

CASE REPORT

Primary lacrimal gland adenocarcinoma of the third eyelid in a horse

Rachel L. Mathes,* Karen Paige Carmichael,† John Peroni‡ and Phillip Anthony Moore*

*Department of Small Animal Medicine and Surgery, College of Veterinary Medicine, University of Georgia, Athens, GA 30602, USA; †Department of Pathology, College of Veterinary Medicine, University of Georgia, Athens, GA 30602, USA; and ‡Department of Large Animal Medicine and Surgery, College of Veterinary Medicine, University of Georgia, Athens, GA 30602, USA

Address communications to:

R. L. Mathes

Tel.: (706) 206-7948

Fax: (706) 542-6460

e-mail: rmathes@uga.edu

Abstract

A 5-year-old Draft Horse gelding presented for evaluation of a large, fleshy, ulcerated third eyelid mass OD of 3 weeks duration. Complete ophthalmic examination, ocular ultrasound and skull radiographs revealed a large soft-tissue mass involving the entire third eyelid OD and extending into the ventral right orbit to the level of the globe equator. No other abnormalities were noted on physical or ophthalmic examination. Surgical removal via exenteration was performed 3 months after initial presentation. A lacrimal adenocarcinoma of the third eyelid was diagnosed based on histopathology. Concurrent asymptomatic intra-ductal and intra-acinar *Demodex caballi* parasites were found in the eyelid sebaceous glands, likely as an incidental finding. No tumor recurrence or metastasis has occurred 12 months after excision. To the author's knowledge, this case is the first reported primary lacrimal adenocarcinoma in a horse. Complete surgical excision was curative.

Key Words: adnexa, demodex, equine ophthalmology, exenteration, lacrimal adenocarcinoma, third eyelid neoplasia

INTRODUCTION

Primary neoplasia of the third eyelid, or nictitans membrane, in horses is well described with the most common tumor being squamous cell carcinoma.^{1–3} These tumors are epithelial in origin and are thought to be primarily UV-mediated tumors.^{4–6} Other tumors that reportedly may affect the third eyelid in horses include lymphangioma,⁷ lymphangiosarcoma,⁸ papilloma,^{3,9} hemangiosarcoma,^{2,10} basal cell tumor,¹¹ solid carcinoma¹² and sebaceous adenocarcinoma.¹³ Conjunctival pseudotumors have been described arising from the third eyelid, however, these lesions are proliferative inflammatory masses and do not represent true neoplasia.¹⁴

In dogs and cats, primary adenocarcinoma of the gland of the third eyelid has been described.^{15,16} Primary third eyelid tumors in dogs and cats are rare.^{15,16} This tumor is locally invasive and local recurrence is high with surgical excision.^{15,16} Reportedly, complete excision of the third eyelid is the treatment of choice for canine adenocarcinomas arising in this location.¹⁶ The solitary feline case report described diffuse metastasis and a survival of 4 weeks

after initial presentation.¹⁵ The tissue of origin is the large lacrimal gland of the third eyelid located at the base of the third eyelid cartilage. Adenomas of the accessory lacrimal gland, located in the dorsal orbit, have been reported in dogs.¹⁷

Demodex spp. are intrafollicular mites that are found on humans¹⁸ and many species of animals including dogs,¹⁹ ruminants,^{20–25} cats,²⁶ sea lions,²⁷ bears,²⁸ hamsters,²⁹ ferrets,³⁰ voles,³¹ mice³¹ and many others. These mites are species specific and may be found in the nonpathologic state or may be causative in certain types of skin disease. Blepharitis caused by *Demodex* spp. has been reported in humans.³² A case of palpebral demodicosis has been described in cattle³³ and these mites have been found in cattle sebaceous glands.³⁴ In horses, *Demodex* spp. are divided into *Demodex equi*, a species found in the hair follicles, and *Demodex caballi*, found in the sebaceous glands.³⁵ Although there are anatomic differences in these species, the location in which they are found is distinctive, allowing differentiation between these *Demodex* spp.³⁵ *Demodex caballi* are found as an uncommon incidental finding in horses, not reported to cause blepharitis.³⁵

The case report herein describes a primary adenocarcinoma of the lacrimal gland of the third eyelid in a horse treated with surgical excision. Concurrent asymptomatic sebaceous gland *Demodex equi* was found on histopathology and is discussed. To the author's knowledge, this is the first report of a primary lacrimal adenocarcinoma of the third eyelid in a horse diagnosed histologically. This tumor was successfully treated surgically and was locally expansive without distant metastasis.

CASE REPORT

History, physical examination, initial ophthalmic examination and diagnostics

A 5-year-old Grade Draft Horse gelding presented to the University of Georgia Veterinary Teaching Hospital for evaluation of a mass on the right third eyelid with a duration of approximately 3 weeks. The mass had progressed in size rapidly during this time and the horse was not on any prior medications. The horse was on pasture and fed grass hay from round bales in the pasture as well as one-and-one-half scoops of a high fat, high protein balanced feed (Omolene 300, Land O' Lakes Purina Mills, Gray Summit, MO, USA) once per day. Vaccinations for equine encephalomyelitis eastern and western, tetanus (Cephalovac EWT, Boehringer Ingelheim Vetmedica, Inc., St. Joseph, MO, USA), rabies (Imrab 3, Merial, Duluth, GA, USA) and west Nile virus (West Nile Recombitek, Merial, Duluth, GA, USA) were given annually in the spring and were up to date at the time of presentation. Six weeks prior to presentation, the horse was dewormed with ivermectin (Eqvalan, Merial, Duluth, GA, USA). The Coggins test was performed 1 month prior to presentation and the results were negative.

Upon physical examination, the horse was overweight (BCS 7/9) with a normal temperature (38.2 °C), respiration (28 bpm) and pulse (48 bpm). All other findings on the physical examination were unremarkable. The horse was light in color; however, the palpebrae OD were pigmented. A complete ophthalmic examination was performed with slit-lamp biomicroscopy and indirect ophthalmoscopy. On examination, there was a large, fleshy, pink to red, ulcerated, lobulated mass extending from the OD third eyelid with complete involvement of the third eyelid and loss of normal architecture. (Fig. 1) The mass was firm on palpation with purulent mucoid discharge and hemorrhage on the surface. The visible mass measured approximately 3.4 cm horizontally by 2.8 cm vertically. The mass extended to the dorsonasal bulbar conjunctiva and could be seen extending into the ventral fornix. The third eyelid was markedly elevated with pressure noted on the globe and subsequent enophthalmia. There was moderate chemosis (characterized as 2+ on a 0–4+ sequential grading scale) and moderate conjunctival hyperemia (2+) OD. A small superficial corneal ulcer was diagnosed adjacent to the area of corneal contact with the mass nasally. A full intraocular examination was precluded by the large mass, however, no significant findings were noted.



Figure 1. A photograph of the right eye in a 5-year-old Draft Horse gelding at initial presentation is depicted here. There is a large, pink, firm mass originating from the third eyelid with multifocal ulcerations and a moderate amount of surface mucopurulent discharge and hemorrhage. The visible mass measured approximately 3.4 cm horizontally by 2.8 cm vertically and caused moderate enophthalmia.

Schirmer tear test (STT) and intraocular pressure (IOP) OD were not possible due to the large mass and enophthalmia. The left eye was normal on complete ophthalmic examination with a STT value of 26 mm/min (Schirmer Tear Test, Merck and Company, Inc., Whitehouse Station, NJ, USA) and an IOP of 18 mmHg using applanation tonometry (Tonopen XL; Reichert Instruments, Depew, NY, USA).

Differential diagnoses for the mass included squamous cell carcinoma,¹ hemangiosarcoma,² papilloma,³ basal cell tumor¹¹ and pseudotumor¹⁴. Impression smears were evaluated for cytology and showed moderate numbers of neutrophils, bacterial cocci and necrotic cell debris. An ocular ultrasound was performed and showed a large echogenic mass of the third eyelid with extension ventrally and caudally to the level of or caudal to the globe equator. The mass measured 5.2 cm rostral to caudal and 3.4 cm lateral to medial on ultrasonographic evaluation. (Fig. 2) The echogenicity and echotexture of the orbital portion of the mass were similar to that of the visible extra-ocular mass and continuous with it. The mass was routinely biopsied by taking several surface tissue sections for histopathologic evaluation. Recommendations for exenteration of the right orbit were given to the owner at the initial presentation and evaluation. The horse was placed on triple antibiotic ointment (Neomycin and polymyxin B and bacitracin ophthalmic ointment, Bausch and Lomb, Rochester, NY, USA) every 8 h in the right eye, flunixin meglumine (0.5 mg/kg PO Q12 h; Banamine, Schering Plough, Union, NJ, USA) and trimethoprim sulfamethoxazole (25 mg/kg PO Q12 h; Amneal Pharmaceuticals, Hauppauge, NY, USA) for 10 days and discharged pending biopsy results.

Biopsy

Histopathologic examination of the initial biopsies from the mass revealed disorganized clusters of amphophilic to baso-

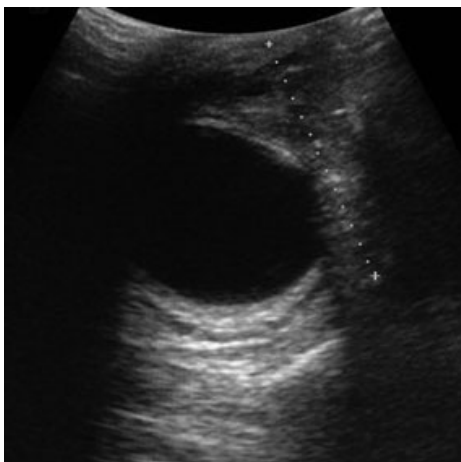


Figure 2. A photograph is shown depicting an 8–5 m Hz ocular ultrasound of the right globe and third eyelid mass in a sagittal plane with the ventral orbital contents positioned to the right in the photograph and the cornea positioned at the top. A mixed echogenic soft tissue mass is noted rostral and ventral to the globe, expanding the ventral orbital space and extending into the ventral orbit to the level of or past the globe equator. The mass measures 5.2 cm rostral to caudal, depicted by the dotted line. The echogenicity and echotexture of the intraorbital portion of the mass is similar to the visible extraocular portion and continuous with it.

philic neoplastic cells. The cells had marked anisocytosis and anisokaryosis, intracellular vacuolation and a mitotic index of 10/10 high powered fields. There were frequent bizarre mitotic figures. Intersecting the neoplastic cells were disorganized connective tissue elements with severe lymphoplasmacytic infiltrates. There was severe multifocal necrosis and severe lymphoplasmacytic inflammation within the neoplastic cell population. Moderate hemorrhage was noted diffusely. Definitive diagnosis was difficult due to the large amount of necrosis. Presumptive diagnosis of squamous cell carcinoma was made with recommendations for histopathologic submission of the entire mass. The owner was contacted and recommendations for exenteration and histopathologic evaluation were given.

Follow-up examination

The horse returned for follow up examination 3 months after initial examination. The mass had significantly improved and regressed with the medications given; however, approximately 2 weeks before the second presentation, had started to grow again. Therefore, the owner elected to have an exenteration performed on the right orbit. On presentation, the appearance of the mass was similar to that at initial presentation, however, it was slightly smaller. There was complete involvement of the third eyelid and the mass extended into the ventral fornix, however, the dorsonasal conjunctiva appeared normal grossly. The left eye was unremarkable. There were no changes to the physical examination and no lymphadenomegaly was noted.

Routine skull radiographs were performed prior to surgery to evaluate the orbital bone. The radiographs revealed a



Figure 3. A partial skull radiograph of the right globe and surrounding bone is shown. There is a large soft tissue mass that extends rostral to the globe, causing moderate enophthalmia. The surrounding orbital bone is normal (arrow), indicating no radiographic evidence of osseous involvement.

large soft tissue mass ventral to and overlying the right globe with normal ventral and dorsal orbital bone. (Fig. 3) Complete blood count and blood chemistry were unremarkable.

Surgical procedure

The horse was premedicated prior to general anesthesia with potassium penicillin (22,000 U/kg IV; Pfizer, New York, NY, USA), gentamicin (6.6 mg/kg IV; Butler Animal Health and Supply, Dublin, OH, USA), phenylbutazone (2.2 mg/kg PO; First Priority, Inc., Elgin, IL, USA), acepromazine (0.03 mg/kg IM; Fort Dodge, Fort Dodge, IO, USA), xylazine (0.25 mg/kg IV; Lloyd Laboratories, Shenandoah, IO, USA), and butorphanol (0.02 mg/kg IV; Akorn, Inc., Decatur, IL, USA). Anesthesia induction was performed using diazepam (0.05 mg/kg IV; Hospira, Lake Forest, IL, USA) and ketamine (2.3 mg/kg IV; Fort Dodge, Fort Dodge, IO, USA). General anesthesia was maintained with isoflurane 1.5% (Abbott Animal Health, North Chicago, IL, USA). The horse was placed in left lateral recumbancy and a transpalpebral exenteration was performed routinely as previously described.³⁶ The excised tissue was submitted for histopathologic evaluation. Small sections of ventral periosteal bone and soft tissue were removed and submitted separately for histopathologic evaluation. Recovery was routine and the patient was discharged the following day with a bandage and oral phenylbutazone 2.2 mg/kg every 12 h for 2 days.

Histopathologic evaluation

Grossly, the third eyelid was markedly expanded by a firm soft tissue irregular mass extending ventral to the globe with

no normal third eyelid architecture recognized. The globe and surrounding adnexa were unremarkable on gross examination. Histopathology revealed clusters of haphazardly arranged basophilic neoplastic glandular epithelial cells forming disorganized acinar structures diffusely and severely expanding the nictitans. (Fig. 4) The neoplastic cells had marked anisocytosis, anisokaryosis, prominent nucleoli and intracytoplasmic secretory material. (Figs 5,6) The mitotic

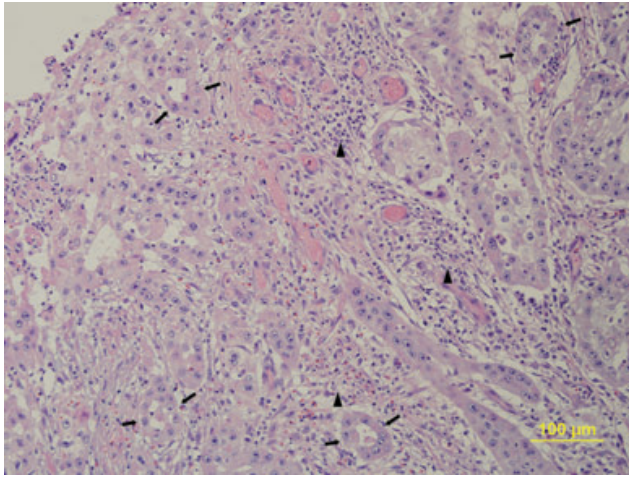


Figure 4. A photomicrograph at 20× magnification of the lacrimal gland adenocarcinoma depicts disorganized clusters of haphazardly arranged basophilic neoplastic glandular epithelial cells forming disorganized acinar structures (arrows). The neoplastic cells are intersected by scant connective tissue elements with inflammatory cell infiltrates (arrowheads). Intralesional necrosis was noted multifocally throughout the neoplastic cell clusters and connective tissue elements.

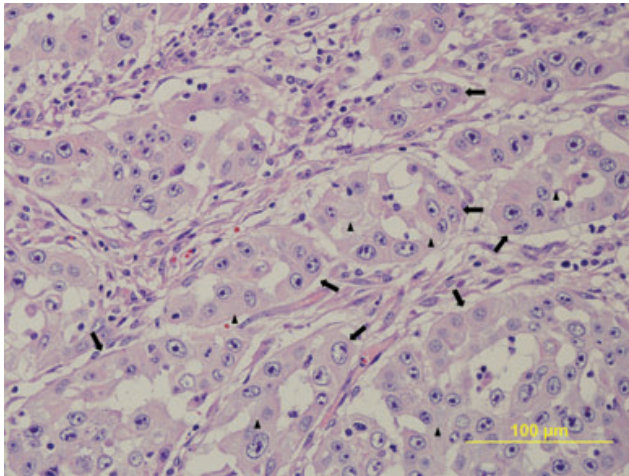


Figure 5. A photomicrograph at 40× magnification of the lacrimal gland adenocarcinoma depicts neoplastic glandular epithelial cells in disorganized acini (arrows) with marked anisocytosis, anisokaryosis, prominent nucleoli and intracytoplasmic basophilic to amphiphilic secretory material (arrowheads). Frequent bizarre mitotic figures were noted. Admixed within the neoplastic cell populations and intersecting connective tissue elements are moderate to severe infiltrates of lymphocytes and neutrophils with moderate numbers of plasma cells, macrophages and a few eosinophils.

index was 24/10 hpf with frequent bizarre mitotic figures noted. There was multifocal moderate central necrosis within the neoplastic cell populations and connective tissue elements. The neoplastic cells and interspersed connective tissue elements were diffusely and severely infiltrated by large numbers of lymphocytes and neutrophils with moderate numbers of plasma cells, macrophages and a few eosinophils. (Figs 4,5) There was multifocal fibrosis present (scirrhous reaction). Neoplastic epithelial cells did not extend to the deep margins of the ventral orbit. Paraffin embedded sections were stained with mucicarmine and periodic acid Schiff-hematoxylin (PASH) stains routinely with positive and negative controls. The neoplastic cells had vari-

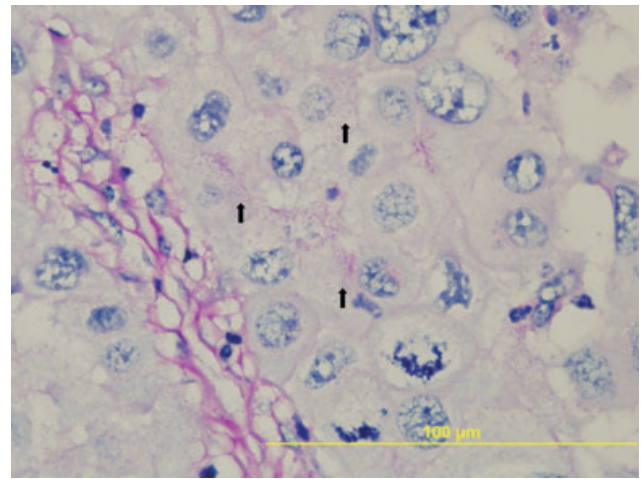


Figure 6. A photomicrograph at 100× magnification of the lacrimal gland adenocarcinoma after staining with periodic acid Schiff-hematoxylin (PASH) depicts neoplastic glandular epithelial cells with PASH positive intracytoplasmic secretory material (arrows). This, along with the negative staining for mucicarmine, indicates that the secretory material is serous and is consistent with lacrimal gland secretions.

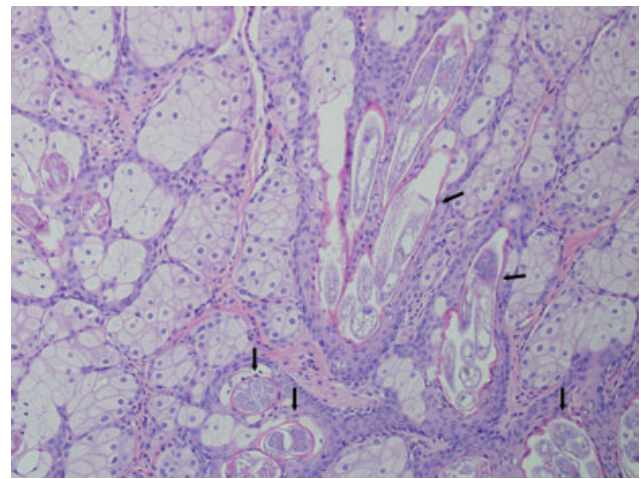


Figure 7. A photomicrograph at 20× magnification depicts intra-acinar and intra-ductal cross sections of parasites multifocally within the Meibomian glands (arrows). There is mild inter-acinar multifocal lymphoplasmacytic inflammation.

able intracytoplasmic PASH positive secretory granules present. (Fig. 6) The neoplastic cells were negative for mucicarmine staining, indicating that the intracytoplasmic secretory material was not mucoid. This along with the PASH positive staining indicates that the secretory material is serous, as would be expected in a tumor of lacrimal gland origin. This staining is identical to that of the normal equine lacrimal gland control. The sebaceous glands were noted to have intra-acinar and intra-ductal cross sections of parasites multifocally with mild inter-acinar multifocal lymphoplasmacytic inflammation. (Fig. 7)

Follow up

The surgery site healed well after exenteration. Fifteen months after initial presentation, the patient remains clinically normal with no evidence of recurrence or metastasis as determined by full physical and ophthalmic examination with right orbital palpation and oral examination.

DISCUSSION

To the author's knowledge, the case herein describes the first report of lacrimal adenocarcinoma of the third eyelid in a horse diagnosed histologically. This tumor was treated successfully with surgical removal. The reported 'regression' of the tumor after initial presentation and medical therapy was likely due to the anti-inflammatory effects of flunixin meglumine.^{37,38} Both histopathologic sections showed moderate to severe intralesional inflammation characterized by primarily lymphoplasmacytic inflammation. Flunixin meglumine, a nonsteroidal anti-inflammatory, inhibits prostaglandin release in inflammation³⁷ and has specific ability to inhibit activation of proinflammatory factors.³⁹ Although the owner reports rapid recurrence of the tumor following apparent regression, the biological behavior of the tumor based on this description is difficult to ascertain. In dogs, surgical excision of third eyelid adenocarcinomas resulted in regrowth, however, this appeared to be slow.¹⁶ One of the seven dogs with reported third eyelid gland adenocarcinoma had evidence of metastasis to the regional lymph node.¹⁶ The reported case in a cat described diffuse distant metastasis 4 weeks after diagnosis, however, the tumor had reportedly been present for 5 months prior to presentation.¹⁵

There is a solitary case report in a horse describing an undifferentiated solid carcinoma thought to originate from the third eyelid lacrimal gland.¹² This tumor was characterized by solid sheets of neoplastic epithelial cells and irregular tubular structures. The tumor had been present for 3 months prior to presentation and, at presentation, had extensive metastasis to the lymph nodes, ventral eyelid, esophagus and salivary glands.¹² Unlike the case reported here, the tumor cells described in the solid carcinoma of the lacrimal gland were undifferentiated and did not have light-microscopic characteristics of lacrimal glandular cells. Secretion granules were identified on electron microscopy and were speculated to indicate serous, mucous or seromu-

cous glandular origin of the neoplastic cell population. This combined with the conversion of lacrimal gland tissue into neoplastic cells lead the authors' to diagnose an undifferentiated solid carcinoma of the lacrimal gland, although a tumor of salivary gland origin could not be definitely ruled out.¹²

In the case reported here, an adenocarcinoma of the third eyelid lacrimal gland was easily diagnosed based on light microscopy as the neoplastic cells retained characteristics of the lacrimal gland cells of origin such as acinar formation and intra-cytoplasmic secretory material. The tumor reported here was present for approximately 4 months prior to surgical intervention. There was no clinical evidence of metastasis and 16 months after initial tumor formation, the patient remains disease-free with no evidence of distant metastasis or local recurrence. The histopathologic characteristics and apparent different biological behavior of the primary lacrimal gland adenocarcinoma reported here likely represents a different, previously unreported type of tumor. While it is difficult to definitively state that this tumor represents a unique previously undiagnosed tumor instead of a more biologically benign variant of the previously reported solid carcinoma, the marked histomorphological differences and clinical presentation would seem to indicate that this is indeed a previously unrecognized tumor type in horses. The lacrimal adenocarcinoma reported here is histopathologically very similar to the previously reported tumors in dogs and cats, further supporting this assertion.

Based on these reports in dogs, cats and horses, it is clear that adenocarcinomas of the third eyelid may metastasize. It is difficult to predict how quickly this will occur, based on the limited case numbers. As with any malignant tumor, early-intervention surgery with complete margins is recommended. In this case, exenteration or removal of the orbital contents resulted in complete excision of the tumor. Removal of the third eyelid was not recommended, in this case, as there was ultrasonographic evidence of deep ventral orbital invasion. The tumor did not invade the surrounding bony orbit. The other descriptions of this tumor in dogs and cats would also suggest that ability to invade bony structures is limited or nonexistent, as this has not been reported.

The initial surface biopsies of the tumor reported here showed neoplastic epithelial cells in clusters with marked inflammation and necrosis. Based on these findings, a presumptive diagnosis of squamous cell carcinoma was made. In horses, squamous cell carcinomas are the most common tumors of the third eyelid and certain breeds, such as Drafts, Appaloosas, Paints and 'white-faced' horses, are predisposed.^{2,5,40} Exposure to ultraviolet (UV) radiation is a major risk factor for development of these epithelial tumors and UV-induced mutations of the p53 tumor suppressor gene have been suggested.⁴ In addition, UV-mediated changes to the subconjunctival tissues, such as solar elastosis, may be found in the surrounding connective tissues when this tumor is present.^{6,41} Adenocarcinoma formation is not linked to UV radiation and no breed predilections have been reported. In our case, the horse was a Draft horse that was

light in color, although the palpebrae were pigmented. This finding is likely coincidental. In addition, there was no evidence of UV radiation damage to the surrounding conjunctival tissue, although surrounding conjunctival tissue was not present on the initial biopsy sections examined. Histopathologically, the neoplastic adenocarcinoma tumor cells did not exhibit intracellular bridging, dyskeratosis, keratosis or keratin pearl formation, all frequent findings in squamous cell carcinomas.^{6,42} Both adenocarcinomas and squamous cell carcinomas may have associated lymphoplasmacytic inflammation and necrosis. After the complete mass was available for histopathologic examination, the diagnosis was clear, underscoring the need for the clinician to obtain large diagnostic samples in cases of third eyelid neoplasia.

On histopathology of the eyelids, concurrent sebaceous gland *Demodex caballi* was found. The surrounding connective tissue contained mild numbers of lymphocytes and plasma cells, suggestive of a mild inflammatory reaction secondary to the intrafollicular mite presence. There were no other pathologic changes to the eyelids or haired skin on physical examination and the owner did not report hair loss, pruritis or excoriations of the right palpebrae. After questioning, the owner also did not report any skin pathology anywhere else on the body or any history of skin disease. *Demodex caballi* is an uncommon incidental finding in horses.³⁵ *Demodex* spp. may be present in a clinically normal state and may be an incidental finding in many species.^{18,43} Concurrent neoplasia and demodicosis has been reported. In a cat, cutaneous xanthomas with clinical demodicosis resolved with oral milbemycin and low-fat dietary changes.⁴⁴ The demodicosis was suspected to be due to immunosuppressive therapy, in this patient, and not directly linked to the xanthomas. In humans, eyelid basal cell carcinomas⁴⁵ and sebaceous adenomas⁴⁶ have been linked to eyelid demodicosis. It has been suggested that the *Demodex* spp. may cause irritation leading to tumor formation. Alternatively, tumor formation may alter the local immunologic environment, allowing demodicosis. In this case, the *Demodex caballi* presence is likely coincidental as no parasitic organisms were found in the conjunctiva or adjacent to the tumor. In addition, no overt pathology was noted in the otherwise histologically normal sebaceous glands, palpebral haired skin and adjacent conjunctiva.

This case describes the first reported equine lacrimal adenocarcinoma of the third eyelid. This tumor was treated with complete surgical excision and 12-months after surgery, the patient remains disease-free with no recurrence or metastasis. Complete surgical excision should be considered the treatment of choice for lacrimal adenocarcinomas in horses and early intervention may prevent distant metastasis.

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