Review of the Treatment of Equine Cutaneous Neoplasia

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There are a variety of treatments available for cutaneous neoplasias in the horse. Therefore, it is important to consider the characteristics of the tumor being treated and the owner requirements when determining a treatment plan. The authors prefer to take an aggressive approach with surgical removal and/or debulking combined with chemotherapy for most tumors. Tumors that are static should be carefully monitored with monthly measurements of the mass. After the tumor starts to grow, it should be aggressively treated, because smaller masses are easier to treat. With careful management, cutaneous neoplasias can be successfully managed with one of the many treatments available. Authors' addresses: College of Veterinary Medicine, Department of Clinical Sciences, Auburn University, 1500 Wire Road, Auburn, Alabama 36849 (Hewes); and Marion duPont Scott Equine Medical Center, PO Box 1938, Leesburg, Virginia 20177 (Sullins); e-mail: cahewes@yahoo.com. © 2009 AAEP.

1. Introduction

The skin is the most common site for equine neoplasia. The most common cutaneous tumors are equine sarcoid, squamous cell carcinoma (SCC), melanoma, fibrosarcoma, and cutaneous lymphosarcoma, respectively. Factors that have been associated with these conditions include ultraviolet radiation, inflammation, trauma, and viral infections. To help the veterinarian make appropriate therapeutic decisions, this paper will review cutaneous neoplasia in the horse and the treatments available.

2. History and Physical Exam

The most relevant history includes the duration of the lesion’s presence and whether or not it is changing. Other health conditions and current medications should be discussed when obtaining the history.

A thorough physical examination should be performed. Other masses, alopecic areas, non-pigmented regions, mucocutaneous junctions, and cutaneous scars should be evaluated. Regional lymph nodes should be palpated, and this may necessitate a rectal exam. It is also important to look for other conditions that may mimic cutaneous or subcutaneous neoplasias, such as regional lymphadenopathy in a horse with a local infection, to ensure treatment of the entire patient and prevent missing metastases.

During and after the physical exam, there are some important questions to consider. Is the mass a cosmetic blemish or does it interfere with the use of tack? Is there a space-occupying effect or could the mass grow and cause a functional problem such as with large perianal melanomas or periorcular sarcoids? Could this mass be locally invasive and/or metastasize? Is the mass quiescent or increasing in size? Is the owner committed to a long course of treatment if required? Can this be treated in the field or does it need referral to a hospital?
3. Diagnosis

Some tumors may be diagnosed presumptively by the physical appearance, but histopathology should still be obtained. In most cases, an excisional biopsy is preferred for the sake of efficiency and to avoid activating or inflaming a tumor from a biopsy. Sarcoi's are known for rapid growth after trauma or irritation of the tumor. If the area is biopsied and rapid growth occurs before treatment initiation, imiquimod can be applied to the area to control transformation and possibly provide resolution (see treatment section). If the suspected tumor would be untreatable or impractical to treat if malignant, a Tru-Cut or other biopsy may be indicated.

Equine Sarcoi's

Sarcoi's are the most common cutaneous neoplasias in the horse. They are cutaneous fibroblastic masses with a proliferative epithelial component that are locally invasive and non-malignant. Particularly when there is no defining epidermal component in the section, sarcoi's are often classified with fibromas and fibrosarcomas, because they involve the connective tissue. All horses can be affected, but Appaloosas, Arabians, Quarter Horses, and geldings have an increased risk. Standardbreds seem to have a decreased risk.

Clinically, sarcoi's appear as linear or focal dermal thickening with a pale color and firm texture. However, there are multiple types of sarcoi's based on physical characteristics and clinical behavior that can occur simultaneously. Occult or flat sarcoi's (Fig. 1) are alopecic with sometimes subtle mild scaling. Verrucous or warty sarcoi's (Fig. 2) have a raised scaly, lichenified appearance with hair loss and epidermal thickening; these may be inactive for long periods of time. Fibroblastic sarcoi's (Fig. 3) are raised subcutaneous masses that are classified as nodular sarcoi's if the skin is unaffected or ulcerative if the skin surface is disrupted. Malevolent sarcoi's spread along fascial planes and vessels.

Sarcoi's most commonly affect the head (pinnae, commissures of the lips, and periorally), neck, legs, and ventral body surface. Sites of trauma or long-standing open wounds are also prone to develop sarcoi's. The head and abdomen may be more commonly affected in colder climates, whereas the legs are affected more often in warmer climates. Quiescent lesions may become aggressive if injured, biopsied, or treated unsuccessfully. There are a variety of differential diagnoses including granulation tissue, papillomas, dermatophytosis, linear hyperkeratosis, rub marks, habronemiasis, infectious granulomas, melanomas, mast cell tumors, SCC, equine eosinophilic granulomas, neurofibromas, fibrosarcomas, fibromas, lymphosarcoma, and staphylococcal folliculitis.
Histopathologic characteristics include epidermal acanthosis, hyperkeratosis, and pseudoepitheliomatous hyperplasia with long rete ridges into the dermal fibroblastic tissue containing immature fibroblasts with mitotic figures in a skewed or whorled fibrocellular mass. Fibroblasts orientated perpendicularly to the basement membrane produce a "picket fence" appearance.

SCC
SCC (Fig. 4) is the second most common cutaneous mass in horses that affects mucocutaneous junctions or external genitalia; ocular and periocular lesions are also common. Less common but important sites include the stomach, esophagus, paranasal sinuses, hard palate, pharynx, larynx, perianal tissue, ear canal, hoof, tongue, and guttural pouches. Appaloosas, Paint Horses, Pintos, and draft horses seem to be predisposed, but any breed or color may be affected. Increased risk also occurs from chronic exposure to sunlight. Penile and pre-putial lesions are more likely with excessive smegma, persistent paraphimosis, or repeated trauma. Burn scars and chronic non-healing wounds may also be predisposed to SCC.

Lesions are often solitary and can be erosive or productive. Nodular masses with seemingly intact skin may appear early followed by ulceration and/or necrosis. Some lesions gradually expand to develop a craterlike appearance or an expansive papillary mass may occur. Early lesions around the eye and on the penis are white raised plaques. Of SCC, ~18.6% metastasize. Differential diagnoses include sarcoids, granulomas, lymphosarcoma, and other nodules on the skin. Histologically, SCC have irregular masses or cords of keratinocytes that invade the dermis and beyond. Focal areas of keratin surrounded by tumor cells (keratin pearls) and inflammation are defining features.

Melanoma
Melanomas (Fig. 5) are masses that arise from melanocytes, dendritic cells of neuroectodermal origin, or melanoblasts. The third most common skin tumor in horses, melanomas are common in aging grey horses with Arabians, Thoroughbreds, Percherons, and dappled horses that undergo depigmentation being predisposed. Common locations include the ventral surface of the tail, the perineal region, and the external genitalia, but they also frequently occur in the parotid region, neck, and ears. Less commonly, eyes, limbs, and spinal cords may be affected, but any external or internal location may have melanomas.

Clinically, melanomas are firm, flat, solitary or multiple, non-ulcerated, discrete to coalescing cobblestone-like subcutaneous masses. Melanomas in grey horses are locally expansible and may become very large. In non-grey horses, these tumors are aggressive and often have widespread dissemination months after diagnosis. These horses often have amelanotic melanomas. They have a high
metastatic potential because of their poor differentiation and rapid mitotic rate, which is similar to melanomas in dogs and humans. Histo-pathologically, melanomas have atypical melanocytes in sheets, nests, or cords, and they have a close association with epidermal sweat glands and hair follicles.

Lymphosarcoma/Lymphoma
Lymphosarcoma (Fig. 6) is a lymphoid neoplasm that may occasionally involve the skin. There is no breed or sex predilection, but most horses with the cutaneous form are between 4 and 9 yr of age. Clinically, there is slow development of solitary or multiple, non-painful, well-circumscribed lesions, but a cobblestone appearance underneath intact skin can occur. Clinically, horses may present as systemically ill with depression, weight loss, anemia, leukemia, and peripheral lymphadenopathy or with a multifocal to generalized exfoliative dermatitis. In one-half of the cutaneous cases, regional lymph nodes are enlarged. Diagnosis is by biopsy of the affected skin with nodular to diffuse infiltration of the deep dermis and subcutis with lymphocytes. Differential diagnoses include dermatitis, urticaria, or another nodular condition of the skin. Prognosis for dermal lymphoma is often poor despite a variety of treatments. However, solitary lesions may have a good prognosis if completely resected.

4. Treatment Options
Treatment should be based on tumor type and location, primary and secondary effects of the tumor, growth rate of the tumor, complications of the treatment, sensitivity of the tumor type to the particular treatment, clinical experience of the veterinarian, available equipment and facilities, treatment cost, patient behavior, and owner compliance. Preparing the owner for repeated treatments and possible tumor recurrence is important before starting treatment.

Surgical Removal
Surgical removal is the simplest treatment available and usually preferable if a primary closure is possible or applicable. If sufficient tissue is available, a margin of 0.5–1.0 cm should be excised. Releasing skin incisions may be necessary to close the defect or the wound bed may have to remain open. Debulking of a tumor is always helpful if adjunctive therapy is planned. Unless complete removal is achieved and the potential of recurrence is consequential, adjunctive therapy should be considered. Local chemotherapy is a practical option, but laser treatment of the wound bed is also beneficial (see other treatment sections).

Success rates for surgical removal alone vary between the different tumor types. Sarcoïds have reported recurrence rates of 15–82% with most tumors recurring in 6 mo. The long rete ridges into the dermal fibroblastic tissue have been mentioned as a potential factor, which would be an issue with surface resection and supports the use of adjunctive local chemotherapy. These deeper dermal extensions of the tumor are visible while performing partial (skin) thickness laser removal of sarcoïds. In the authors’ experience, surgical resection with a primary closure is effective. Focal recurrences that may occur along the suture line can be addressed while they are still very small. SCC also has a tendency to recur with surgical excision alone and commonly recurs after local chemotherapy. Both melanomas and basal cell tumors can be successfully removed without adjunctive treatment. Subjectively, the typical melanoma seems to be relatively metabolically inactive and minimally affected by local chemotherapy, which makes debulking a better choice. There may be surrounding miliary foci of potential new tumors that may benefit from adjunctive chemotherapy, but they will persist longer than the drug. Mast cell tumors also have a high success rate with surgical removal alone; 2 of 25 cases had reported recurrences after 6 yr. Lymphosarcoma is a systemic disease and will be discussed under chemotherapy.

Laser Excision/Vaporization
Laser excision provides a clean, visibly well-demarcated line to remove the tissue along the incision. Appropriate power density and movement along the tissue ensures that the margins remain viable and that primary healing will occur. Laser resection provides coagulation of blood and lymphatic vessels and sanitization of the wound surface by destroying bacteria and fungi. By sealing vessels and having most of the laser energy absorbed by the nearby tissue, the tumor cells are killed just beyond the wound margin. Without proper laser surgical technique, an increased collateral thermal effect can be seen, because the CO2 laser energy penetrates 0.2
mm into the surface of the tissue. Although the CO$_2$ laser definitely vaporizes tumor cells, it affects only the most superficial layers of cells; any tumor cells killed in the process would be considered collateral damage. Additionally, laser energy can be directed to precisely remove the desired margins or depths of tissue. In addition to excision, the CO$_2$ laser can also be used to debulk tumors by vaporization. This is useful for areas that cannot be excised such as the sheath, peri-orbital tissue, cornea, or flat tumors. The vaporization should be performed at least one cell layer past all abnormal cells. If recurrence occurs, it is likely because of incomplete removal of abnormal fibroblasts from inadequate depth or inadequate laser settings. Complications from this treatment include tumor return and dehiscence of the primary wound. In a series of cases, only 5 of 15 sarcoids and 2 of 9 SCC recurred after removal with the CO$_2$ laser.

Cryosurgery

Liquid nitrogen destroys cells through the formation of intracellular ice, causing rupture of the cell membrane. It should be administered with a thermocouple in place to monitor the temperature and depth of the freeze. A total of three freeze and thaw courses is used with the temperature reaching from $-20^\circ$C to $-30^\circ$C. Normal tissue within 1 cm of the tumor is also treated to prevent recurrence of the tumor. Cryotherapy is used commonly, and reported success rates are 9–100%. Multiple treatments may be necessary to cure the tumor, because it only penetrates a short distance beneath the skin. In the authors' experience, cryotherapy is best used for early pre-cancerous lesions, especially on the penis and prepuce. Although direct cell death occurs, immune stimulation may occur, because tumors have regressed elsewhere after cryosurgery on the primary mass. Many complications can occur post-treatment, including local swelling, hyperemia, hemorrhage, and edema. Because the freezing can injure all nearby tissue, the nearby anatomy may require protection to prevent serious complications, such as weakening cortical bone, nerve damage, septic arthritis, or evisceration of the globe. Extreme scar contraction or cosmetic blemishes may also occur with white hairs at the treated site.

Hyperthermia

Hyperthermia is a relatively conveniently applied technique that raises tissue temperature to 50°C for 30 s. Tumor growth is affected, because neoplastic cells are more sensitive to heat than normal cells; only small areas are affected, which limits the collateral heating of normal tissue. Its limitation is that only foci $\leq$1 cm in diameter can be treated per application; multiple applications are required for anything larger. This works well for focal lesions such as corneal SCC or periocular sarcoids. Palliation of inoperable tumors is a useful application. Radiofrequency current-induced hyperthermia was reported to induce regression in 3 sarcoids 7–12 mo after treatment in one study. The treatment was repeated multiple times at 1- or more wk intervals.

Immunotherapy

Mycobacterium cell-wall extracts, whole cell bacille Calmette-Guérin (BCG), and propionibacterial cell wall extracts are thought to stimulate cell-mediated immunity by causing recognition of tumor antigens as foreign. Success rates from 83–100% were seen with periorcular sarcoids, but lower success rates (48%) were seen with sarcoids on the remainder of the body. BCG has not been effective in treating melanocytic tumors or SCC.

Although excellent success rates with treatment of periorcular sarcoids have been seen, severe inflammatory reactions can occur including extensive swelling, fevers up to 104°F, ulceration and necrosis of the tumor, leukocytosis, and general malaise. Death from anaphylactic shock, non-fatal anaphylaxis, and septic arthritis has occurred. Pre-medication with flunixin meglumine and corticosteroids is strongly recommended. However, an inflammatory reaction is an expected and desirable occurrence after the sensitizing injection.

Other forms of immune stimulations have included taking a small biopsy of the sarcoid, treating the biopsied mass with cryotherapy, and implanting small pieces of the biopsied mass under the mane. Success rates of 100% have been seen in the one field study. For horses with multiple masses or masses in difficult locations to treat, some veterinarians have tried to produce vaccinations from small pieces of the excised tumor to allow for tumor-antigen recognition. This has seemed to be successful in some individual cases but has not gained widespread use.

Topical Immune Modulation

XXTerra is an herbal solution of bloodroot powder (sanguinarine), zinc chloride, and water. It has been used with a $>95\%$ success rate with sarcoids (according to the manufacturer), but 40% of horses need a second treatment 60 days after the first. The cream is applied to the tumor in a thin layer, and it results in sensitivity to the region. By altering the antigenicity of the tumor and stimulating the host’s immune system, the sarcoid is destroyed. Extreme activation of sarcoids has also occurred.

Imiquimod 5% is an imidazoquinolinamine that is an immune response modifier. The ointment is applied to the mass three times per week on non-consecutive days for 32 wk or until the mass resolves. Twelve of fifteen sarcoids (80%) showed a $>75\%$ reduction in size. Nine sarcoids (60%) totally resolved between 8 and 32 wk. The most common adverse effects of exudation, erythema, erosions, depigmentation, and alopecia were limited to
the tumor and adjacent areas. It has also been successfully used to treat epidermal and melanoma lesions. It is administered daily or every other day for 3–5 treatments. It has been primarily used on sarcomas, and the tumor necroses 5–10 wk after treatment. During treatment, the mass appears to worsen with a more inflamed appearance before resolution. Preferential necrosis and sloughing of sarcoïd-affected skin occurs, whereas normal tissue is left unaffected. If no change is seen in 5–10 wk, then repeated treatment or a different treatment should be considered. With the initial version of the cream, 80% of sarcoïds resolved. The use of this cream is controlled by the University of Liverpool and is only sold for use by veterinarians.

5-fluorouracil is available as a topical cream that is often used for early or small neoplastic lesions. A 90% success rate has been reported for early SCC lesions on the male external genitalia. The authors often use it concurrently with intralesional therapy with cisplatin for sarcoïds at the recheck examination if the skin is flat and alopecic. The cream should be used daily until the affected region is red, inflamed, and irritated (10–14 days). The skin should be allowed to heal, and application of the ointment begins again until irritation occurs. Fluorouracil is retained in the prepuce for 10–14 days, which simplifies treatment of SCC in that location. Because fluorouracil works best in lesions that are active, debulking or laser debridement is recommended before use.

Intralesional Chemotherapy

Intralesional cisplatin (injectable suspension or absorbable beads) is the most common locally applied chemotherapeutic agent used in the horse. To make the suspension, 10 mg of powdered cisplatin, 1 ml of sterile saline, and 2 ml of medical-grade sesame oil are mixed to make a solution that is 3.3 mg cisplatin/ml. One milligram of cisplatin is injected per 1 cm³ of tissue. The injections should be repeated every 2 wk for four treatments and should start at the time of surgery if surgical debulking is performed.

The cisplatin beads are available pre-made from a commercial source. To implant the beads, the tumor is debulked if it is >1.5 cm in size. The beads are then placed through stab incisions in the surrounding skin, tumor bed, or subcutaneous tissue and secured with absorbable suture at 1.5-cm intervals. If no debulking is performed, the mass is blocked with local anesthetic, and the beads are placed through stab incisions every 1.5 cm throughout the mass. In an area with minimal soft-tissue covering, such as the eyelids and distal limbs, overdosing the chemotherapeutic agent can produce tissue sloughing. In these areas, the authors have cut beads in half and implanted at 3-cm intervals. The beads release cisplatin over 30 days. Reapplication is generally advisable. In general, intervals are 2 treatments for sarcoïds, 3 treatments for SCC, and 1 treatment for other tumors. However, every tumor is different, and requirements may vary. SCC, in particular, can appear greatly improved and later relapse, which makes extended treatment advisable. All horse should be rechecked 30 days after their last chemotherapeutic treatment to monitor for tumor recurrence.

The success rates with the injections and the beads are similar. A long-term study of cisplatin injections revealed that overall tumor resolution at 4 yr was 96.3% for sarcoïds, 96% for lymphomas, 88% for SCC, 85% for soft tissue sarcomas, and 81% for melanomas. A lower prognosis was found for large tumors, tumors with gross post-operative residual disease, and tumors that had been treated previously with other modalities. Although treatment was well tolerated, local reactions were more likely to occur and to be more severe after the third and fourth treatment sessions.

The success rate with the cisplatin beads 2 yr after treatment was 91% of animals (20 of 22) with spindle cell tumors (sarcoïds, fibrosarcomas, and fibromas), 60% of animals (6 of 10) with SCC, 93% of animals (13 of 14) with melanomas, and 67% of animals (2 of 3) with other tumor types. Adverse effects were minimal and included small areas of alopecia, short-term local swelling, and mild scarring. Advantages of the cisplatin beads over the cisplatin injection is the ease of handling, improved safety over injections into firm tissue, and less frequent treatment. This may improve owner compliance and allow for successful treatments for cutaneous neoplasias.

Other intralesional chemotherapeutic agents include bleomycin, 5-fluorouracil, and carboplatin. Bleomycin is very expensive and has a narrow spectrum of activity. Fluorouracil was not as effective as cisplatin in treating SCC in horses but was effective for treating basal cell carcinomas.

Other Systemic chemotherapy has been used for cutaneous lymphosarcoma, because the disease is systemic and has a very poor prognosis. Multi-agent chemotherapy is recommended. One protocol includes cytosine arabinoside, chlorambucil, and prednisone. Another protocol includes L-asparaginase, cyclophosphamide, intralesional cisplatin, and combinations of cytosine arabinoside with prednisone. Vincristine can be added if remission has not been seen in 4 wk. One horse responded well to low-dose cyclophosphamide and an autogenous tumor-cell suspension.
Cimetidine is a histamine (H₂) receptor antagonist that may enhance cell-mediated and humoral immunity by antagonizing the stimulating effects of histamine on suppressor T cells. The recommended dose to treat melanomas is 2.5 mg/kg orally every 8 h. This drug may impede progression of melanomas and possibly decrease the size and number of melanomas by 50–90%. If no effect is seen in the first 3 mo of treatment, cimetidine should be discontinued. Others find that the cimetidine treatment is not effective.

**Radiotherapy**

Radiotherapy is the use of ionizing radiation to kill tumor cells and is often used when surgical resection would have an unacceptable functional outcome. With radiation, cell death occurs by injuring DNA to prevent replication and by injuring critical proteins to prevent cell function. Because of the inhibition of growth, three prognostic factors for response to radiation are tumor volume, type, and location. Fast-growing tumors are more responsive to radiation than slow-growing masses. SCC, papillomas, and sarcoids are more responsive to radiation than other soft-tissue sarcomas and melanomas. Surgery should be combined with radiation, if possible, to minimize the radiation dose.

Two forms of radiation are available: teletherapy and brachytherapy. Teletherapy is where the radiation source is a long distance (80–100 cm) from the tumor. This would be a linear accelerator or cobalt-60 unit providing high-energy X- or γ-rays. This is often used for ocular neoplasias, nasal cavity, paranasal sinuses, and oral-cavity tumors with bony involvement. The treatment requires multiple anesthetic episodes for the typical 6–9 treatments over 3–4 wk. It is a very expensive treatment and is often palliative, because most of the tumors are advanced by the time of treatment. Success rates of >50% have been seen with lymphoma, SCC, and odontogenic tumors.

Brachytherapy is where a sealed radiation source is applied to the affected area. This allows for a high dose of radiation to be applied directly to the tumor. Examples include strontium-90 and interstitial brachytherapy (iridium-192 and iodine-125). With strontium-90, the radiation source is β radiation and is directly applied to the abnormal region. Because the radiation only penetrates within 2 mm of the probe, lesions must be superficial. General anesthesia is required for acute positioning of the probe. Small superficial tumors of the eye (SCC of the limbus, cornea, or nictitating membrane) are often treated with a success rate of 83% when combined with a superficial keratectomy and permanent bulbar conjunctival grafts. Minimal complications occur with this radiation source because of the focused source of radiation and minimal penetration of tissue.

Local implantation of iridium-192 is the most common form of interstitial brachytherapy performed in the horse and is most commonly used for soft tissue neoplasms of the head, distal extremities, and genitalia. Because it is available in grains or wires for implantation, the radiation source is most easily implanted into the tissue after surgical debulking during anesthesia. This also improves the effect on the residual neoplastic cells. The radiation source remains in the tissue for the next 3 wk. Success rates for treatment of sarcomas were 86.6% at 1 yr and 74% at 5 yr. Success rates for treatment of carcinomas were 81.8% at 1 yr and 63.5% at 5 yr. Complications include hair depigmentation, permanent epilation, palpebral fibrosis, cataract, keratitis, and corneal ulceration. Although the complications can be severe, radiation may be the only option for invasive tumors.

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