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## Clinical Reports



### Ocular angiosarcoma in four horses

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REPORTS OF OCULAR and orbital neoplasms in horses are few. Squamous cell carcinoma and equine sarcoid are reported most commonly.<sup>1-8</sup> In 2 reports, orbital vascular tumors are mentioned briefly,<sup>1,2</sup> but no information concerning the clinical findings was included. This report deals with the clinical findings and progression of disease in horses with histopathologic diagnoses of ocular angiosarcoma.

A 9-year-old Thoroughbred gelding (horse 1) was first examined at the University of California, Davis-Veterinary Medical Teaching Hospital (UCD-VMTH) because of a lesion of the left eye. The lateral aspect of the cornea was thickened by vascularization and edema. Fluorescein stain was not taken up by the cornea; therefore, prednisolone acetate<sup>a</sup> was prescribed to be used topically 4 times daily. Three weeks later, the lesion had not resolved. Multiple orange masses with jelly-like consistency were seen laterally, in the conjunctival fornix. The right eye was unremarkable.

A biopsy specimen was obtained; the findings were consistent with hemangiosarcoma. During the following 13 months, we performed  $\beta$ -irradiation of the lesion with strontium 90, enucleation and, because of the recurrence of the lesion within the orbit, orbital exenteration followed by cesium 137 needle implantation. Improvement after each treatment was temporary.

The horse was examined 14 months later because of masses under the jaw. Submandibular lymphadenopathy and palpable masses over the trachea and pectoral muscles were found. Pitting edema was detected in the pectoral area. A needle biopsy specimen was obtained from the submandibular masses. Results of the biopsy were consistent with hemangiosarcoma.

The horse reportedly died of complications associated with colic 18 months after the initial referral. At

that time, a submandibular lymph node was obtained. The histopathologic diagnosis was hemangiosarcoma, with a differential consideration being lymphangiosarcoma.

A 15-year-old Appaloosa mare (horse 2) had a mass involving the dorsomedial bulbar conjunctiva and cornea and the membrana nictitans of the left eye. A biopsy by the referring veterinarian revealed a potentially malignant tumor of vascular origin.

When examined at the UCD-VMTH 2 months later, the right eye was normal. A cystic mass, approximately 4 mm by 15 mm, was found at the left dorsomedial aspect of the limbus, extending 4 mm onto the left cornea (Fig 1). The ventromedial region of the bulbar conjunctiva was markedly thickened and firm. Biopsy specimens were taken and the mass was irradiated, using iridium 191 implant brachytherapy.<sup>9</sup> The biopsy revealed poorly differentiated sarcoma, possibly of vascular origin.

One month later, the mare again was examined because the tumor had enlarged and corneal, con-

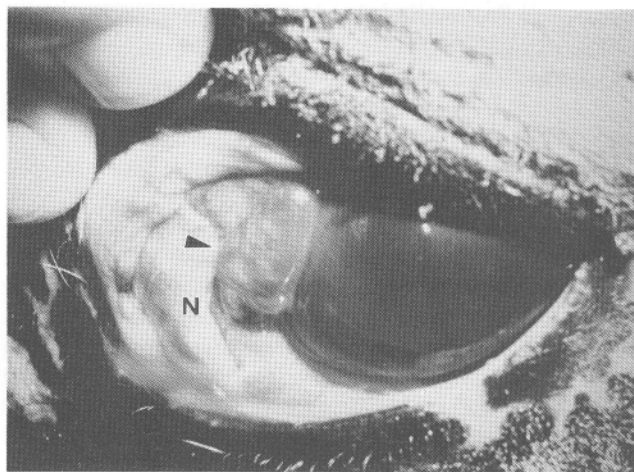


Fig 1—Left eye of horse 2. The mass (arrowhead) is on the bulbar conjunctiva between the membrana nictitans (N) and the cornea.

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<sup>a</sup>Pred-Forte, Allergan Pharmaceuticals, Inc, Irvine, Calif.

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Fig 2—The left eye of horse 2, at the time of surgery, one month after Figure 1 was obtained. Entire bulbar conjunctival area is invaded by tumor.

conjunctival, and palpebral inflammation was detected (Fig 2). Because of the malignant nature of the tumor, the orbit was exenterated. The histopathologic diagnosis was lymphangiosarcoma.

The mass recurred within the exenterated orbit 4 months later. The horse subsequently was euthanatized because of limb edema and colic. Necropsy was not done.

A 12-year-old Quarter Horse gelding (horse 3) was seen first by the referring veterinarian. The left membrana nictitans was excised because of a mass. Histologic examination was not done. A mass recurred at the original site and the horse was referred 1 year later to the UCD-VMTH. The right eye was normal. A firm mass obliterated the ventromedial region of the left conjunctival fornix and invaded the cornea 4 mm. The mass was biopsied and irradiated with iridium 191 implant brachytherapy. The limbus and cornea were irradiated with strontium 90  $\beta$ -irradiation. The histopathologic findings were consistent with lymphangiosarcoma. Following implant removal, the horse was discharged, and was reported doing well 3 months later.

Six months after the radiation treatment, the horse was examined because of anorexia and debilitation. Distal limb edema and a mass caudal to the left ear were found. The horse was euthanatized.

At necropsy, the temporalis muscle was found to be thickened and to contain an 8 cm by 10 cm by 10 cm mass. The mandibular and cervical lymph nodes were large. A firm 10 cm by 10 cm by 1 cm mass was found in the cranial mediastinum. Biopsy specimens obtained at necropsy were labeled incorrectly and misplaced. Only the left globe and a portion of the temporalis muscle, removed before necropsy, were available for histologic examination. Neoplastic tissue consistent with lymphangiosarcoma was found in the periocular and temporalis muscle tissues.

A 17-year-old Arabian gelding (horse 4) was examined at the UCD-VMTH because the left eye was

swollen and had been tearing for 1 year. Examination revealed the right eye to be normal. The left eyelids were swollen and firm and the left side of the face was swollen. The left globe appeared normal. The submandibular lymph nodes were large. Examination of specimens obtained via fine needle aspiration of the left lower eyelid revealed cells that were probably neoplastic in origin. Examination of punch biopsy specimens of the eyelid revealed a malignant tumor of vascular origin. Radiography of the skull revealed soft tissue density in left frontal sinus, soft tissue density in the area of the left orbit, and left retropharyngeal lymphadenopathy. The most probable diagnosis was invasive neoplasm. Because of the poor prognosis, the horse was discharged without treatment.

Five months later, the horse was seen again because of further swelling of the left orbital area. A mucohemorrhagic discharge from the left nostril had been visible for 1 week. The right eye remained normal. Biopsy specimens were obtained from the left lower eyelid, left parotid salivary gland area, and left submandibular lymph node. The tentative diagnosis was hemangiosarcoma. The client elected to take the patient home without further work-up or treatment.

The horse was examined 12 days later because of serosanguineous discharge from the left nostril. The client elected to have the horse euthanatized at this time. At necropsy, a firm, 2-cm diameter mass was found on the sclera dorsally. The orbital contents and eyelids and cranial and caudal cervical lymph nodes were infiltrated with neoplasm. The histopathologic diagnosis was hemangiosarcoma.

In each case, excisional biopsy specimens were fixed in neutral-buffered 10% formalin. Globes were fixed in either Zenker's-acetic acid solution or Bouin's fixative. The tissues were processed for light microscopy and sections were stained with hematoxylin and eosin. Selected sections also were stained with an immunoperoxidase method to detect factor VIII related antigen (VIII:RAg).<sup>10</sup> Factor VIII:RAg is synthesized by blood vascular endothelial cells. Megakaryocytes and platelets also contain this antigen.<sup>11</sup>

The microscopic architecture of the tumors varied considerably from area to area within the same tumor. Capillary and solid growth patterns were observed. The capillary pattern was characterized by the presence of a network of well developed vascular channels lined by plump, hyperchromatic, pleomorphic endothelial cells. Scant collagenous stroma separated the channels, and circulating red blood cells usually were not detected (Fig 3). The solid pattern was composed of sheets of pleomorphic cells that had hyperchromatic, large oval nuclei and poorly defined cytoplasmic borders (Fig 4). Rudimentary vascular channels, in the form of clefts, often were observed between small bundles of these cells. Mitotic activity was observed frequently in the neoplastic cells in both patterns of tumor growth. An intense lymphocytic, plasmacytic inflammatory infiltrate was observed frequently within the tumor tissue and at the borders. In sections consisting almost entirely of the

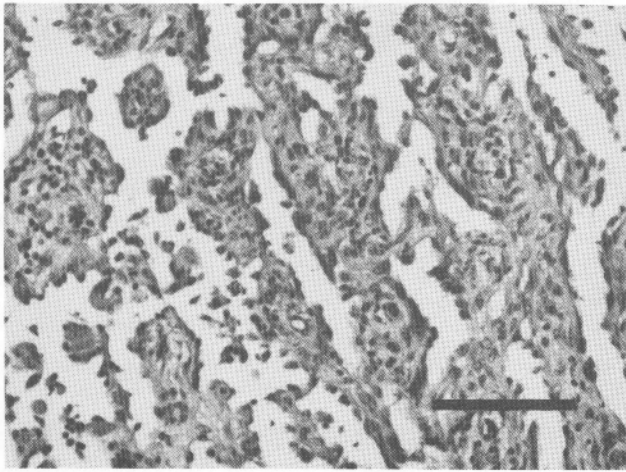


Fig 3—Capillary pattern of angiosarcoma. Notice scant collagenous stroma separating endothelial-lined vascular channels. Bar = 100  $\mu$ m.

solid growth pattern, the inflammatory infiltrate and the scirrhous response to the tumor made recognition of the underlying neoplastic nature of the process difficult.

Preliminary studies indicated that lymphatic endothelial cells were largely devoid of factor VIII:RAg. The cells lining vascular channels in the capillary regions of the ocular angiosarcomas were stained intensely for factor VIII:RAg. Less intense staining also was observed in the less differentiated solid regions regardless of the presence of rudimentary vascular channels or clefts. Despite the paucity of erythrocytes in vascular channels of the tumors, these results were more consistent with a blood vascular endothelial origin for the tumors rather than a lymphatic endothelial origin.

Hemangiosarcomas are malignant tumors arising from the blood vascular system. Lymphangiosarcomas are described as tumors, indistinguishable from hemangiosarcomas at the light microscopic level, arising from the lymphatic rather than the blood vascular system.<sup>12</sup> Diagnosis of lymphangiosar-

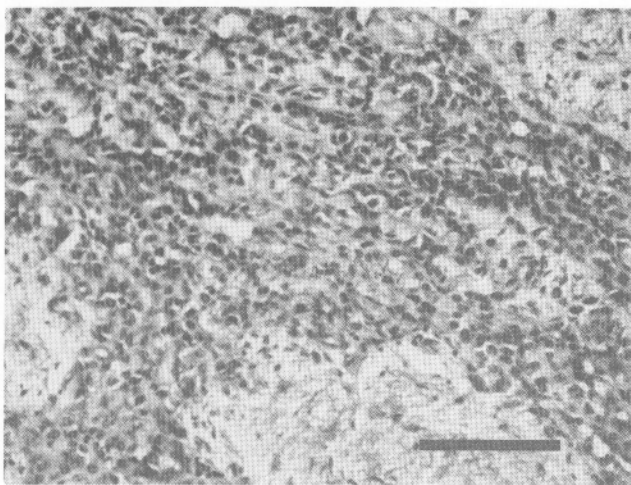


Fig 4—Solid pattern of angiosarcoma. Solid sheets of pleomorphic cells with hyperchromatic, large oval nuclei and indistinct cytoplasmic borders. Bar = 100  $\mu$ m.

coma usually is made on the basis of clinical signs and a paucity of erythrocytes seen within endothelial lined vascular channels. Differentiation between the 2 vascular tumors at the microscopic level, without the aid of immunohistochemical markers, is difficult. The term angiosarcoma is used when the tissue of origin is uncertain.

In man, dogs, and cats, lymphangiosarcomas have been reported as cutaneous or subcutaneous neoplasms.<sup>13-20</sup> In man there is an association with chronic lymphedema, mastectomy, or trauma.<sup>13-15</sup> In the dog and cat, similar associations have not been reported. We could find no reports of orbital lymphangiosarcoma in man or domestic animals.

In domestic animals, hemangiosarcomas are vascular tumors variable in histopathologic appearance. The tumor may be highly cellular in which vascular channels are collapsed and the appearance is of fibrosarcoma.<sup>21,22</sup> They may be composed of vascular channels or cavernous channels lined with immature endothelial cells, with blood content being variable.<sup>12,23</sup> Hemangiosarcoma in the horse is an infrequently reported neoplasm. Cutaneous manifestation of this neoplasm has a prevalence of less than 1%<sup>23</sup> and, to the best of our knowledge, there are only 2 reports of ocular hemangiosarcoma in horses mentioned in the literature.<sup>1,2</sup>

Our immunohistochemical studies indicated that the tumors in the horses in this report were likely of blood vascular origin, on the basis of the detection of factor VIII:RAg in all tumors. More complete studies, including detection of the major histocompatibility (Ia) antigen and ATPase<sup>24</sup> in the tumor cells, would be necessary to establish that the tumors arose from blood vascular rather than lymphatic endothelium. Hence, the tumors were designated angiosarcomas, though they were most likely hemangiosarcomas.

The definitive cause of any neoplasm in a clinical situation is speculative. Viruses, solar radiation (UV light), and dust have been associated with ocular neoplasms.<sup>25-27</sup> In a colony of Beagle dogs,<sup>26</sup> 3 of 19 proliferative lesions were found to be hemangiosarcomas. It was concluded that the environmental conditions of a sunny, smog-free area at a high altitude contributed to the development of the neoplasms. The ocular neoplasms of these Beagles as well as UV light-induced neoplasms in man tended to be on the unpigmented bulbar conjunctiva.<sup>27</sup>

Although the horses in our report were not from an area of high altitude, they were from an area of intense solar radiation during the period from March to October. Thus, UV light may have been a causative agent. The lesions tended to be first recognized on conjunctival surfaces that had exposure to light.

Treatment of angiosarcoma in man and domestic animals is limited to surgical excision of the lesion.<sup>28,29</sup> To date, no chemotherapeutic regimen has proven effective in domestic animals.<sup>28</sup> As noted in the cases reported here, angiosarcomas appear to be radioresistant.

In man, prognosis for long-term survival of patients with facial or scalp angiosarcoma is poor. Of 36

cases for long term follow-up in 1 report, 26 patients were dead within 2 years, 7 died between 2 and 4 years, and 3 survived for more than 4 years.<sup>30</sup> In the report of ocular hemangiosarcoma in Beagle dogs, no deaths were attributed to the ocular neoplasm during a 10-year period from 1967-1977.<sup>26</sup> Our experience with ocular angiosarcoma in the horse indicated that the clinical course of the neoplasm follows that of facial angiosarcoma in man; metastasis appears to be common.<sup>29</sup> The difference in survival rates between horses and the Beagles may be due to the frequency of ocular examinations and, therefore, the early detection and excision of the neoplasms in the Beagles<sup>26</sup> or a difference in biologic behavior of the neoplasm in the 2 species.

The common characteristics of the 4 cases of ocular angiosarcoma included initial involvement of conjunctiva, slow growth, and metastasis despite excision and radiation treatment. Metastasis appeared to occur via the blood or lymphatic system. The time interval from finding the earliest lesion until the horses became debilitated and were euthanized or died was approximately 18 months. Because of the refractory and aggressive nature of this neoplasm, we recommend radical excision, including orbital exenteration, of tissue that is confirmed histologically as angiosarcoma. A guarded prognosis must still be given.

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