hypereplastic keratitis, granuloma, and papilloma; also, other neoplasms such as angiokeratoma, mastocytoma, lymphosarcoma, amelanotic melanoma, and hemangioma or hemangiosarcoma (4).

Corneal squamous cell carcinoma appears to share the similar etiology, or risk factors, with the SCC of other origins. The previous researches have speculated that corneal SCCs would most likely to appear in brachycephalic breeds such as the pug and bulldog with chronically irritated cornea by keratoconjunctivitis sicca or abnormal hair growth, and thus, with the history of prolonged immunosuppressive therapy of cyclosporine (9). Also, the commonly discussed factor of SCC includes the chronic damage to the epithelial surface such as ultraviolet B radiation (13), a Marjolin's ulcer (6), a nonhealing scar tissue by various causes such as burn wound and pressure wound in humans (18). The previous research of corneal SCC (9) also had proposed the superficial trauma as the potential etiology. In this case, the pretumoral corneal dysplasia has been recognized during the ophthalmic examination as well as during the surgery and from histopathologic examination. The exact origin of the corneal scarring is unknown. However, the fact that the tumoral change arose on the site of pre-existing dysplasia can be meaningful ground to propose that the previous damage left as fibrosis or granuloma could also be a source of corneal SCC.

In dogs, there is a previous report that the monotherapy using 1% 5-FU ointment had successfully control the corneal SCC of a pug without a recurrence for up to 10 months after the cessation of the treatment (8). However, still the most indisputable treatment of a corneal surface neoplasm in dogs remains the surgical excision of grossly affected tissue with the adjunctive therapies to treat microscopic disease using various modalities such as radiation therapy, topical chemotherapy, and cryotherapy. In the current case, pulse-dosing 1% 5-FU was used as an adjuvant therapy following lamellar keratectomy. 5-FU is a pyrimidine analogue inhibiting both DNA and RNA synthesis of cells in the synthesis phase; thus, it has antifibroblastic and antineoplastic effects (15). Commonly in human medicine, 5-FU is utilized to reduce fibroblastic proliferation and subsequent scarring after ocular and periorbital surgeries including glaucoma drainage implantation, dacryocystorhinostomy and vitreoretinal surgery (1). As a topical chemotherapy agent, it is safe and inexpensive tool in reducing the recurrence of ocular surface neoplasia that had routinely adapted in human conjunctival SCC (16) and other intraepithelial tumors of ocular structures (21). It is commonly used in the pulse-dose regimen that is as effective, better tolerated, and has reduced adverse side effects. The frequently utilized regimen is administering the topical 1% 5-FU four times daily for the duration of four days with repeated cycles every 30 days for four to six cycles. The requirement for multiple treatment cycles may result from the differential susceptibility of tumor cells during their life cycle (21). However, in the current case, since the surgical margin was dirty with remaining neoplastic cells, the longer dosing period of 7 days with six planned cycles was imple-

mented based on the previous research (11) until the adverse side effects were confirmed after the second cycles. Even with the cessation of chemotherapy early in fifth cycle by the will of the owner, the mass has not recur for nine months of follow up.

In humans, although there are no randomized studies directly comparing topical chemotherapeutic agents for ocular surface neoplasms, there are a few reviews (17,19) comparing different agents including mitomycin C (MMC), interferon a2b (IFN-a2b), and 5-FU. Even though these agents have different mechanisms of antimetabolic action, the efficacy of these agents for the treatment of an ocular surface squamous neoplasia is similar (80-88%; 19). Thus, when choosing which agents to utilize along with the surgical resection depends mostly on the cost, how easily the agent can be utilized, and on the level of side effects. IFN-a2b reported to have the least side effects in humans when given topically; however, it is most expensive which limits its use in veterinary clinics. Even though MMC has been successfully utilized as the therapeutic regimen of a veterinary patient in the previous report (12), MMC has reported side effects of corneal epitheliopathy, conjunctivitis, and possibly punctal stenosis in human medicine (14). These side effects are similar to that caused by 5-FU such as eyelid erythema, conjunctival and corneal inflammation, corneal epithelial defects, and toxicity to the lacrimal drainage apparatus (2), but are reported in higher incidence (14). Also, the cost of the agent is not compatible compared to 5-FU (17,19). Therefore, 5-FU would be the preferred choice of chemotherapeutics for the veterinary patients.

When prescribing topical chemotherapy agents, such as 5-FU, it is necessary to educate owners on proper handling of the agents with possibly detrimental side effects. While handling the topical chemotherapy agents, gloves made of latex, nitrile rubber, neoprene rubber, or polyurethane should be worn for the agents are not permeable through these substances. Before and after administration, hands should be thoroughly washed. If any part of body is uneventfully exposed, skin should be thoroughly cleaned with soap and water; eyes with normal saline. When the agents are spilt on a surface, sodium hypochlorite solution known to deactivate these antimetabolite agents should be used to decontaminate the surface. If the handler is either pregnant or breast-feeding, the exposure to the topical chemotherapy agents is strictly contraindicated, and the handling should be delegated to other adult caretakers (3,5,14).

In conclusion, the primary corneal SCC that had been presumed to arise from the previous corneal fibrosis was treated without recurrence for nine months adapting superficial keratectomy and the modified pulse-dose regimen of 1% 5-FU.

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