

**A Real Pain(t)**

Sarah Phillips

Mississippi State University

College of Veterinary Medicine

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Advisor: Caroline Betbeze, DVM, MS, DACVO

## **Introduction:**

Ocular neoplasia accounts for approximately 10-30% of all neoplastic conditions in the horse.<sup>2,7</sup> When presented with a case of ocular neoplasia, it is important to remember that a variety of tumor types may be similar in physical appearance and clinical course. Squamous cell carcinoma, sarcoids, and melanoma are more common ocular tumors, however hemangiosarcoma and lymphosarcoma may also manifest as an ocular or periocular mass.<sup>8,9,11,14</sup> Treatment options and prognosis may rely heavily on accurately diagnosing and staging the disease process occurring in the eye, as ocular tumors are likely to be malignant.<sup>7</sup> Early and aggressive treatment is typically necessary to achieve a favorable outcome for the patient.<sup>14</sup>

Hemangiosarcoma is a neoplastic disease arising from vascular endothelial tissues that occurs most commonly in dogs. Vascular neoplasia such as hemangiosarcoma is rare in horses, and few reported cases exist in published literature. Conjunctival or corneal hemangiosarcoma is rarer still. As such, no published classification system has currently been established for equine hemangiosarcoma. Different clinical manifestations of this neoplasia have been reported in horses, including disseminated, musculoskeletal, cutaneous, and ocular forms.<sup>5,13,17,18</sup> Clinical signs vary depending on the clinical manifestation, but metastasis is likely to occur early on in cases of visceral hemangiosarcoma. Corneal hemangiosarcoma tends to behave in a more locally invasive way and does not readily metastasize.<sup>14</sup> In dogs, conjunctival hemangiosarcoma is more likely to occur unilaterally with focal masses arising from the conjunctiva or nictitating membrane. These masses occasionally invade the cornea.<sup>12</sup>

In regards to signalment, no gender predilection is reported for equine conjunctival hemangiosarcoma. Hemangiosarcoma most commonly occurs in middle-aged to older horses. A true breed predilection has not been established for equine hemangiosarcoma. Horses with

lightly pigmented eyes and skin of the face may be more likely to develop ocular and periocular tumors. Evidence suggests that exposure to UV light may increase the risk of developing hemangiosarcoma associated with the eye or lightly pigmented skin surrounding the eye.<sup>8,9,11,14</sup> Clinical signs may include serosanguinous discharge from the affected eye or the nose and the presence of a red to purple vascularized mass arising from the conjunctiva or nictitating membrane of the affected eye.<sup>11,14,16,19</sup> The mass may be locally invasive and could involve the cornea, the orbit, deeper structures surrounding the eye, and local lymph nodes.<sup>6,16</sup> A biopsy is typically necessary to obtain a definitive diagnosis of conjunctival hemangiosarcoma. Treatment options vary and may depend on the stage of the neoplasm present.

### **History and Presentation:**

Apache Reaves is an approximately 13 year old Paint gelding who presented to Mississippi State University College of Veterinary Medicine on November 27<sup>th</sup>, 2020 for a blister-like mass on the conjunctiva of the left eye. The mass was first noted by Apache's owners approximately 5 days prior to presentation. Serosanguinous fluid ruptured from the mass when pressure was applied to Apache's lower eyelid. He also experienced intermittent serosanguinous epiphora from the left eye. Apache was started on Tucaprim (trimethoprim and sulfadiazine 1:5) at onset – however the mass remained unchanged. Apache did not have any previously reported eye issues or other health concerns.

A full physical examination was performed. Apache was bright, alert, and responsive on presentation. He weighed 1145 lbs (519 kg) with a body condition score of a 5 out of 9. His vitals were within normal limits with a rectal temperature of 98.9F, a pulse of 36 beats per minute, a respiratory rate of 28 breaths per minute. Oral mucus membranes were moist and pink with a capillary refill time of less than 2 seconds. Cardiothoracic auscultation was within normal

limits, with no crackles, wheezes, arrhythmias, or murmurs detected. Apache had normal gastrointestinal motility in all 4 quadrants and his digital pulses were negative in all 4 limbs. Both nares were patent and his coat was clean and smooth and free of abrasions. There were three circular patchy areas of hair loss noted on the left side of his face. A quarter-sized mass was appreciated on the bulbar conjunctiva and ventrolateral paraxial cornea of the left eye. The eye was not painful. Fluorescein staining was negative bilaterally. Intraocular pressures were within normal limits bilaterally. The remainder of his physical exam was unremarkable, and all lymph nodes palpated normally.

### **Diagnostic Approach and Considerations:**

As with any patient, a diagnostic workup begins with a thorough history and full physical exam. In the case of ocular hemangiosarcoma, serosanguinous ocular discharge is a common presenting complaint. Serosanguinous nasal discharge may also be present. Depending on the location and size of the mass within the conjunctiva, the eyelid may appear swollen or the mass may be visible.<sup>11</sup> Corneal involvement or corneal neovascularization may be observed.<sup>6,7,9,11</sup> The physical appearance of the mass may vary from smooth and blister-like to ulcerated and irregular. Hemangiosarcomas are typically red to purple in color and are highly vascularized. Patients with metastatic or disseminated hemangiosarcoma may exhibit anorexia, weight loss, depression, lethargy, anemia, or hemorrhage into a body cavity.

For any conjunctival mass, a biopsy should be obtained to achieve a definitive diagnosis.<sup>11</sup> Obtaining tissue samples from the eye and surrounding tissues can be challenging, depending on the location and size of the tumor.<sup>8</sup> Other ocular tumors are more likely to arise than hemangiosarcoma, and prognosis may vary depending on the type and grade of the tumor present.<sup>8,9,11,14</sup> In otherwise healthy patients, bloodwork may be unrewarding. Palpation of local

lymph nodes should be performed. Enlargement of submandibular, superficial cervical, or parotid lymph nodes may indicate metastasis and warrants performing biopsy of the lymph nodes.<sup>11</sup> Fine needle aspirates may be unrewarding in horses and are commonly non-diagnostic.<sup>2</sup>

Further staging and evaluation of metastasis includes diagnostic imaging. Thoracic and abdominal radiographs are typically unrewarding in adult horses due to their size. However skull radiographs may be performed to assess the orbit, and surrounding sinuses to assess for possible local invasion of the tumor.<sup>11</sup> Thoracic and abdominal ultrasound may be performed, particularly if metastasis to internal organs is suspected. Areas of lung consolidation and pleural effusion may be noted.<sup>15</sup> Endoscopy of the upper airway and guttural pouches should also be considered in horses with suspected local invasion of an ocular or peri-ocular tumors. Abdominocentesis may also be considered, especially if hemorrhage into a body cavity is concerned.<sup>17</sup>

In Apache's case, his physical exam was largely unremarkable, except for the presence of a conjunctival mass in the left eye. The conjunctival mass appeared to be localized. Digital palpation did not reveal any immediate evidence of extensive tumor growth into the orbit. A punch biopsy of the mass was performed. No further diagnostics associated with the mass were performed at this time, as metastasis of conjunctival hemangiosarcoma is unlikely.

The biopsy results were most consistent with an epithelioid variant of hemangiosarcoma. Epithelioid hemangiosarcomas are characterized by neoplastic cells with variable growth patterns, epithelioid morphology, and the rare presence of cytoplasmic vacuolation.<sup>4</sup> In some areas, the conjunctival mucosal epithelium was ulcerated. Solar elastosis was present within the superficial submucosa beneath some conjunctival epithelium. Solar elastosis is defined as damage to the skin caused by repeated exposure to UV radiation over time. Degradation of the dermal matrix and synthesis of elastin fibers indicate the formation of solar elastosis.<sup>15</sup> Given the

presence of solar elastosis in the specimen, Apache's conjunctival hemangiosarcoma was likely induced by exposure to UV radiation in a region of the body that was lightly pigmented.

Apache's conjunctival tumor would be removed via a conjunctivectomy and a superficial keratectomy. Surgical removal of ocular and peri-orbital neoplasia is considered to be the treatment of choice, particularly in cases where metastasis has been ruled out.<sup>2</sup> In other reported cases or equine ocular hemangiosarcoma, enucleation or extirpation have also been considered.<sup>14</sup>

### **Pathophysiology**

Hemangiosarcoma is a neoplastic disease arising from vascular endothelial tissues which can take many forms, including disseminated, musculoskeletal, visceral, cutaneous, and ocular forms<sup>4,13,16,17,18</sup>. Hemangiosarcoma, and other neoplasms of vascular origin, are rare in horses. When discussing the pathophysiology of periocular hemangiosarcoma, much of the existing research has only been performed in canines. Etiologies for hemangiosarcoma are still poorly understood, however there is suspicion that exposure to UV radiation may contribute to the formation of hemangiosarcoma in multiple species.<sup>6,9,13</sup> In most species, a diagnosis of hemangiosarcoma may carry negative connotations with it. Visceral hemangiosarcoma typically has a poor prognosis. Masses that rupture may be fatal in many cases. However, periocular hemangiosarcoma has a better prognosis than visceral hemangiosarcoma in most species. Surgical removal of the neoplasm may be curative. Tumors may recur, but periocular hemangiosarcoma is less likely to metastasize than visceral hemangiosarcoma.<sup>14</sup>

Histopathologically, hemangiosarcoma is typically associated with moderate to severe hemorrhage and evidence of necrosis within the mass. Cells may exhibit abnormal mitotic

figures and polygonal shapes. Local inflammation and angiogenesis (formation of new blood vessels) are frequently identified in cases of hemangiosarcoma. Tortuous vasculature and frequent clotting have also been observed in hemangiosarcoma. This clotting frequently leads to the regions of necrosis previously described, as the tumor is not receiving adequate nutrients to grow. These regions of necrosis may eventually rupture. In cases of disseminated hemangiosarcoma, this rupture due to necrosis is typically why hemorrhage into body cavities is seen with this neoplasia.<sup>7</sup>

As hemangiosarcoma is a tumor of vascular epithelial cells, it can occur or spread to any region of the body with vascular tissue. Corneal hemangiosarcoma is unlikely to widely disseminate to other body systems and more frequently takes on locally invasive qualities. If widespread metastasis does occur in the horse, it is likely to spread to the respiratory tract, spleen, and less frequently, the brain, pericardium, or gastrointestinal tract.<sup>11</sup> It is important to remember that hemangiosarcoma, regardless of its location, can be aggressive and may metastasize early in the disease process. Therefore, early and aggressive treatment is necessary to achieve favorable outcomes for the client and patient.

## **Treatment**

Surgical removal of a mass is considered to be the treatment of choice for neoplastic disease affecting the eye. Depending on the location of the mass, surgical removal may be challenging.<sup>9</sup> Cutaneous tissues around the eye may be especially unforgiving, particularly if surgical debulking is extensive. For small, simple conjunctival tumors that do not extend deeper into the surrounding tissues of the eye, surgical removal of the mass may be rewarding. In one study, a horse with ocular hemangiosarcoma only underwent removal of the third eyelid and had no evidence of recurrence two years post-operatively.<sup>14</sup> In another study, superficial keratectomy

alone led to an outcome of no recurrence 21 months post-operatively.<sup>11</sup> Enucleation and exenteration may also be considered as treatment options for ocular hemangiosarcoma, particularly when the invasion of the mass into the globe is extensive.

Several adjunctive therapies have been utilized in the treatment of equine ocular and periocular tumors. Indocyanine green (ICG) dye-enhanced diode laser photocoagulation and cryotherapy may be performed. In Apache's case, ICG dye was painted onto the stroma of the left eye and injected subconjunctivally in the tissue surrounding the surgical site. A diode laser treatment was performed to prevent excessive neovascularization of the tissues associated with the keratectomy site. Other adjunctive therapies have previously been utilized to combat recurrence of ocular and peri-ocular neoplasia, including 5-Fluorouracil chemotherapy or Mitomycin C.<sup>2</sup> These have been more frequently used in cases of squamous cell carcinoma or sarcoids and have not been regularly utilized to treat equine ocular hemangiosarcoma. Cryotherapy, the use of freezing or near-freezing temperatures, may be used in cases of conjunctival neoplasia.<sup>9</sup>

Risks and complications should be discussed with owners prior to any surgery. In Apache's case the risk of complications was relatively low. Complications associated with keratectomies include corneal infection and excessive granulation tissue formation.<sup>1</sup> Performing a keratectomy essentially creates an iatrogenic ulcer and post-operative topical ophthalmic antibiotic solutions should be prescribed to patients to prevent corneal infection. If enucleation or exenteration are considered as treatment options for equine ocular hemangiosarcoma, the risk of post-operative hemorrhage and infection should be discussed with owners.<sup>1</sup>

## **Case Outcome**

On December 3, 2020, Apache underwent a superficial keratectomy and conjunctivectomy. During surgery, it was determined that the third eyelid may have also been affected by the mass. Surgical excision of the third eyelid was performed and the excised tissues were submitted for histopathology. A sub-palpebral lavage system was placed in the left eye to facilitate administration of topical medications post-operatively. Apache's recovery from anesthesia was uneventful. Apache was discharged on December 4, 2020 with instructions to administer Neo/Poly/Gram Triple Antibiotic ophthalmology solution via the subpalpebral lavage system three times daily. He was also discharged with a 5 day prescription of Banamine paste for pain control. During Apache's recovery, he would need to wear a protective eye mask to prevent excessive rubbing of the eye while it healed. An initial recheck appointment was scheduled for December 11, 2020.

On December 5, 2020, Apache's owners contacted MSU-CVM to discuss an incident with his sub-palpebral lavage system. Apache's sub-palpebral lavage system had been pulled out from his eyelid. After discussing options with the owner, it was determined that Apache would not have his sub-palpebral lavage system replaced and that his owners would continue to administer Apache's Neo/Poly/Gram solution topically as directed. At this time, we discussed the use of left-over ophthalmic medications from another horse for Apache and informed the owners that any ophthalmic medications with steroids should not be administered to Apache at this time, as they may delay wound healing and could predispose patients to fungal keratitis.

On January 12, 2021, Apache's owners provided photos and video of Apache's left eye. At this time, Apache seemed comfortable and healthy granulation tissue was appreciated at the surgical site. A recheck appointment was scheduled for March 11, 2021. At this time, Apache will be evaluated for any recurrence of the tumor.

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