Periorbital Squamous Cell Carcinoma in the Equine Patient

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Introduction

Squamous cell carcinoma (SCC) is the most common neoplasm of the equine eye and ocular adnexa and it is the second most common tumor affecting the horse overall [5, 11, 17]. Commonly affected areas involve any or all of the corneoconjunctiva, bulbar conjunctiva, limbus (corneoscleral junction), nasal canthus, nictitating membrane (third eyelid), and palpebra (eyelids) [5, 11, 12, 17]. In horses squamous cell carcinoma of the eyelid is common, although less so than other ocular sites [14]. In a survey of 49 equine cases, single lesions involved the eyelids in 14% of patients, the third eyelid in 26%, and the limbus in 25% [14]. These tumors tend to be locally invasive and slow to metastasize and local recurrence is more commonly seen than metastasis [12, 17]. Untreated ocular and periocular SCC may invade the local soft tissues, the bony orbit, sinuses, and brain [11]. Though rare metastasis can occur to regional lymph nodes, salivary glands, and thorax [11, 12]. The exact etiology of the SCC is unknown but there are several risk factors that have been identified that contribute to the formation of SCC. In the majority of cases horses greater than 10 years of age and possessing one or multiple risk factors develop SCC [4, 14, 17, 19]. Several studies have shown that there are higher prevalence rates in certain breeds including Belgians, Clydesdales, Appaloosas, and Paint horses [10].

History and Presentation

Joe, a 16 year old Paint gelding, presented to the Mississippi State University College of Veterinary Medicine ophthalmology service on June 22nd, 2017 for progressive SCC in both eyes. Joe was first evaluated for possible SCC in his left eye approximately two years ago by his primary care veterinarian. At that time, a mass was removed from his left eyelid and followed with cryotherapy; in addition, his right eye had electrocautery and cryotherapy as well for

possible early signs of SCC in the medial periorbital area. Since the initial treatment two years ago, Joe had not received any additional treatments. The area where the mass was removed on his left eye never healed following the cryotherapy and has remained ulcerated. Roughly two months prior to his visit at MSU-CVM, a small lesion on his right upper eyelid was noticed that progressed quickly to a large, pedunculated mass. As preventative care, Joe usually wears a fly mask and sunscreen whenever possible.

Upon presentation, Joe's vital signs were within normal limits. Close physical examination of his muzzle revealed multiple raised areas of plaque-like lesions. Ophthalmic examination revealed a 3x5cm pedunculated mass arising from the right upper eyelid covering the right eye. An area of necrotic tissue was noted medially to the mass on the right upper eyelid. Several ulcerated lesions on the upper and lower right eyelids were also present. The right eye was visual, but a 1cm area of keratitis with vascularization was present ventromedially. Slit lamp biomicroscopy was otherwise within normal limits on the right eye. A 1.5cm area of ulceration was noted on the skin just medial to the medial canthus of the left eye. A 1cm area of ulceration was present on the lateral aspect of the upper left eyelid. The cornea was within normal limits, as was the anterior chamber on the left eye. The posterior segment was not fully evaluated. Other than the ocular and periocular lesions, Joe had no other major medical history and was up to date on vaccines and Coggins test.

Pathophysiology

Carcinomas originate from epithelial cells and tend to form clumps of cells with distinct borders [22]. The progression of growth for SCC in the areas of the globe (conjunctiva, cornea, and

limbus) and the third eyelid have a plaque as an initial precursor lesion [15]. A plaque then progresses to a papilloma, which often has a roughened surface, and usually progresses to a mass that is frequently pedunculated and moveable [15]. Generally the appearance of plaques and papillomas are white to light pink in color in the beginning, rough and flat, and then form masses [10, 15]. On the eyelids, the precursor lesion is a keratoma, which looks brown and crusty, and at times, a hornlike lesion [15]. Carcinoma in situ can arise from any of the precursor lesions or papillomas and are often asymptomatic [10]. The term carcinoma in situ is used to describe the stage before the neoplastic cells have infiltrated into the basement membrane of the epithelium and entered the subepithelial connective tissue to become true SCC [15]. In Joe's case, it is likely that when he first received treatment two years ago that the lesions were small and in the keratoma or papilloma stages, but the margins after resection were not clean and the cryotherapy was insufficient at exterminating the neoplastic cells.

Although the exact etiology of the SCC is unknown there are several key risk factors that a horse may have that enables SCC to begin to form and proliferate. One of the most documented risk factors is the prolonged exposure to ultraviolet radiation through sunlight [4, 5, 10, 15, 17]. Horses living in regions with increased longitude altitude and mean annual solar radiation have a higher likelihood of being diagnosed with ocular and periocular SCC [4]. Increased ultraviolet light exposure has been linked to causing mutations in the p53 gene [4, 5, 10, 15, 17]. The p53 gene is an important regulator of cell growth and proliferation, so mutations to it can compromise DNA repair and therefore cause abnormalities in apoptosis, which stimulates the formation of neoplastic cells [5, 17]. Overexpression of the p53 gene has been detected in both horses and humans with SCC [5]. In recent research,it has been hypothesized that SCC could be induced by papillomaviruses, but this has yet to be truly supported for ocular and periocular SCC

[19]. Finally, a higher frequency of ocular and periocular SCC has been reported in horses lacking pigmentation around their eyes [10, 15, 17].

Diagnostic Approach/Considerations

Joe's initial presentation to the ophthalmology service on June 22nd, 2017 allowed for us to format a plan of action against aggressive bilateral SCC. Again, ophthalmic examination revealed a 3x5cm pedunculated mass arising from the right upper eyelid that covered the right eye and a 1.5cm area of ulceration on the skin just medial to the medial canthus of the left eye. Patients presenting for an initial work up of potential SCC should undergo careful evaluation of the globe and adnexal structures and digital palpation of the bony orbit to determine the extent of the tumor [6]. Diagnosis by excisional biopsy is ideal for tumors that are small or in a favorable location, whereas incisional biopsy that includes normal tissue at the lesion margin is necessary for large masses that are in areas in which an incision with primary closure is not an option [6, 20]. Differential diagnoses for equine ocular and periocular SCC include: equine sarcoid, papilloma (third eyelid), mast cell tumor, exuberant granulation tissue, habronemiasis, phycomycosis, cutaneous lymphoma, and melanoma [15, 20].

Since Joe had been diagnosed with SCC by his referring veterinarian and presented for tumor recurrence, the initial biopsies were not performed. The other diagnostic tests carried out included fluorescein stain, slit lamp biomicroscopy, and digital palpation of the orbital rim. Slit lamp biomicroscopy revealed a 1cm area of keratitis on the right eye. The fluorescein stain was within normal limits and the orbital rim palpation had no evidence of bony invasion. Both of the dorsal eyelid lesions on the right eye were suspected to be SCC and were invading the medial canthus. Since this was a large area of eyelid that would not be able to be fully resected while

maintaining a healthy eye, exenteration was recommended. This would allow for the best chance to prevent recurrence of the mass. Because SCC is locally invasive, it is recommended to take 2 cm margins around tumors for complete removal. In the periorbital area, this is typically not possible due to the lack of tissue to close these large resections; in these cases, resection is performed with adjunctive treatment, such as chemotherapy or radiation. Because Joe's tumor was so large and was a tumor recurrence, it was decided to take the recommended 2 cm margins and to leave the orbit open to heal by second intention. This was done because we were already removing the eye and we knew it would not be able to be closed with these large margins. This technique has been reported in the literature for invasive tumors of the periorbital area [1]. For the left eye, a course of four carboplatin (chemotherapeutic agent) injections at two week intervals and surgical resection would be the best course of therapy. This area would not be able to be fully resected due to its location near the medial canthus, so the adjunctive chemotherapy was recommended. The first carboplatin injection was performed at the initial visit and the exenteration surgery of the right eye and surgical resection of the periorbital SCC was scheduled for two weeks later on July 6th, 2017.

Treatment and Management

There are several different treatment options and protocols available for management of periorbital SCC [18]. Treatment of ocular and periocular SCC depends on tumor location, tumor size, extent of invasion, vision status, the horse's purpose, available equipment, and the owner's financial constraints [10]. Modalities of treatment include: surgical excision including enucleation and exenteration (salvage procedures), surgical debulking (3rd eyelid resection and blepharoplasty), topical or intralesional chemotherapy (cisplatin injections, cisplatin beads, or

carboplatin injections), cryotherapy, radiofrequency hyperthermia, immunotherapy (bacilli Calmette-Guerin), radiation therapy, photodynamic therapy, and CO_2 laser ablation [2, 3, 10, 11, 15, 17]. Reported success rates vary and the extent of tumor involvement is not always well characterized [17].

The recommended course of treatment for Joe included exenteration of the right eye and the surgical resection and intralesional chemotherapy injections (carboplatin) for the lesions affecting the left eye. Complete exenteration of the eye is often required because of direct involvement of the intraocular structures or because of the affected periorbital structures needing to be excised to the extent that it would interfere with normal eye function, resulting in secondary pathology to the eye itself [1]. This procedure can be performed under standing sedation with local nerve blocks and allowed to heal by second intention due to the lack of tissue present allowing for primary closure. This is uncommonly reported in the literature. In reported cases where horses healed by second intention following exenteration, the majority of horses had a healthy bed of granulation tissue covering the surgical site by two months post-operatively and were fully healed with no evidence of recurrence by nine months. Postsurgical wound care was easily accomplished by owners and well tolerated by the patients in these cases [1]. Carboplatin, like cisplatin, is an active cytotoxic drug and when used as a systemic chemotherapeutic agent is limited by side effects such as substantial nephrotoxicity, neurotoxicity, and gastrointestinal toxicity. Combining the carboplatin in a water and sesame oil emulsion has been proven to be an effective and nontoxic formulation that slows the release of carboplatin. In addition the intralesional administration of the carboplatin emulsion has been proven to improve the therapeutic index by increasing the local drug concentration, thereby avoiding the general

circulation and the side effects that might ensue. The only main side effect of intralesional chemotherapy is acute local tissue reactions (tenderness, erythema and slight edema) [21].

Joe was sedated using acepromazine, then started on a CRI of detomidine and butorphanol to achieve standing sedation. Local blocks including: retrobulbar, auriculopalpebral, supraorbital, lacrimal, zygomatic, infratrochlear, and a ring block were performed on the right eye. The eyelids were sutured together and a two centimeter margins were measured in all directions from the affected tissue before beginning the incision. The globe and all orbital tissues were dissected out using sharp and blunt dissection in a transpalpebral fashion. The incision and orbit was left open to heal by second intention because of the size of the wound. Then on Joe's left eye, a ring block was placed around the ulcerated lesion at the medial canthus. The lesion was excised and closed with tension relieving sutures. This surgical site was expected to open due the tension, but the majority of the tumor tissue was removed. Continued adjunctive therapy for this tumor recurrence site included intralesional carboplatin injections and then adding in hyperthermia once the site had healed.

A course of treatment including both surgery and chemotherapy the prognosis for recurrence of SCC ranges from 25% to 67% [7, 8]. It is reported that in 85% of horses treated with both perioperative and post-operative injections of chemotherapy were still tumor-free after four years [20]. Patients that received intralesional chemotherapy injections followed by hyperthermia therapy saw a tumor time to response ranging from one to eight weeks [16]. With taking the research into consideration and applying it to Joe's case there is a good prognosis that he will remain tumor free for the next one to four years with the course of treatment he has received, but a main key to long-term success and management of SCC is the owner's willingness to return for re-examination [7].

Case Outcome

Histopathology of the right eyelid confirmed the diagnosis of SCC with an expansive, invasive, exophytic mass composed of cells arranged in nests and sheets in a fine fibrovascular to thick fibrous connective tissue stroma, containing 2-3 mitotic figures per high-powered field and the surgical excision was complete. While the histopathology of the biopsy collected from the left eye's medial canthus confirmed a diagnosis of SCC , the neoplastic cells did extend into the surgical margins and complete excision was not achieved. Joe returned to Mississippi State University College of Veterinary Medicine for three more visits; at each of these visits Joe received carboplatin injections and hyperthermia therapy in the area of the left medial canthus. A thorough examination of the exenteration site and wound management was performed at these visits. At the last visit, Joe's right surgical site had almost completely healed via wound contraction and growth of new skin over the orbit. The left medial canthal region had healed completely and one last set of carboplatin injections was performed with hyperthermia. It was recommended to watch this site closely for any regrowth and set a time monthly to closely evaluate the eyes. A fly mask that prevents 97% of UV light absorption was also recommended.

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