

Equine Melanocytic Tumors

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KEYWORDS

- Horse • Melanoma • Treatment • Immunotherapy • Genetics • Vaccine • Chemotherapy

KEY POINTS

- Melanomas are among the most common skin tumors in horses (second only to sarcoids), with prevalence rates reaching as high as 80% in adult gray horses.
- The overwhelming majority of melanocytic tumors are benign at initial presentation; however, if left untreated up to two-thirds can progress to overt malignant behavior.
- Standard local treatment options can be used to treat solitary early-stage lesions but do not address the underlying risk of recurrent tumor formation or the transformation to a malignant phenotype.
- Advances have been made in elucidating the molecular link between the normal process of graying and the development of melanocytic tumors with the goal of identifying new therapeutic options for affected horses.



Video of melanoma vaccine administration in horses accompanies this article

INTRODUCTION

Melanocytes are dendritic cells derived from neuroectodermal melanoblasts that have migrated during embryogenesis to the epidermis, dermis, and other sites (eg, eye, inner ear, meninges). Through the process of melanogenesis, these cells produce a pigment called melanin, which can be found in the skin, eyes, and hair. The color of this pigment is dark and so it absorbs UV-B light and blocks it from passing the skin layer into the hypodermis, protecting it from the harmful effects of solar radiation.¹

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Melanomas are tumors that arise from the malignant transformation of normal melanocytes. The cause of melanocytic tumor development is still not completely understood; however, current data suggest that tumors develop secondary to genetic mutations in the melanin metabolism molecular pathway. These mutations may increase the activity of resident melanoblasts, leading to a relative overproduction of melanin in the dermis and ultimately the malignant transformation of these cells. Genetic mutations are most commonly inherited, and certainly related to gray coat color; however, an association between increased UV radiation exposure and tumor growth has also been suggested.² Melanocytic tumors have been described in various domestic animal species, including dogs, cats, cattle, sheep, alpacas, and swine, although their prevalence and economic impact appear to be the highest in the horse.^{3,4}

EPIDEMIOLOGIC ASPECTS OF EQUINE MELANOCYTIC TUMORS

Melanocytic tumors have been recognized for centuries in horses and are among the most common skin tumors noted in this species, comprising between 3.8% and 15.0% of all skin tumors, second only to sarcoids.⁵⁻⁸ According to some studies, the incidence of these tumors in horses in North America may be increasing in parallel with the incidence of human melanoma.^{9,10} Although it has been suggested that a gender predisposition exists, this has not been established.^{7,11,12} In contrast, although melanomas have been diagnosed in horses of all colors, a marked predisposition has been extensively reported in gray horses, with prevalence rates reaching as high as 80% in older animals.^{7,11-14} Melanocytic tumors are seldom observed in gray horses younger than 5 years and congenital tumors are rare.^{11,15} Reports of breed predilection have suggested an increased risk for Arabian, thoroughbred, Lipizzaner, Camargue, and Percheron horses, but this association may simply reflect the higher number of gray horses in these breeds.^{12,16-20} Although melanomas clearly are more frequent in gray horses, they also occur in nongray horses, where they are more likely to exhibit malignant behavior.⁷

MOLECULAR GENETIC BASES OF EQUINE MELANOMA

The increased incidence of melanomas in gray horses has been linked to the graying process these horses experience at approximately 5 to 8 years of age when they start a gradual loss of follicular pigmentation while maintaining a dark skin.^{21,22} This graying process is an autosomal dominant trait that is associated with an increased risk of both melanoma and vitiligo.²¹⁻²⁴ Studies have been undertaken to elucidate the molecular basis of the graying process and associated melanocytic tumors as a comparative model for human melanoma.^{13,24,25} Recent work has identified the genetic basis for the premature graying as a 4.6-kb duplication in intron 6 of the syntaxin 17 gene (*STX17*), which leads to the overexpression of *STX17* and the neighboring gene *NR4A3*.²² This duplication also appears to contain regulatory elements that have melanocyte-specific effects; transforming a weak enhancer to a strong melanocyte-specific enhancer that encodes binding sites for the microphthalmia-associated transcription factor (*MITF*).²⁶ *MITF* regulates melanocyte development and these binding sites within the *STX17* gene provide a plausible explanation for the melanocyte-specific effects of the Gray allele, including hair graying, melanoma susceptibility and vitiligo. Although the *STX17* mutation is inherited in an autosomal dominant fashion, the risk for melanocytic tumor formation and the other traits associated with this mutation appear to be polygenic.^{22,26}

Mutations in melanocortin-1 receptor (*MC1R*) signaling have also been studied to determine their role in melanocytic tumor development.^{27–29} Specifically, a single nucleotide polymorphism in *MC1R* (C901T) has been linked to chestnut coat color and resultant low risk of melanocytic tumor development.²⁸ A loss of function mutation (AEx2) in the agouti signaling protein (*ASIP*), a known antagonist of *MC1R*, has been linked to black coat color and an increased risk of melanoma formation.²⁸ In addition to the upregulation of downstream genes, such as tyrosinase, enhanced signaling through the *MC1R* pathway has also been shown to result in markedly increased expression of the *NR4A* nuclear receptor subgroup in melanocytic cells.²⁹ As pointed out previously, overexpression of *NR4A3* has been found in gray horse melanomas, although it has not been directly associated with the development of melanocytic tumors in humans or horses.^{22,30}

The genetics underlying the malignant transformation of melanocytic tumors has also been investigated. For example, copy number expansion of the *STX17* duplication has been identified within the tumor tissue of gray horse melanoma; the authors have speculated that the increasing copy number may be associated with tumor aggressiveness.³⁰ The Receptor for Activated C Kinase 1 (*RACK1*), a protein that serves as an anchoring point for protein kinase C, and in this role, likely plays a vital part in cellular signaling, has also been associated with melanocytic tumor transformation. Immunofluorescence studies suggest that *RACK1* expression levels can be used to differentiate between benign and malignant melanocytic tumors.³¹

PATHOLOGY AND NATURAL BEHAVIOR

Equine melanocytic tumors have been recognized for centuries as slow-growing, low-grade neoplasms. Although most cutaneous melanomas are benign at initial presentation, if left untreated, up to two-thirds can progress to overt malignant behavior capable of extensive local invasion and widespread metastasis.^{3,7,12} The most common external locations for melanocytic tumors include the perineal region, the ventral surface of the tail, the prepuce, the commissures of the lips, and the head/neck, whereas the parotid salivary gland, ears, eyelids, and limbs are less common sites (**Fig. 1**).^{2,4,7,8,12,32} From these primary locations, metastasis may occur by either hematogenous or lymphatic spread to any region of the body, including lymph nodes and other cutaneous sites,^{4,7,33} although there is an apparent predilection for the serosal surface of the spleen, liver, and lungs (**Fig. 2**).^{10,12,32} Major blood vessels (including the aorta), and even the heart, appear to be other structures commonly associated with metastatic disease.^{4,32,33} Other reported metastatic locations include the spinal cord, vertebrae, kidneys, adrenal glands, and guttural pouches.^{32–36} Rarely, melanomas may occur solely in visceral locations without any noticeable external disease sites.²

Tumor Classifications

The term melanocytic tumors encompass all histologic and clinical variants from the benign melanocytoma (nevus) to the more anaplastic malignant variants.³ In nongray horses, these tumors include only benign and malignant variants. In gray horses, however, there seems to be a clinical continuum between benign and malignant tumors and the “melanocytic” disease process is further extended to include hyperpigmentation and infiltration of the dermis and epidermis, resulting in plaque-like lesions rather than true masses or tumors.^{12,36} Tumor histology typically reveals a mildly to moderately pleomorphic population of neoplastic melanocytes, with an epithelioid to spindle shape, euchromatic nuclei, rare binucleation, variable and often high cytoplasmic

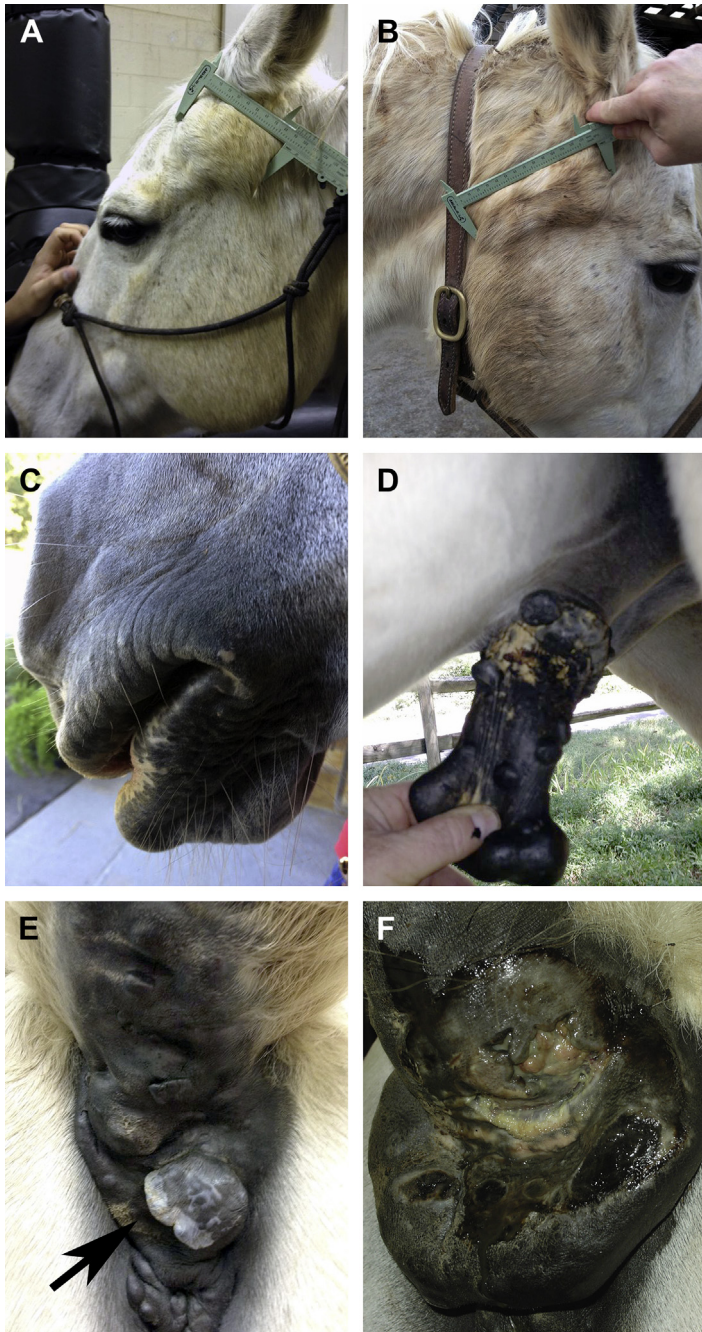


Fig. 1. Classical presentations and locations of equine melanomas. (A) Subcutaneous melanoma located in the temporal region. (B) Invasive melanoma associated with the parotid salivary gland. (C) Dermal melanoma located at the commissure of the lip. (D) Multiple dermal melanomas on the penis and prepuce. (E) Multiple confluent perianal melanomas (dermal melanomatosis); note areas of marked depigmentation within the tumors (arrow). (F) Large dermal melanoma at the ventral surface of the base of the tail; note further complication by ulceration and infection.

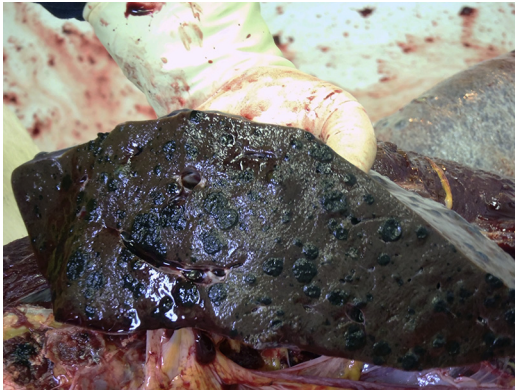


Fig. 2. Splenic parenchyma severely compromised by diffuse metastatic lesions. This image was obtained at necropsy of a gray horse that presented with a large necrotic dermal melanoma at the base of the tail. (Courtesy of Dr Karla Clark, Nashville, TN.)

pigmentation, and occasional mitoses.^{3,37} Tumors in gray horses are classified into distinct histologic subtypes based on a combination of tumor cell morphology and location within the cutaneous adnexa. Benign-appearing collections of melanocytes located in the superficial dermis or dermo-epidermal junction are classified as melanocytomas (melanocytic nevi). Tumors located within deep dermal locations composed of well-differentiated melanocytes that exhibit dense cytoplasmic pigmentation and minimal malignant criteria are classified as dermal melanomas. Dermal melanomas are further subdivided clinically into those with few discrete nodules and those with a more disseminated variant with multiple, frequently confluent tumors (dermal melanomatosis) (see **Fig. 1E**). An alternate descriptive classification relies only on tumor cell morphology and traditional malignancy criteria to group tumors into either benign or malignant variants. Benign variants contain well-differentiated and heavily pigmented melanocytes that can exhibit a variable mitotic index and are often contained within a pseudocapsule. Malignant tumors are characterized by increased pleomorphism, variable pigmentation, moderate to high mitotic rates, evidence of vascular and/or lymphatic invasion, epidermal invasion, and indistinct tumor margins.^{3,7,12}

OVERVIEW OF CLINICAL PRESENTATION

Cutaneous melanocytic tumors tend to be easily recognizable as darkly pigmented nodules; however, depigmented areas can often be identified within tumors (see **Fig. 1E**). Furthermore, amelanotic or poorly pigmented tumors may occur in both gray and nongray horses. Tumors can be localized in the deeper dermal tissues or may involve more superficial dermis and epidermal tissue. The latter will often ulcerate through the epidermis as they progressively enlarge (see **Fig. 1F**), which can also result in central portions becoming necrotic as they outgrow their blood supply.

Clinical signs in affected animals are determined by tumor location. Signs can range from simple interference with bridle and saddle caused by cutaneous lesions (which can be further complicated by ulceration and infection) (see **Fig. 1F**) to more severe signs associated with the local invasion and the compressive effects caused by internal metastatic lesions.³² Among the latter, weight loss, constipation, impaction, and even colic associated with serious obstructive lesions in the gastrointestinal tract

have been reported.^{18,32} Furthermore, neurologic signs, including lameness, ataxia, and even paresis secondary to spinal cord compression by metastatic lesions, and less commonly Horner syndrome and unilateral sweating have also been reported.^{32,34–36,38–40}

DIAGNOSIS AND WORKUP

The diagnosis of melanoma in equine patients is usually made on the basis of signalment (gray horse) and the physical appearance of the tumors. In select cases, including nongray horses and/or poorly pigmented tumors, biopsy can provide a definitive diagnosis. The differentiation between benign and malignant variants is typically made on the basis of all of these factors in addition to local growth pattern and the presence/absence of systemic involvement.^{7,10,12,32} Molecular tests may also be useful^{3,30,31,37}; however, their wide-scale reliability for differentiating benign from malignant tumors has yet to be demonstrated.

Diagnostics, such as blood work and imaging, are rarely pursued unless specific signs are present that cannot be directly accounted for by visible tumor burden, such as weight loss, chronic colic, neurologic deficits, and lameness, among others.^{32,35} Blood work findings are nonspecific and may show elevated globulins, increased white cell count, thrombocytosis, or increased fibrinogen presumably attributed to the inflammatory effects of tumor burden. Diagnostic imaging can be used to determine the cause of clinical signs, although the limited number of effective treatment options for internal tumors limits their usefulness. Rectal palpation can also be useful, especially in patients with perianal melanomas, to assess the extent of these lesions and determine if they may interfere with normal defecation or could do so in the future.

TREATMENT OPTIONS

Treatment options can be divided into those therapies intended to treat the local tumor and those meant to treat and/or prevent systemic disease spread. Appropriate management of advanced cases, however, will require the combination of both approaches to achieve a successful outcome.

Local Therapies

Local therapeutic options are used to treat solitary tumors or control locoregional disease. Treatments are typically applied directly to the tumor or into the peritumoral tissue.

Surgery

Surgical resection is considered the mainstay of local therapy and is often curative, especially for small benign lesions. In some patients, however, large tumor size or anatomic location (eg, parotid region) may preclude surgery as a feasible option. Surgery can also be used to debulk more advanced tumors for palliation of symptoms and can be variably successful.^{4,7,12,32,33,41}

Radiation therapy

Radiation therapy is limited in applicability because of the difficulty in treating large and/or deeply seated tumors, along with the limited availability of this modality for equine patients. Radiation, including both teletherapy and brachytherapy, has been used, however, to treat smaller tumors.⁴² Teletherapy refers to treatments where radiation is supplied by an external source located some distance from the patient

and requires the use of a linear accelerator or cobalt-60 unit. Horses must also be under general anesthesia during the process and the total prescribed dose is typically delivered through multiple treatments. Few reports have documented the efficacy of this type of radiotherapy in the horses because of the inherent difficulties of use in the equine patient.⁴² Brachytherapy, on the other hand, refers to treatments in which the source of radiation is placed either close to or directly within the tumor tissue and the total prescribed dose is delivered in a single or small number of treatments.⁴² Although both approaches have been successfully used to treat/control solitary melanomas in horses, in the authors' opinion, brachytherapy holds the most promise in the equine patient because of lower costs and ease of use. A recent advance in brachytherapy has been provided by the Axxent brachytherapy system (Xoft, Inc, San Jose, CA), which is completely radio electronic and allows therapeutic radiation to be delivered without the use of radioactive sources and with minimal shielding.

Intratumoral chemotherapy

Intratumoral chemotherapy involves the injection or placement of cytotoxic drugs directly into the tumor or peritumoral tissue (Fig. 3A). This approach has the advantage of delivering high drug concentrations to the tumor (higher than those obtained by



Fig. 3. Intratumoral chemotherapy and hyperthermia administration. (A) Large perianal melanoma that is being treated with intratumoral injections of cisplatin. Needles are pre-placed evenly throughout tumor. (B) The tumor was then treated with local hyperthermia using a prototype microwave therapy unit (Thermofield System; Parmenides, Inc). Massive tumor shrinkage was achieved clinically in this patient.

systemic infusion of the same drug) in a cost-effective manner while avoiding systemic drug side effects. Drugs that have been used effectively in horses include carboplatin and cisplatin.^{2,4,7,33,43} These can be injected directly or combined with oil (3:1 ratio) at a dosage of approximately 1 mL drug per cm³ of tumor tissue (maximum of 100 mL of drug for the average horse). Oil emulsions are created with the goal of delaying systemic absorption; however, in the authors' experience, their main effect is transient swelling and edema of the peritumoral tissue. Response rates for equine melanomas treated with intratumoral cisplatin have been reported as high as 81%, and are suggested to be inversely related to tumor volume.⁴³

Chemotherapy can also be delivered into the tumor through the use of biodegradable drug-containing beads. Such beads are marketed under the trade name Matrix III beads (Royer Biomedical, Inc, Frederick, MD) and can be impregnated with either cisplatin (1.6 mg/bead) or carboplatin (4.6 mg/bead). In one retrospective study, a variety of cutaneous tumor types, including 14 melanomas, were treated by the surgical implantation of cisplatin-containing beads. Treatment consisted of either the implantation of a single bead directly into smaller tumors or multiple beads (~2 cm apart) into the wound bed of surgically debulked larger tumors. Most horses received a single treatment and all but one remained tumor free more than 2 years after implantation.⁴⁴

Strategies have also been developed to improve the activity of intratumoral chemotherapy for the treatment of solid tumors in horses. Drug additives, such as epinephrine or sesame oil, may be used to delay systemic absorption. Other modalities, including hyperthermia and electrochemotherapy, can also be used to increase tumor cell uptake of chemotherapy and thus improve clinical response. Hyperthermia is a therapeutic modality in which localized heat is used either alone or in combination with chemotherapy to treat solid tumors. Tumor tissue can be effectively heated using ultrasound, radiofrequency, or microwave energy.⁴⁵ Radiofrequency techniques have been described for the treatment of equine melanomas but are limited to small (~2–3 cm) and easily accessible lesions.⁴⁶ A novel system that uses microwave energy (Thermofield System, Parmenides, Inc, Franklin, TN) has also been reported and allows for the treatment of larger and more invasive tumors and is especially effective when combined with intratumoral chemotherapy.⁴⁷ In a recent preclinical study, this novel system was used to treat a series of patients, including 2 horses with locally advanced solid tumors. Complete clinical responses were achieved in both equine patients, one of which had an extremely large tail-base melanoma. These clinical results led to the development of an advanced commercial thermotherapy unit that is now available (Thermofield System, Parmenides, Inc). In the authors' experience, this combination of hyperthermia and intratumoral chemotherapy has proven quite effective for treating locoregionally advanced disease that is often resistant to treatment with chemotherapy alone (see [Fig. 3B](#)).

Electrochemotherapy uses controlled electrical pulses delivered directly to the tumor as a means to enhance the uptake of cytotoxic drugs by tumor cells. The electrical pulses are delivered immediately after drug injection via a set of electrodes placed directly into the tumor while the horse is under general anesthesia.⁴⁸ This modality appears to be effective for the treatment of equine sarcoids (<5 cm diameter),^{48,49} but only 2 clinical reports have described its use for equine melanomas. In the first report, a relatively large buccal tumor was treated and resulted in a 50% reduction in size that was maintained for more than 1 year before being lost to follow-up.⁵⁰ The second report involved a horse with multiple melanomas that was treated with a combination of surgical resection and electrochemotherapy. Tumor control appeared to be poor, with the horse experiencing tumor progression 5 months after treatment.⁵¹

Intratumoral immunotherapy

Other agents that have shown activity when injected directly into equine melanomas include DNA plasmids encoding the cytokines interleukin (IL)-12 and IL-18.^{52,53} These cytokines have antitumor effects through the activation of cytotoxic T cells, the production of interferon- γ , and the induction of apoptosis in tumor cells.⁵⁴ Two studies evaluated the use of these agents in tumor-bearing gray horses. The first involved the intratumoral injection of DNA plasmids encoding the human IL-12 gene in a cohort of 7 gray horses.⁵² The second involved the intratumoral injection of DNA plasmids containing either equine IL-12 or IL-18 in a cohort of 26 gray horses.⁵³ Shrinkage of the injected tumors was observed in most horses from each study and the therapy appeared to be safe and well tolerated.^{55,56} Unfortunately, these treatments are not commercially available and their benefits appear to be limited to injected lesions (ie, no systemic antitumor effects).

Miscellaneous

A variety of other agents have been anecdotally used to treat melanocytic tumors. These compounds range from topical 5-Fluorouracil (5-FU) and Imiquimod 5% (Aldara) creams to herbal compounds, such as XXterra (Larson Labs, Fort Collins, CO) based in bloodroot powder. Bacillus Calmette-Guerin intratumor injections have also been proposed; however, results for equine melanomas have been disappointing.⁷ Cryotherapy can also be considered as a complementary measure to sterilize surgical wound beds or to treat small tumors. These treatments can typically be performed in standing sedated horses.^{2,7,10,25,57}

Systemic Therapies

In comparison to the variety of available local treatment options for horses with melanoma, there are few effective systemic therapies available to treat/prevent disease spread. The only reported options are immunotherapeutics. These are treatments that are meant to indirectly or directly stimulate an antitumor immune response.

Nonspecific (indirect) antitumor immunotherapy

Nonspecific immunotherapies do not directly target tumor cells or tumor-related antigens; rather, they stimulate the immune system in a general way that may also result in increased activity against tumors. An example of nonspecific immunotherapy is the use of cimetidine for the treatment of horses with melanoma. Cimetidine is a well-known histamine (H₂) receptor antagonist that may exert antitumor effects by several mechanisms, including the inhibition of H₂ receptors on tumor cells as well as the “immune stimulatory” effects of activating natural killer cells and the blocking of H₂ receptor-mediated activation of immunosuppressive regulatory T cells.^{58,59} Described oral doses for horses with melanoma range from 1.6 mg/kg every 24 hours to 7.5 mg/kg twice a day or 3 times a day.^{60–63} Although one small case series has described a clinical benefit in treated horses,⁶⁰ several larger clinical trials have failed to replicate these results,^{61–63} and, thus, the clinical effectiveness of cimetidine “immunotherapy” remains questionable.

Specific antitumor immunotherapy

An alternate approach for systemic immunotherapy involves the direct targeting of tumor-associated antigens (TAA). These are proteins that are preferentially expressed in tumor tissue.⁶⁴ This preferential expression may occur either in a temporal or spatial fashion and allows for the targeting of tumor tissue while sparing normal tissue. An example of temporally restricted expression is a tumor that expresses an embryologic

antigen in an adult animal (eg, CEA in human colon cancer). A spatially restricted protein is one in which the expression is limited to tumor tissue with minimal to no expression in other tissues. Identification of these proteins allows for the creation of immunotherapeutics or “vaccines” designed to elicit specific immune responses against cells that contain them regardless of their location within the body. The ultimate goal in creating a “cancer vaccine” is the generation of an antitumor immune response that results in clinical regression of a primary tumor and any associated metastatic lesions. There are numerous types of cancer vaccines, but only 2 have been specifically used for the treatment of equine melanoma; namely, whole-tumor cell autogenous vaccines^{32,65} and a DNA-based vaccine.⁶⁶ Autogenous vaccines are created by isolating cells from the excised tumor of an individual equine patient, which are then processed *in vitro* into a vaccine formulation, and then readministered to the same patient. There are 2 reports describing the use of an autogenous vaccine in melanoma-bearing horses.^{32,65} Tumor regressions and subjective improvement in well-being were reported in both studies. Unfortunately, the studies involved relatively small numbers of horses that were also treated with more than just the vaccine, and, thus, the true benefit of these vaccines is unknown.

DNA-based vaccines are created by first identifying an appropriate tumor-associated antigen. These antigens are tumor-specific proteins whose DNA sequence is used to create the vaccine. The DNA sequence is typically cloned into a molecular vector that allows for the *in vivo* expression of the encoded protein. Most molecular vectors also have immune stimulatory properties that improve the efficiency of the vaccine in generating an immune response against the expressed protein. This molecular construct (ie, DNA sequence cloned into vector) is often administered to the patient by intramuscular injection and thus resembles a “vaccination,” although it may be more appropriately referred to as gene therapy. One logical tumor-associated antigen that can be targeted in melanomas via a DNA-based vaccine is the protein tyrosinase, an enzyme crucial for melanin pigment synthesis. Tyrosinase has the ideal characteristics for a tumor-associated antigen because its expression is virtually limited to melanocytes.⁶⁷ Furthermore, in melanomas (including equine variants), the tyrosinase expression appears to be constitutively increased compared with normal melanocytes.⁶⁸ A USDA-approved xenogenic DNA vaccine encoding human tyrosinase (HuTyr) is available for treatment of canine melanoma (Oncept; Merial, Ltd, Athens, GA).⁶⁹ This vaccine exploits the close homology (92%) between human and canine tyrosinase to generate a tyrosinase-specific antitumor response and dramatically improves survival in treated dogs.⁷⁰ In comparison, the equine tyrosinase sequence shares 90% homology to the human sequence; therefore, cross-reactivity of HuTyr DNA vaccine in the horse would be expected.

The use of this vaccine has been evaluated in a small cohort of normal horses (see [Video 1](#)).^{66,71} The results from this report suggest the vaccine is safe and effective in generating antityrosinase-directed immune responses in horses.⁶⁶ The authors have also used this vaccine in an off-label fashion to treat a large number (>50) of tumor-bearing horses, with some exhibiting dramatic tumor shrinkage. A clinical trial was funded by the Morris Animal Foundation (D12EQ-037) to further evaluate the safety and activity of various doses of the Oncept vaccine in tumor-bearing horses ([Fig. 4](#)). Initial results are promising, with most horses demonstrating tumor shrinkage following vaccination. Although the vaccine is not currently labeled for use in the equine patient, these studies suggest off-label use may be beneficial in horses with melanoma.^{66,68,71} Further work evaluating the role of other melanocyte-specific proteins as targets for immunotherapy is ongoing. Researchers at the University of Florida are also investigating a tumor-targeting vaccine based on the disialoganglioside GD3

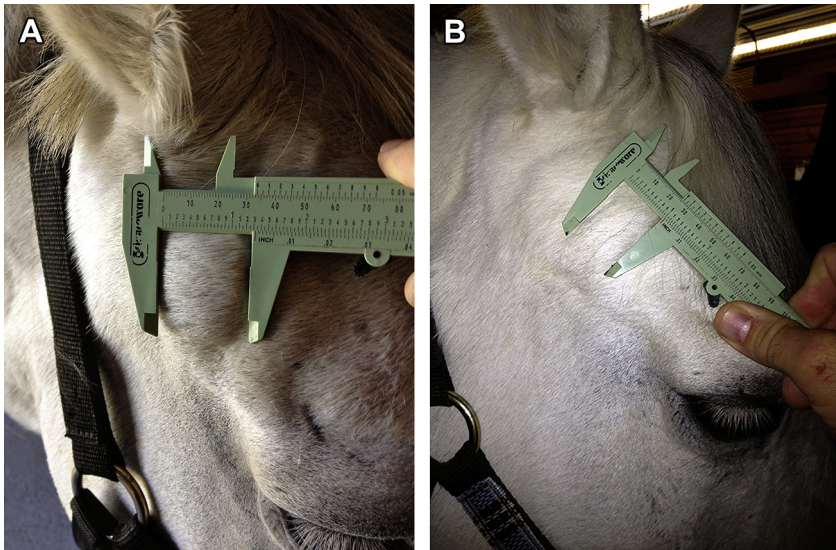


Fig. 4. Dermal melanoma being treated with the Oncept melanoma vaccine (Merial, Ltd, Athens, GA). (A) Tumor before treatment. (B) Results after treatment with 4 doses of vaccine; note reduction in tumor size and volume (tumor appears significantly flatter).

cell surface antigen to treat horses with melanoma, although no published information on the clinical activity of this vaccine is available.

PROGNOSIS AND COMPARATIVE ASPECTS

The clinical outcome in horses with melanoma(s) is mainly determined by initial tumor size and extent.^{2,12} Histopathologic classification and availability of treatment options also has some impact.³ In general, melanomas in gray horses expand slowly or may show tumor dormancy for long periods, even years. If left untreated, many will eventually acquire malignant clinical behavior with respect to both local growth and systemic spread.⁷ Ultimately, the time from tumor appearance and/or diagnosis to the time that advanced locoregional or systemic disease is diagnosed will vary from animal to animal and no formal survival time studies have been performed in the horse. In both humans and dogs, malignant melanomas may result in widespread life-threatening metastases; however, unlike in humans, most horses will not die from metastatic disease but are euthanized because of local disease complications (eg, large perianal melanomas that prevent normal defecation or rupture, become ulcerated, infected, and painful). Systemic signs associated with advanced metastatic disease in both humans and horses are varied, including chronic weight loss, neurologic symptoms, and respiratory signs, among others. Some of the more common equine-specific signs associated with advanced disease include colic symptoms from gastrointestinal invasion, difficulty defecating from obstructive lesions, nasal bleeding, or neurologic signs from guttural pouch involvement. When such advanced symptoms are observed in horses, they can be difficult to treat and will commonly be the cause of death or reason for euthanasia. The development of new local and systemic therapies, including advances in accessible radiotherapy and molecularly targeted therapies, will prove useful in managing these challenging cases.

SUPPLEMENTARY DATA

Video related to this article <http://dx.doi.org/10.1016/j.cveq.2013.08.008>.

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