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Adjunctive bevacizumab therapy in an equine corneal stromal invasive squamous cell carcinoma with a 53-months follow-up

Adjuvante Bevacizumab-Therapie eines equinen kornealen stromal-invasiven Plattenepithelkarzinoms mit einer Nachbeobachtungszeit von 53 Monaten

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ABSTRACT

A 17-year-old Appaloosa mare was referred for evaluation of presumed refractory keratitis of the left eye. Gross examination revealed ocular discomfort and corneal neovascularization with a nasal focal opacification affecting approximately 40 % of the corneal surface. On ophthalmic examination, extensive subepithelial to mid-stromal vascular branching accompanied by a homogeneous white, dense opacification, which affected up to 80 % of the total corneal thickness, were apparent. Signs of concurrent uveitis were absent. Deep-stromal lamellar keratectomy with a conjunctival pedicle graft was performed under general anesthesia. Histopathology confirmed a poorly differentiated corneal stromal invasive squamous cell carcinoma (SI-SCC) with neoplastic cell extension to the surgical margins. Postoperatively, 4 topical mitomycin C 0.04 % chemotherapy cycles combined with oral firocoxib therapy were initiated. Seven months after surgery, regrowth of the SI-SCC was clinically suspected. A total volume of 1 ml bevacizumab 2.5 % was administered in the standing sedated horse via 3 mid-stromal corneal injections. Four weeks later, intrastromal bevacizumab injections (ISBIs) were repeated, however, this time the solution was injected directly into the main corneal vessel branches. Seven weeks after the second ISBIs, the left eye was comfortable and significant remission of corneal vascularization and opacity was recognized. No recurrence has been noted for a follow-up period of more than 53 months.
Equine SI-SCC usually has a very poor prognosis for globe maintenance. To the authors' knowledge this is the first report of well-tolerated intrastromal antivascular endothelial growth factor adjunctive therapy with bevazicumab 2.5 % and SI-SCC resolution after a multimodal treatment approach.

ZUSAMMENFASSUNG

Das equine korneale stromal-invasive Plattenepithelkarzinom zeigt ein anderes klinisches Erscheinungsbild als klassische Plattenepithelkarzinome im Bereich der Nickhaut, der Augenlider, der Konjunktiva oder des Limbus. Eine 17-jährige Appa-

loosa Stute wurde aufgrund einer vermuteten, therapieresistenten Keratitis des linken Auges überwiesen. Bei der Distanzbetrachtung zeigten sich Blepharospasmus, korneale Neovaskularisation und eine, von nasal kommende, fokale Trübung, die ca. 40 % der Hornhautoberfläche einnahm. Die ophthalmologische Untersuchung ergab subepitheliale bis mid-stromale verzweigte korneale Gefäßeinsprossungen begleitet von einer dichten, homogen weißen Trübung, die ca. 80 % der Hornhautdicke einnahm. Uveitisanzeichen waren nicht vorhanden. In Allgemeinanästhesie wurde eine tief-stromale lamelläre Keratektomie mit gestieltem Bindehauttransplantat durchgeführt. Histopathologisch wurde ein wenig differenziertes korneales stromal-invasives Plattenepithelkarzinom mit Tumorzellen im Bereich der Schnittränder diagnostiziert. Postoperativ erfolgten 4 Behandlungszyklen mit topischer Mitomycin C 0,04 %-Chemotherapie kombiniert mit oraler Firocoxib-Therapie. Sieben Monate nach der Operation traten klinische Rezidivanzeichen auf. Beim stehend-sedierten Pferd wurden 3 mid-stromale Bevacizumab 2,5 %-Injektionen mit einem Gesamtvolumen von 1 ml durchgeführt. Vier Wochen danach wurde diese adjuvante Behandlung wiederholt, wobei das Bevacizumab direkt in die kornealen Hauptgefäßäste injiziert wurde.
Sieben Wochen nach den zweiten Bevacizumab-Injektionen war das linke Auge komfortabel und eine signifikante Remission der kornealen Vaskularisation und Trübung erkennbar. Während der Nachbeobachtungszeit von über 53 Monaten wurde kein erneutes Tumorwachstum festgestellt.
Dies ist die erste Beschreibung eines equinen kornealen stromal-invasiven Plattenepithelkarzinoms nach erfolgreicher multimodaler Therapie einschließlich adjuvanter Bevacizumab 2,5 %-Injektionen ohne unerwünschte Wirkungen. Diese Neoplasie ist üblicherweise mit einer ungünstigen oder infausten Prognose für den Erhalt des Auges verbunden.

Introduction

Squamous cell carcinoma (SCC) is the second most common neoplasia in horses and the most common tumor of the equine eye and periocular structures. It typically develops at the nictitating membrane, eyelids, conjunctiva, and limbus [1]. Progressive transition from benign to malignant stages is characteristic in cattle and in horses [2]. Corneal stromal invasive squamous cell carcinoma (SI-SCC) shows an intrastromal growth pattern and can clinically be mistaken as chronic keratitis [3]. Consequently, late recognition and delayed initiation of targeted therapy occurs.

Treatment approaches consist of surgical and adjunctive therapies planned individually for each case. Deprivation of the tumor's vascularization is described for different forms of primary cancer and metastases. The antivascular endothelial growth factor (anti-VEGF) bevacizumab is a humanized monoclonal anti-VEGF antibody with FDA-approval for colorectal cancer. Off-label applications in human ophthalmology are primary or recurrent ocular surface squamous neoplasia, anterior segment neovascular disorders, neovascular glaucoma, age-related choroidal neovascularization, and diabetic retinopathy [4–7]. Ranibizumab is another anti-VEGF beneficial to treat conjunctival SCC with or without corneal extension [8, 9].

Recently, Muellerleile et al. [10] showed variable reduction of persistent corneal vascularization after topical bevacizumab 0.25 % treatment in dogs. Edelmann et al. [11] hypothesized life-long resolution of a sebaceous cell carcinoma in a tiger due to surgical excision combined with intralesional injection of bevacizumab 10 mg. To the authors' knowledge no peer-reviewed literature describing intracorneal bevacizumab 2.5 % administration in horses is available. This case report provides the first observation of equine SI-SCC resolution following multiple treatment approaches including anti-VEGF adjunctive therapy.

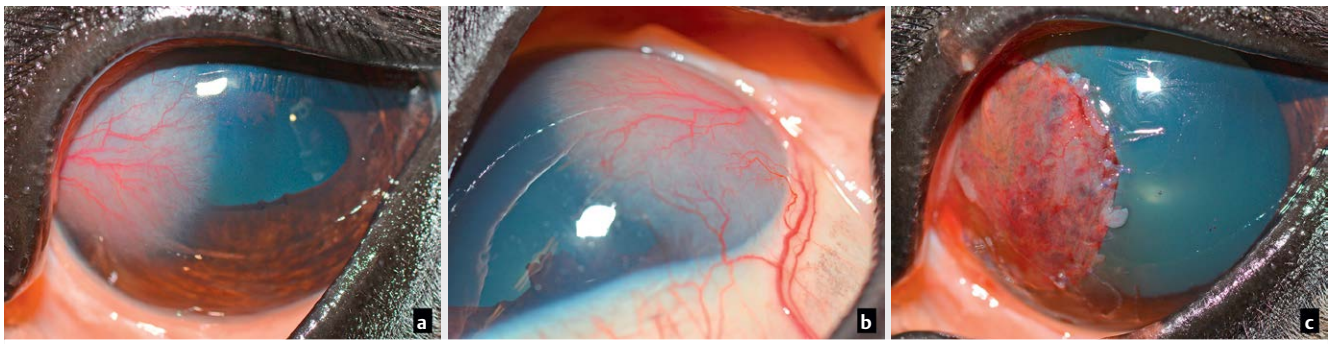
Case description

History and initial examination

A 17-year-old Appaloosa mare with progressively painful presumed keratitis, resistent to topical anti-inflammatory and anti-viral therapy, was referred to the ophthalmology service of the University of Veterinary Medicine Vienna. Distant examination showed mild seromucous discharge, moderate blepharospasm and enophthalmus as well as mild conjunctival hyperemia and chemosis of the left eye. Approximately 40 % of the corneal surface were affected by extensively branching neovascularization and a dense white opacification without signs of concurrent anterior uveitis. Neuro-ophthalmic testing, including palpebral reflex, menace response, dazzle-, direct- and indirect pupillary light reflexes, was within normal limits. Slit-lamp biomicroscopy (Kowa SL-17; Kowa Company Ltd, Tokyo, Japan) after blowpipe sedation, because approaching the horse otherwise was impossible, using 20 µg/kg intramuscular detomidine hydrochloride (Equidor; Richter Pharma, Wels, Austria) revealed an intact corneal epithelium, but extensively arborized vascular branching throughout the subepithelial to mid- stromal cornea accompanied by a mid- and deep-stromal homogeneous white, dense opacification (▶ **Fig. 1a, b**). Photographs were taken with a color camera (Nikon 7100; Nikon Corporation, Tokyo, Japan). Depth of the corneal abnormalities was estimated 80 % of its full-thickness although transillumination to the endothelial level was only possible in the unaffected area. Bilateral nuclear sclerosis and sparse chorioretinal scars were insignificant additional findings.

Surgical treatment and histopathology

A complete incision technique, deep-stromal lamellar keratectomy was performed by the first author (KOB) and depth of the corneal defect necessitated a conjunctival pedicle graft (CPG). General anesthesia was required since the horse had become uncooperative and extremely sensitive to manipulation of the head due to chronic ocular pain. After completion of the keratectomy and the

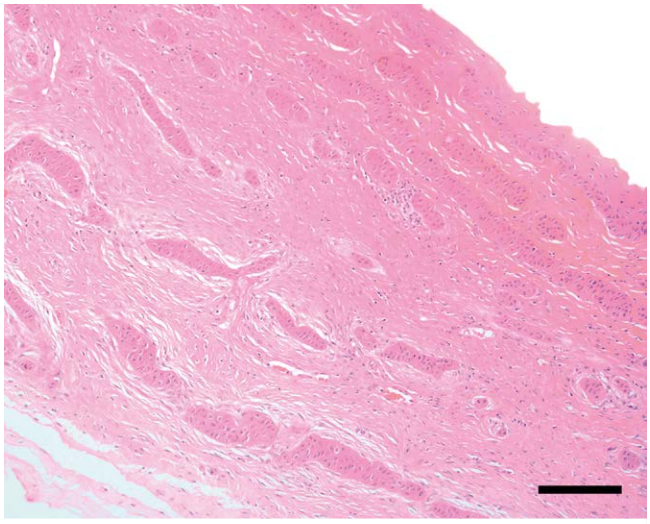


▶ **Fig. 1 a, b** Initial presentation of the cornea with extensively branching subepithelial to mid-stromal vascularization and deep-stromal homogenous, white opacification. **c** Three days after deep-stromal keratectomy and CPG placement. Source: K.-O. Blohm, Vetmeduni Vienna.

▶ **Abb. 1 a, b** Initiales Erscheinungsbild der Hornhaut mit hochgradig verzweigter subepithelialer bis mid-stromaler Gefäßeinsprossung und tief-stromaler homogener, weißer Trübung. **c** Zustand 3 Tage nach tief-stromaler Keratektomie und Bindehauttransplantat. Quelle: K.-O. Blohm, Vetmeduni Vienna.

CPG, a dorsal subpalpebral lavage (SPL) catheter (MILA International Inc., Florence, Kentucky/USA) and a lateral partial temporary tarsorrhaphy were placed. Postoperatively, ofloxacin q6h (Floxal; Bausch and Lomb GmbH, Berlin, Germany), atropine hydrochloride 1 % q24h (compounded on-site) eye drops via SPL and flunixin meglumine 1.1 mg/kg q24h (Niglumine; Henry Schein Animal Health, Vienna, Austria) via intravenous catheter (MILA International Inc., Florence, Kentucky/USA) were administered. Three days after surgery the CPG graft was vital and in situ, temporary tarsorrhaphy was removed and atropine was discontinued due to profound pupil dilation (▶ **Fig. 1c**). Considering financial constraints, the mare was discharged 5 days postoperatively with the SPL left in place.

Histopathologic evaluation of the corneal sample showed disseminated nests and bands of highly proliferative epithelial cells throughout the entire stroma (▶ **Fig. 2**). The hyperchromatic cell nuclei revealed parachromatic clearing, moderate anisokaryosis, loss of polarity and 10 mitotic figures per 10, 400x high-power fields. Demarcation of neoplastic epithelial islands consisted of fiber-rich tissue, neutrophils, and lymphocytes. Neoplastic cells extended to the surgical margins in all reviewed planes. A high density of microvessels and intrastromal bleedings were present. Histopathologic diagnosis confirmed a poorly differentiated SI-SCC with mild purulent keratitis.



▶ **Fig. 2** Microphotography of invasively disseminated nests and bands of proliferative epithelial cells throughout the entire corneal stroma (hematoxylin eosin staining, 10x magnification, bar = 160 µm). Quelle: A. Fuchs-Baumgartinger, Vetmeduni Vienna.

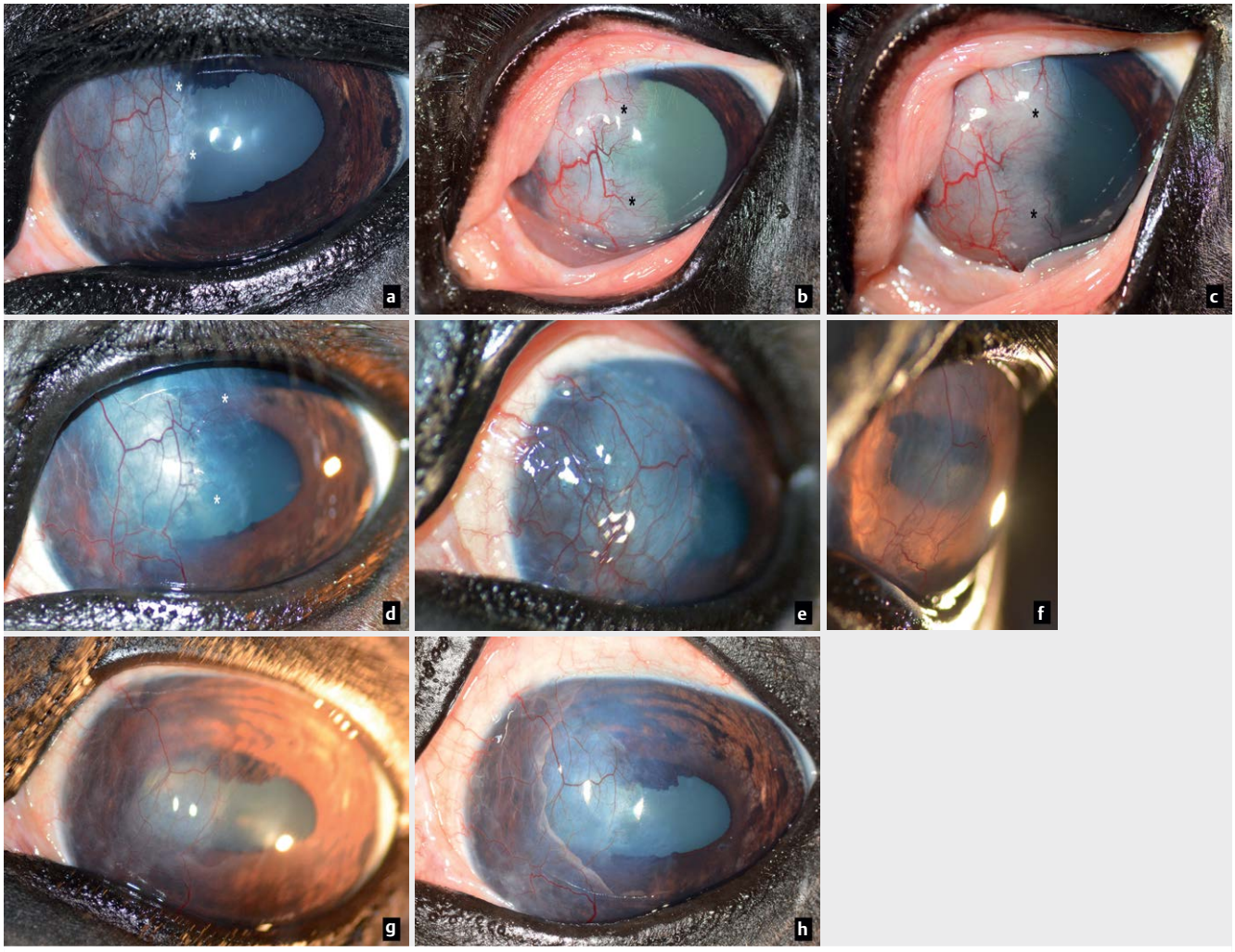
▶ **Abb. 2** Mikrofotografie invasiv disseminierter nestförmiger bis bandartiger proliferierender Epithelzellen im gesamten Hornhautstroma (Hämatoxylin-Eosin-Färbung, 10x Vergrößerung, Balken = 160 µm). Source: A. Fuchs-Baumgartinger, Vetmeduni Vienna.

Adjunctive mitomycin C and non-steroidal therapy

Since incomplete excision of the SI-SCC was confirmed by histopathology, adjunctive mitomycin C 0.04 % q6h (Mitomycin medac 2 mg; medac GmbH, Wedel, Germany) via SPL was initiated 14 days postoperatively. Four chemotherapy cycles of 1 week with 1 week off in-between were accompanied by firocoxib orally 0.2 mg/kg q24h for 2 days and 0.1 mg/kg q24h for 5 days (Equioxx 57 mg; Boehringer Ingelheim, Ingelheim, Germany).

Follow-up examinations

Three weeks after surgery the CPG was integrated with bridging vascularization. Mild postoperative corneal edema resolved completely but moderate paraxial anterior-stromal cellular infiltrate (ASCI) was recognizable. After 9 weeks, the fourth mitomycin C/firocoxib cycle was completed. The left eye was comfortable with positive menace response from medial and lateral, ASCI resolved completely as assessed by slit-lamp examination (▶ **Fig. 3a**). Treatment was discontinued and the still patent SPL was removed. Although the next recheck was scheduled after 3 months, the horse presented 5 months following the previous examination (7 months postoperatively) with intermittent pain of the left eye since 4 weeks. Ophthalmic examination revealed moderate seromucous discharge and blepharospasm as well as progression of extensively branching corneal neovascularization with adjacent moderate dense opacifications beyond the CPG border (▶ **Fig. 3b**). Accord-



▶ **Fig. 3** **a** Nine weeks postoperatively the CPG leading edge (asterisks) was without abnormalities. **b** Seven months after surgery SI-SCC recurrence was assumed due to corneal neovascularization and opacifications proliferating beyond the CPG leading edge (asterisks). **c** One month after the first ISBIs, suspected SI-SCC regrowth progressed (asterisks). **d** Seven weeks after the second ISBIs, corneal vascularization and opacifications reduced significantly (asterisks). **e** Four months after the second ISBIs no signs of SI-SCC recurrence were visible. **f** Nine months after the second ISBIs the CPG became semitransparent (transilluminated). **g** Eight months and 1 week after the second ISBIs the vascular caliber was thin and no proliferative corneal abnormalities were noticed. **h** Forty-five months postoperatively and 37 months after the second ISBIs only the established CPG vascularization without signs of SI-SCC regrowth were apparent. Source: a-c K.-O. Blohm, Vetmeduni Vienna; d-h V. M. Herb, Vetmeduni Vienna.

▶ **Abb. 3** **a** Neun Wochen postoperativ zeigte der axiale Rand (Sterne) des Bindehauttransplantates keine Abnormalitäten. **b** Sieben Monate postoperativ wurde aufgrund der über den Rand des Bindehauttransplantates hinausgehenden kornealen Neovaskularisation und Trübungen (Sterne) ein Tumorrezidiv angenommen. **c** Einen Monat nach den ersten Bevacizumab-Injektionen zeigte sich eine Progression des vermuteten Tumorwachstums (Sterne). **d** Sieben Wochen nach den zweiten Bevacizumab-Injektionen (n. d. z. B.-I.) waren eine signifikante korneale Gefäßreduktion und Aufklarung der Trübungen sichtbar (Sterne). **e** Vier Monate n. d. z. B.-I. waren keine Rezidivanzeichen sichtbar. **f** Neun Monate n. d. z. B.-I. wurde das Bindehauttransplantat semitransparent (transilluminiert). **g** Acht Monate und 1 Woche n. d. z. B.-I. waren ein dünnes Gefäßkaliber und keine kornealen Proliferationen erkennbar. **h** Fünfundvierzig Monate postoperativ und 37 Monate n. d. z. B.-I. waren nur die etablierten Blutgefäße des Bindehauttransplantats ohne Rezidivanzeichen sichtbar. Quelle: a-c K.-O. Blohm, Vetmeduni Vienna; d-h V. M. Herb, Vetmeduni Vienna.

ing to this combination of clinical findings, regrowth of SI-SCC originating from the surgical site was suspected.

Adjunctive bevacizumab injections

Due to non-affordability of a second surgery and assumed tumor recurrence after chemotherapy, the first author (KOB) suggested experimental intrastromal bevacizumab injections (ISBIs). Two weeks later, the owner provided written consent for adjunctive bevacizumab treatment.

The mare was sedated by blowpipe as described previously and an intravenous catheter was placed. Preparation of the left eye included palpebral and frontal as well as retrobulbar nerve block by mepivacain 2 % (Mepinaest; Gebro Pharma GmbH, Fieberbrunn, Austria) and topical anesthesia by oxybuprocaine hydrochloride 0.4 % (Novain; Agepha Pharma, Senec, Slovakia). A total volume of

1 ml bevacizumab 2.5 % (Avastin; Roche, Basel, Switzerland) was drawn up in 3 (aliqots of 0.33 ml) 1-ml syringes with attached 30-gauge needle (B. Braun, Melsungen, Germany) under sterile conditions. Following ocular surface irrigation with dilute iodine 1 % and balanced saline solution, 3 mid-stromal injections were performed by the first author (KOB) under 10x slit-lamp magnification. The needle was inserted 2 millimeters temporally to the suspected SI-SCC regrowth, as parallel as possible to the corneal surface, and advanced underneath the margin of the original CPG to the nasal limbus. Each 0.33 ml volume was injected slowly along the mid-stromal lamellar planes. When no further flat extension was observed, the needle was withdrawn to create a new overlapping injection until the entire abnormal stroma was infiltrated. A rice grain-sized superficial corneal biopsy was harvested. Topical chloramphenicol (Chloramphenicol; Agepha Pharma, Senec, Slovakia) and clotrimazole 1 % (compounded on-site) ointments q8h and oral firocoxib (as previously described) were prescribed for 10 days. Histopathologic evaluation was limited due to crushing artifacts and features of the epithelial cell clusters were equivocal hence definite confirmation of SI-SCC regrowth was not possible.

Four weeks later, ocular discomfort had improved only temporarily, and corneal abnormalities progressed (▶ **Fig. 3c**). The owner agreed to repeat ISBIs which were performed similarly, however, the first author (KOB) specifically aimed to insert the needle into the main corneal vessel branches to mechanically damage the vascular walls and to enhance bevacizumab penetration.

Extended follow-up examinations

Seven weeks after the second ISBIs the left eye was comfortable and significant remission of corneal neovascularization and opacifications was recognized (▶ **Fig. 3d**). Afterwards the mare competed in show-jumping without complaints and was assessed in 4 post-treatment examinations. No ophthalmic findings of tumor regrowth occurred (▶ **Fig. 3e-h**) over 61 months since corneal surgery and 53 months after the second ISBIs. Due to this favorable outcome no other measures than attentive monitoring were required until the time of publication.

Discussion

The described multimodal therapy including adjunctive ISBIs was effective treating an equine SI-SCC which usually carries a grave prognosis for globe maintenance. Images showing the clinical appearance of invasive SCCs have been published [2, 3]. However, the current case was misdiagnosed as stromal keratitis. In the authors' experience, primary keratitis may be distinguished clinically from SI-SCC by its heterogenous cellular infiltrates, corneal discoloration and edema as well as a less dense vascular branching pattern. Nevertheless, any suspicion of SI-SCC must be confirmed histopathologically.

Chronic inflammatory conditions in canine and equine ophthalmology are often symptomatically (glucocorticosteroids, non-steroidal anti-inflammatories, calcineurin-inhibitors) managed. To achieve the treatment goal of an avascular, immune-privileged cornea, neovascularization can be addressed by a targeted anti-VEGF therapy. While previous publications investigated anti-VEGF-A in human oncology, reports in veterinary literature are sparse [10–12].

In-vitro sequence homology of canine, feline, equine VEGF to human VEGF-A was 93 %, 92 %, 89 %, respectively, but binding property results indicated lack of bevacizumab immunoreactivity with equine VEGF [13]. In contrast, Lessiak et al. [14] currently showed a significantly decreased VEGF expression in equine umbilical vein endothelial cells exposed to bevacizumab concentrations of 1, 2, 4, 6, and 8 mg/ml. Furthermore, no cytotoxic effect of bevacizumab on endothelial cells was observed at concentrations of 4 mg/ml or lower [14].

Therefore, bevacizumab administrations in equine adnexal, corneolimbal, and stromal-invasive neoplasia could be a promising field of prospective, clinical research. Considering the 89 % homology of equine and human VEGF amino acids, under in-vivo conditions not only direct binding, but non-specific interactions with epitopes and secondary or tertiary protein structures are conceivable. According to most recent in-vitro results, bevacizumab inhibited equine umbilical vein endothelial cell migration and delayed their tube formation [14]. Previous non-peer-reviewed conference abstracts claimed therapeutic efficacy in horses with keratitis after subconjunctival and/or intracorneal bevacizumab injection [15, 16].

Topical bevacizumab 0.25 % q12h in one eye over 28 days was a safe treatment in healthy beagles [17] and adverse effects appeared unlikely in diseased dogs [10]. In the present case, only subconjunctival [18] or intrastromal applications were considered effective since the corneal epithelium was intact. Subconjunctival injection was deemed less promising due to the axial localization of suspected SI-SCC regrowth. Several therapeutic options were discussed but due to financial constraints another surgery, plesiotherapy, brachytherapy or photodynamic therapy were impossible. The first author (KOB) made the owner aware of unknown safety and potential devastating complications of high concentrated ISBIs. The rationale using bevacizumab 2.5 %, instead of the topically applied 0.25 % in dogs [10, 17], was extrapolated from intrastromal voriconazole injections in equine fungal abscesses [19]. In the present patient, a tenfold higher dose in the injection volume of 1 ml potentially counterbalanced the suspected lack of specific bevacizumab binding [13] to equine VEGF. Furthermore, bevacizumab is a larger molecule than the less affordable aflibercept which might be a disadvantage accessing binding sites. It was tried to address this assumed drawback by a higher bevazicumab concentration.

The results of Edelmann et al. [11] and the favorable outcome reported in our case support that intralesional bevacizumab injections may be an effective adjunctive treatment in adnexal and ocular carcinomas, respectively. Nevertheless, conclusions remain speculative based on these two descriptions and need to be verified by randomized, controlled clinical studies. In the present patient SI-SCC recurrence is likely given the location and temporal association with the previous surgery and histopathologic confirmation of tumor cell extension to the margins of the sample submitted following deep-stromal lamellar keratectomy. To avoid complications of a major corneal ulceration only a tiny corneal sample was excised when the first ISBIs were performed. This finally led to a remaining limitation of this report because histopathologic findings of the corneal biopsy were equivocal. Due to this the therapeutic contribute of ISBIs must be interpreted with caution, however, during the progressive multimodal treatment approach significant and

long-term improvement occured following the second ISBIs which is comprehensively documented by photographs. The extent of tumor progression was not measured by an imaging software but the main vessel T-branching adjacent to the CPG leading edge served as landmark to clinically appreciate extension. Optical coherence tomography was not available but might be an additional future monitoring modality.

In a study of equine corneolimbal SCCs 40 % recurred within the first 3 months after combined keratectomy, strontium-90 irradiation and bulbar conjunctival graft whereas the majority of that study population showed regrowth at a later time [20]. This corresponds with assumed recurrence after approximately 7 months in our patient. The paramount importance of regular, long-term re-examinations in SCC and SI-SCC cannot be overemphasized. Although the owner of the present case was a human nurse capable of chemotherapy via SPL after discharge from the hospital, her compliance for rechecks well after the first 3 months was limited. Lack of improvement before ISBIs reflects the first author's (KOB) experience of reduced mitomycin C efficacy in SI-SCC compared to corneolimbal SCC.

Corneal injections are less expensive than surgical interventions. Strontium-90 irradiation must be available and authorized while mitomycin C handling requires significant safety precautions. Both treatments entail the risk of scleral and/or corneal malacia with globe perforation. The treatment success following the second ISBIs might be associated with intended direct needle damage to the established main vessels combined with suppression of further neovascularization by bevacizumab. Additionally, post-injectional corneal edema may have caused mechanical compression of the microvessels.

Sixty-one months postoperatively and 53 months after the second ISBIs, improvement of corneal transparency and remission of vascularization without adverse findings has been documented. The patient is scheduled for yearly ophthalmic re-evaluations because despite this favorable long-term outcome tumor recurrence cannot be excluded.

In conclusion, this is the first description of ISBIs as an adjunctive treatment in equine SI-SCC. To emphasize the difficulty of objective interpretation of multimodal therapy, further research is warranted to investigate intralesional bevacizumab as primary approach to reduce tumor surface and/or depth. Finally, the effectiveness of subconjunctival and intrastromal bevacizumab should be compared to postoperative strontium-90 plesiotherapy or topical mitomycin C and treatment protocols following surgical excision of SCC at different locations need to be implemented.

CONCLUSION FOR PRACTICE

In case of therapy-resistant corneal neovascularization with opacification, the rare stromal invasive squamous cell carcinoma in horses must be considered. Adjunctive intracorneal bevacizumab 2.5 % injections were well-tolerated and appeared beneficial. Further studies of this potentially radiation-sparing and/or chemotherapy-sparing targeted treatment option are necessary.

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Additional information

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This case was seen during the first author's residency in comparative ophthalmology at the University of Veterinary Medicine Vienna.

Conflict of interest

The authors did not receive any commercial company funding and have no conflicts of interest. Open Access fee was paid by the University of Veterinary Medicine Vienna.

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