Journal of Equine Veterinary Science 33 (2013) 515-522

Journal of Equine Veterinary Science

journal homepage: www.j-evs.com

Original Research

Marjolin's Ulcer in Two Horses with Hereditary Equine Regional Dermal Asthenia

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ARTICLE INFO

Article history:
Received 19 July 2011
Accepted 6 November 2011
Available online 10 April 2012

Keywords:
Marjolin's ulcer
HERDA
Horse
Squamous cell carcinoma

ABSTRACT

Two Quarter Horse mares with hereditary equine regional dermal asthenia (HERDA) were diagnosed with metastatic squamous cell carcinoma (SCC) associated with chronic nonhealing wounds. The lesions were similar to the development of SCC from chronic nonhealing ulcers, known as Marjolin's ulcers in humans. The horses showed recurrent skin wounds in the saddle and paralumbar regions and were confirmed by molecular techniques as having HERDA. Both horses were maintained as research animals for prolonged periods and received regular veterinary care and wound treatment. Both horses were ultimately euthanized because of their chronic progressive wounds, coupled with declining health. At necropsy, the nonhealing wounds were found to be complicated by infiltrative SCC; both horses had metastasis to lungs. Chronically inflamed, recurrent skin wounds that heal slowly and incompletely as a consequence of HERDA are proposed as a major pathogenetic factor in tumorigenesis. Consistent findings with respect to proliferation index (Ki-67) and mutations of p53 tumor suppressor gene were confirmed by immunohistochemistry in one horse. SCC consistent with Marjolin's ulcer has been previously suggested in association with chronic ulcers or burn scars in horses, but this is the first report of an association with chronic poor healing wounds in HERDA horses.

1. Introduction

Hereditary equine regional dermal asthenia (HERDA) is an autosomal recessive disease affecting Quarter Horses and horses of Quarter Horse lineage [1]. Clinical signs typically appear at approximately 1.3 years of age and can progressively worsen with time [2]. HERDA is characterized clinically by loose, thin, and hyperextensible areas of skin that are easily damaged after minor trauma. These areas often develop chronic wounds with slow-healing and atrophic scars [2-5]. Presumptive diagnosis of HERDA is based on history, clinical signs, histological examination of skin biopsies, and pedigree analysis [4]. Definitive diagnosis requires molecular evidence of the c.115G>A

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http://dx.doi.org/10.1016/j.jevs.2012.03.004

missense mutation in cyclophilin B (peptidylprolyl isomerase B [PPIB]) [6].

Squamous cell carcinoma (SCC) is a malignant neoplasm of keratinocytes and is the second most common neoplasm observed in equine skin [7]. Prolonged exposure to ultraviolet light, in areas of unpigmented skin with sparse hair coat, is frequently implicated in the pathogenesis of this neoplasia [8]. However, case reports have noted an association between SCC and burn scars or other chronic nonhealing wounds in horses [9-11]. The development of SCC from chronic nonhealing ulcers or scars is well established in humans, and these lesions are known as Marjolin's ulcers [12,13].

This report describes the clinical, laboratory, and pathological findings in two HERDA Quarter Horse mares that developed Marjolin's ulcer associated with chronic wounds.

2. Case Reports

2.1. Case 1

2.1.1. History

A 4-year-old, chestnut Quarter Horse mare was referred to the Veterinary Hospital at São Paulo State University, Botucatu, São Paulo, Brazil, for evaluation of skin wounds in the saddle area and right paralumbar region that had been present for more than 2 years (Fig. 1A). The owners reported that the mare's sire and dam had no clinical skin abnormalities; however, her full brother had similar skin lesions.

Clinical examination revealed an 8 × 8 cm^2 cutaneous ulcer on the right paralumbar region. The owners were unaware of any traumatic incident to cause the lesion. Multiple skin areas along the dorsum appeared more fragile, thin, and loose when compared with normal tissue, and were easily elevated when pinched (i.e., hyperextensible skin). Pain was elicited when the hyperextensible skin was manipulated. Pedigree analysis revealed a common ancestor on both sides of the mare's lineage. Incisional skin biopsies were taken from the lateral neck, dorsum, and abdominal region, and these samples were routinely processed and stained with hematoxylin and eosin and Masson's trichrome. The most remarkable histopathological finding was the presence of thin small collagen fibrils, which created a loose arrangement of collagen fibers within the deep dermis [5]. A presumptive diagnosis of HERDA was made on the basis of the clinical and histopathological findings. On diagnosis, the owners chose to donate the horse to the HERDA herd for research purposes.

The mare was housed in an individual paddock and received daily wound dressing. To avoid myiasis, a repellent insecticide (cypermethrin, 0.4 mg/100 g and dichlorvos, 1.6 g/100 g) was applied daily around the wound. The wound healed after wound care and became an atrophic scar. The skin in the right paralumbar region tore several times in the following years, as did skin in other body regions (Fig. 1B). The same treatment was performed and the wounds always healed well.

Five years after referral to the hospital, the mare exhibited anorexia, progressive weight loss, lethargy, and an extensive right paralumbar wound at the initial site described earlier in the text. Physical examination revealed a cutaneous ulcer (8 × 12 cm^2) with purulent exudate. No evidence of local pain or pruritus was observed. Treatment consisted of wound dressing as previously described, penicillin G benzathine (30,000 IU/kg, intramuscular [IM], once daily) and trimethoprim-sulfadoxine (20 mg/kg, IM, once daily) for 7 days, as well as flunixin meglumine (1.1 mg/kg, intravenous [IV], twice daily) for 3 days.

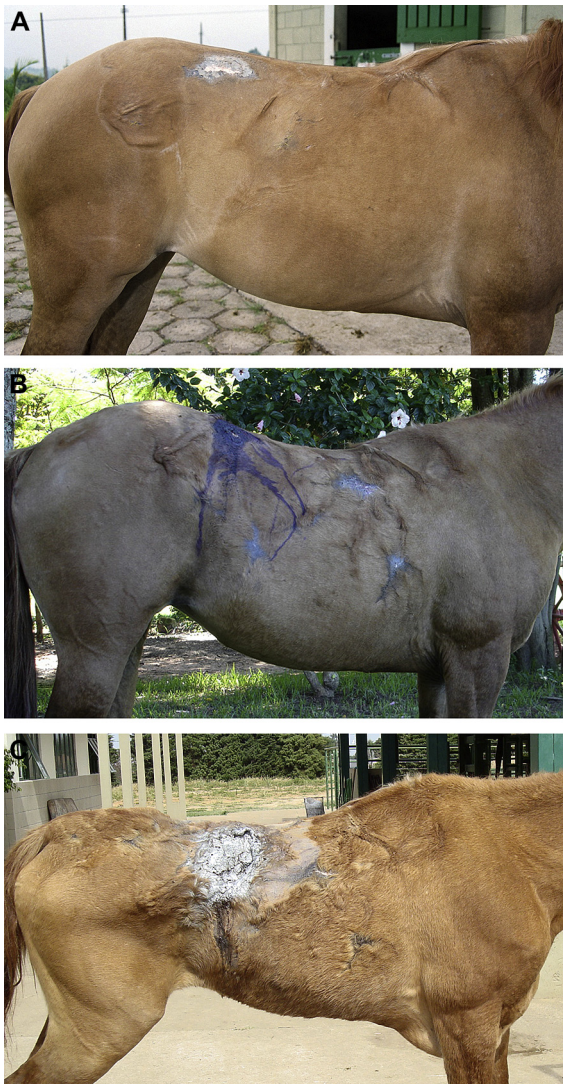

Fig. 1. Skin wound of a Quarter Horse mare with hereditary equine regional dermal asthenia. (**A**) Atrophic scar at the right paralumbar region after the first topical treatment of the wound; the mare was 4 years old. (**B**) In subsequent years, the skin broke several times at the same region. (**C**) Progressive weight loss and wound deterioration of the mare on the day she was humanely euthanized; the mare was 10 years old.

Despite local treatment, the wound over the right paralumbar region had not healed 12 months later. Physical examination revealed a persistent cutaneous ulceration (18 × 18 cm^2) with thickened areas, necrotic foci, and purulent exudate distributed along the right paralumbar region (Fig. 1C). The mare appeared to be experiencing pain during wound handling, and evidence of self-mutilation of

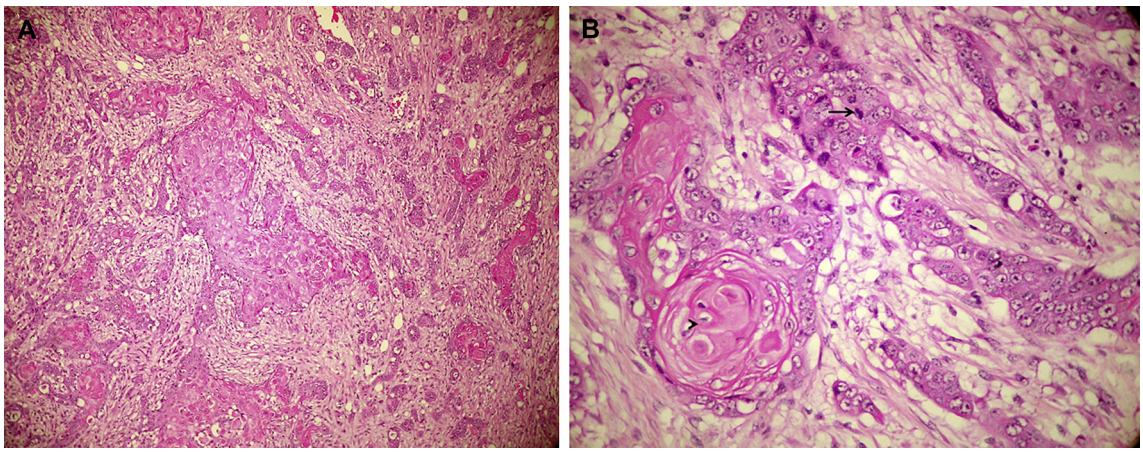

Fig. 2. Moderately differentiated squamous cell carcinoma. (**A**) Squamous cells at different stages arranged in irregular trabeculae and islets within a dense desmoplastic stroma (hematoxylin and eosin, 100×). (**B**) Nonkeratinized squamous cells arranged in trabeculae, demonstrating large, vesicular nuclei, prominent nucleoli, and mitotic figures (arrow). Cell islets with keratin pearls (arrow head) and a desmoplastic stroma can be observed (hematoxylin and eosin, 400×).

the wound site was also observed. In addition, the mare presented signs of abdominal pain, including looking at the flank and abdominal retraction. The right inguinal lymph node was grossly enlarged, firm, and adherent to the overlying skin. Diffuse edema of the chest, anorexia, tachycardia (75 beats/min), tachypnea (40 breaths/min), and moderate hyperthermia (38.8°C) were also observed.

Hematology revealed mild anemia (packed cell volume: 30%; reference range [rr]: 32%-53%) and leukocytosis (16.6×10^3 cells/μL; rr: 5.4-14.3 $\times$ 10^3 cells/μL), with marked neutrophilia (14.3×10^3 cells/μL; rr: 2.3-8.6 $\times$ 10^3 cells/μL). Serum chemistry revealed azotemia (Blood urea nitrogen: 110 mg/dL; rr: 12-27 mg/dL and creatinine: 3.2 mg/dL; rr: 0.9-2 mg/dL), and urinalysis revealed aciduria (pH: 5.0; rr: 7.0-9.0). Analysis of peritoneal fluid revealed hyperfibrinogenemia (200 mg/dL; rr: <100 mg/dL), hyperproteinemia (3 g/dL; rr: <2.0 g/dL), erythrophagocytosis, and increased nucleated cells (3,650 cells/μL; rr: <2,000 cells/μL) with approximately 65% neutrophils, 25% macrophages, and 10% lymphocytes. Ultrasonography of the paralumbar region indicated thickening of the subcutaneous wound tissue and loss of peritoneal surface continuity.

At this stage, the differential diagnosis list included a chronic draining tract associated with a foreign body, severe osteomyelitis of the rib, and neoplastic disease. Because of progressive weight loss and wound deterioration, the horse was humanely euthanized and immediately submitted for necropsy.

2.1.2. Molecular Diagnosis of HERDA

Skin samples were harvested during necropsy to perform the definitive diagnosis of HERDA by polymerase chain reaction (PCR) characterization of the equine PPIB gene (NM_001099761.1) [6]. DNA was extracted from paraffin-embedded skin samples using the QIAamp DNA FFPE Tissue Kit (QIAGEN Inc., Valencia, CA). PCR was performed to amplify a 227-base pair (bp) amplicon of the equine PPIB gene. The correct fragment length (227 bp) was confirmed using agarose gel electrophoresis. The PCR product was purified and submitted to automated direct sequencing analysis. The sequence was analyzed and the c.115G>A missense mutation in the PPIB gene was confirmed.

2.1.3. Postmortem Examination

On necropsy, a fistula was noted between the paralumbar ulcer and the abdominal cavity. Macroscopically, multiple 1 $\times$ 1 cm^2, whitish, circular nodules were observed on the deep margin of the wound. These nodules were hard and firmly adherent to the paralumbar muscles and the peritoneum. The same nodular lesions were also present in the thoracic cavity and were distributed along the parietal and visceral pleura, mediastinal region, diaphragm, and pericardium. Marked right inguinal lymphadenopathy was also observed. Samples of the wound, paralumbar muscle, right inguinal lymph node, diaphragm, parietal pleura, visceral pleura, and lung were obtained for histopathology. Tissue samples were fixed in 10% neutral buffered formalin, embedded with paraffin and processed routinely, stained with hematoxylin and eosin, and examined microscopically.

2.1.4. Histopathology

Histopathology of the skin, subcutaneous lesions, and visceral nodules revealed similar microscopic findings that included invasive irregular islands and anastomosing trabeculae of squamous cells that revealed varying degrees of differentiation (Fig. 2A). Cells with a lesser degree of differentiation predominated in the majority of the specimens. These cells featured large and vesicular nuclei, prominent nucleoli, and small amounts of pale amphophilic cytoplasm. The more keratinized cells had a moderate to large amount of eosinophilic cytoplasm. The islands of squamous cells had variable abnormal keratinization, which eventually formed a central mass of compact laminated keratin (i.e., keratin pearls) in variable numbers and shapes (Fig. 2B). The desmoplastic stroma often exhibited variable lymphocytic infiltrate, focal necrosis, and very occasional dystrophic calcification. Additionally, individual cell necrosis and moderate mitotic activity were frequently observed. Similar findings were also observed in paralumbar muscle, right inguinal lymph node, diaphragm,

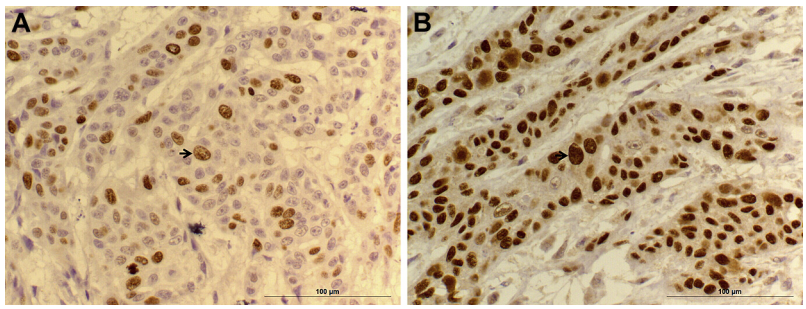

Fig. 3. Immunohistochemistry. (**A**) Positive reaction to Ki-67 indicated by the presence of nuclear staining (arrow). (**B**) Nuclear p53 immunoreactivity can be seen in the neoplastic cells of tumor island (arrow).

pleura, and lung. On the basis of macroscopic and histopathological findings, the diagnosis was cutaneous SCC with metastasis.

2.1.5. Immunohistochemistry

To assess the proliferation index and abnormal protein expression in the primary neoplasia and lung metastases, immunohistochemistry for Ki-67 and p53 was performed. Ki-67 was evaluated using the Ki-67 monoclonal antibody MIB-1 (Dako Cytomation, Copenhagen, Denmark) at a dilution of 1:50. Expression of p53 was determined using the p53 monoclonal antibody DO-7 (Novocastra Laboratories, Newcastle upon Tyne, England, United Kingdom) at a dilution of 1:4,000. Negative control slides were prepared for both markers. Detection was accomplished using the highly sensitive, two-step polymer system Advance HRP (Dako, Copenhagen, Denmark) and liquid DAB substrate chromogen system (Dako Cytomation, Copenhagen, Denmark). All slides were counterstained with Mayer's hematoxylin, and a cover slip was placed for microscopic examination. The methodology proposed by Carvalho et al. [14] was used for evaluation. Cells positive for Ki-67 (Fig. 3A) and p53 (Fig. 3B) staining were observed both in the primary neoplasia and in the lung metastases. The mean labeling index values (calculated as the percentage of positive cells) for Ki-67 in the primary neoplasia and lung metastases were 35% and 50%, respectively. The mean labeling index values for p53 in the primary neoplasia and lung metastases were 34% and 50%, respectively.

2.2. Case 2

2.2.1. History

An 8-year-old, pregnant liver chestnut Quarter Horse mare was donated to the HERDA research program at the Veterinary Medical Teaching Hospital at Mississippi State University. Clinical examination revealed numerous healed wounds over the dorsum, the dorsal aspect of both tarsi, and the left fore cannon bone. In addition to scars, the mare exhibited other signs typical of a horse with HERDA, including soft, loose, "mushy" skin with areas of wrinkling and sagging. At the time the mare was donated to the program, the DNA test for HERDA was not available, so the mare's mane hair and blood were banked and multiple skin biopsies were taken for histopathology. DNA testing later confirmed that the mare was homozygous for HERDA.

During the following 2 years, the mare experienced two normal pregnancies and foalings and developed numerous spontaneous wounds, a corneal ulcer, and a corneal stromal abscess. Serum chemistry analysis and complete blood cell counts were performed twice each year and were within normal limits.

Twenty-one months after presentation, one of the scars (Fig. 4) on the mare's dorsal loin region became ulcerated

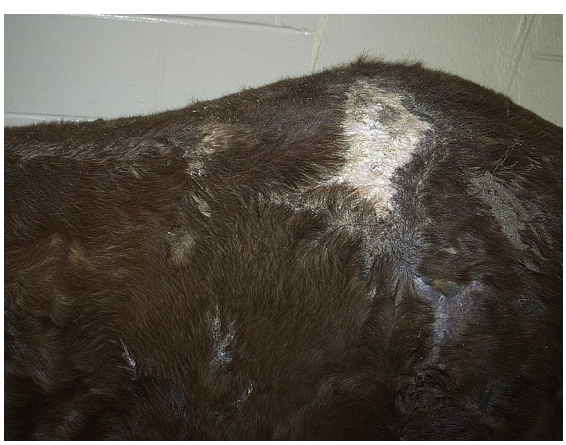

Fig. 4. Atrophic scar at the dorsal loin region of an 8-year-old Quarter Horse mare with hereditary equine regional dermal asthenia.

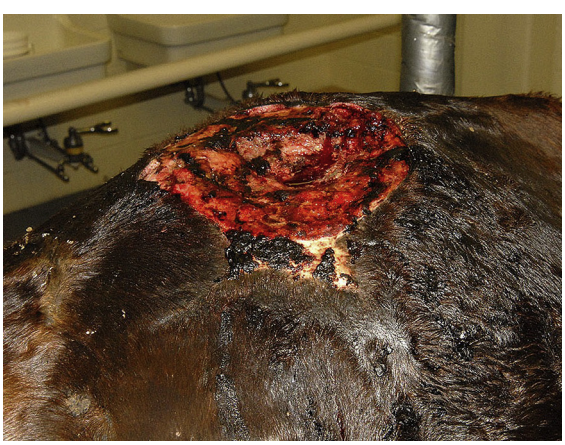

Fig. 5. Chronic nonhealing wound on mare in Figure 4 shortly before euthanasia.

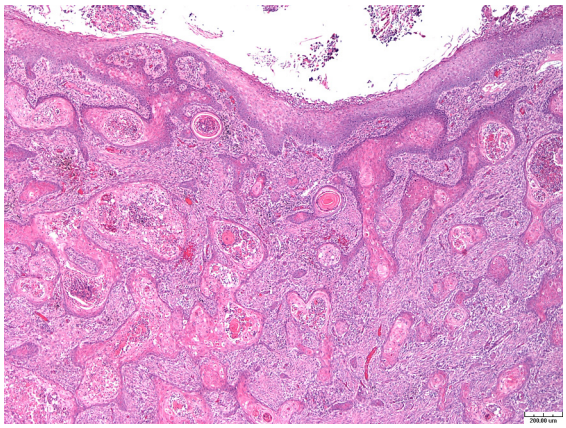

Fig. 6. Large trabeculae of neoplastic squamous epithelial cells with some keratin pearls and focal connection with epidermis. Some necrotic lobules with neutrophilic infiltrates and inflamed desmoplastic stroma are also features.

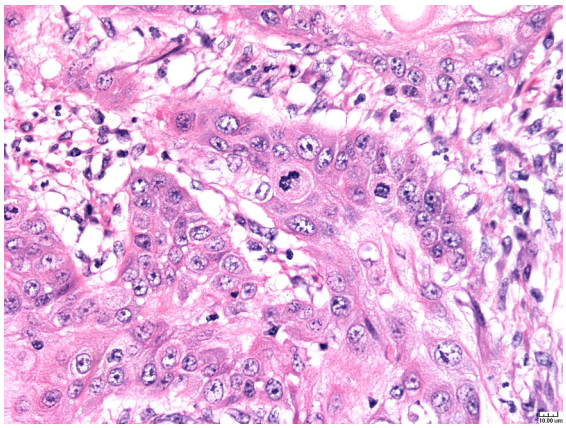

Fig. 7. Polyhedral nonkeratinized cells are present at the periphery of the neoplastic trabeculae, which display abundant premature and faulty keratinization at the center.

(Fig. 5). Local wound care was instituted, which included daily washing with an antibacterial soap (chlorhexidine, Xttrium Laboratories Inc., Chicago, IL, USA or betadine, Medline Industries Inc., Mundelein, IL, USA) and application of an antimicrobial ointment (silver sulfadiazine, Watson Laboratories, Carona, CA, USA). Systemic antibiotics were administered several times with no effect (Trimethoprim Sulfa, Mutual Pharmaceutical Co., Inc., Philadelphia, PA, USA 30 mg/kg PO, twice daily for 14 days, followed by procaine penicillin 22,000 IU/kg IM, twice daily with gentamicin 6.6 mg/kg, IV, once daily for 14 days).The mare was housed indoors, and the wound was covered with sterile wraps. Topical insecticides were not used. Despite daily care, the wound continued to progress.

At this time, hematology revealed severe anemia (red blood cells: 3.01×10^6 cells/μL; rr: 6.0-12.0 $\times$ 10^6 cells/μL, hemoglobin: 5.9 g/dL; rr: 8-15 g/dL, packed cell volume: 17%; rr: 28%-42%) and leukocytosis (13.9×10^3 cells/μL; rr: 5.0-11.9 $\times$ 10^3 cells/μL), with marked neutrophilia (12.1 $\times$ 10^3 cells/μL; rr: 2.3-8.6 $\times$ 10^3 cells/μL), hyperfibrinogenemia (600 mg/dL; rr: 100-500 mg/dL), and hypoproteinemia (6.7 g/dL; rr: 6.8-7.9 g/dL). Serum chemistry analysis revealed azotemia (creatinine: 2.1 mg/dL; rr: 1.2-1.9 mg/dL).

The mare lost weight (body condition score from 7/9 to 5/9) without a reduction in food or appetite and developed a quieter demeanor. Despite appearing comfortable, she developed persistent tachycardia (72-80 beats/min), tachypnea (32 breaths/min), and became febrile (39.0°C). The mare was treated with ceftiofur (4.4 mg/kg, IM, once daily for 10 days) and flunixin meglumine (1.1 mg/kg, IV, twice daily for 7 days), with no resolution in fever. The mare's wound continued to deteriorate, and euthanasia was performed immediately after her foal was weaned.

2.2.2. Postmortem Examination

Necropsy revealed a deep cutaneous ulcer, 30 cm in diameter, over the left paralumbar fossa. The ulcer had a rough irregular base that grossly appeared similar to granulation tissue. Marginal epidermis was thickened and raised. Dense white tissue with some interspersed exudates extended approximately 10 cm into the underlying muscle. The lungs had five firm discrete nodules ranging from 3 to 10 cm in diameter. The cut section of the nodules revealed firm pale tan tissue with scattered friable foci of necrosis.

2.2.3. Histopathology

Histopathological sections of the lesion from the dorsal loin region revealed normal epidermis, which transitioned into areas that were thicker and ulcerated. At the margin of the normal tissue, the epidermis had abrupt transition to proliferative and infiltrative lobules of neoplastic squamous epithelial cells that extended deeply into the dermis and subcutis. The neoplastic cells had round to oval, large, and variable-sized nuclei with prominent multiple nucleoli and moderate basophilic cytoplasm. The cells had distinct cell margins and occasional intercellular bridges. There were one to two mitotic figures per high-powered (40×) field (Fig. 6). Cellular fibrous connective tissue (desmoplastic response) with interspersed chronic inflammation was associated with the neoplastic lobules. The diagnosis was SCC.

Histopathology of the lungs revealed locally extensive areas of nonencapsulated neoplastic lobules with necrosis and inflammation. Infiltrative islands of moderately well-differentiated neoplastic epithelial cells were separated by collagenous stroma attributed to a desmoplastic response (Fig. 7). The neoplastic cells were similar to those in the skin as described earlier in the text, confirming pulmonary metastasis of the SCC.

The remainder of the necropsy was unremarkable other than the typical skin and corneal lesions seen in horses with HERDA [15].

3. Discussion

This report describes two unusual cases in which SCC was associated with a chronic ulcer. SCC associated with chronic ulcers or burn scars has been described in humans and is called Marjolin's ulcer [12,16]. Only a few reports have described Marjolin's ulcer caused by chronic ulcers [10,11] or burn scars [9,17] in horses.

Marjolin's ulcer in humans can arise from chronic wound beds that repeatedly heal and break down [12]. The HERDA skin disorder results in easily traumatized skin with delayed healing. These animals suffer repeated episodes of

injury and have chronic skin wounds with associated chronic inflammation. We postulate that the initiation and maintenance of wounds associated with this collagen defect predispose to malignant wound transformation and cutaneous SCC similar to those described in Marjolin's ulcer in humans [12].

Although SCC associated with chronic ulcers or burn scars has been previously reported in adult horses aged between 11 and 14 years [9-11,17], the tumors in this case study occurred in 8- and 10-year-old Quarter Horse mares. This early occurrence of the tumor may be attributable to the fragile skin that made the horse susceptible to repeated wound formation in the same region following minor trauma. Marjolin's ulcer is most likely to occur in humans aged 10 to $\geq$40 years after chronic ulcer presentation [18]. Previous reports indicated that the time elapsed between the primary injury and the diagnosis of Marjolin's ulcer in horses was 1.5-8 years [9-11,17]. For these cases, we do not know exactly when the chronic ulcer was transformed into SCC. Marjolin's ulcer is frequently aggressive and associated with metastasis in humans [16,18]. The presence of metastasis worsens the prognosis and survival rate [12] and contributes to the patient's death [18]. In this study, the pronounced decrease in the health status of the horses, which ultimately led to euthanasia, could have been caused by metastasis. In three other case studies, euthanasia was the outcome for two horses with Marjolin's ulcer associated with burn scars [9,17] and for one horse with Marjolin's ulcer associated with chronic ulcer [11].

To prevent myiasis, the wound treatment described in case 1 in this study involved the topical application of a repellent substance. Previous studies have described the possible involvement of pyrethroids in canine mammary carcinoma [19] and murine skin tumors [20]. However, an association between dichlorvos exposure and risk for cancer was not observed in humans [21]. In addition, factors such as prolonged exposure to ultraviolet radiation [8] and chronic wounds [9-11] are also involved in the pathogenesis of equine skin SCC. The hypothesis that HERDA horses have a solar or heat-related stress should also be considered [4]. The pathogenesis of Marjolin's ulcer in humans remains unclear and controversial. It was previously hypothesized that an initial trauma leads to neoplastic transformation that remains dormant until stimulated by a cocarcinogen [22]. In the present study, we do not know whether chronic wound, topical application of the repellent substance, and prolonged sun exposure were associated as cocarcinogenic factors. In addition, fly repellent was not used in case 2, and therefore, was not associated with tumorigenesis in that horse.

Early diagnosis of Marjolin's ulcer in humans is imperative for managing the neoplasia and improving the survival rate [12]. Only one case of Marjolin's ulcer associated with a chronic wound in a horse did not result in euthanasia; however, the treatment for that case was long in duration and expensive [10]. Therefore, even if early diagnosis had been achieved and treatment had been instituted in our current cases, the mares would likely have died because of a severe decline in health status and metastasis.

The clinical signs observed in the horses in this study were vague and nonspecific. Nevertheless, a previous retrospective study observed that inappetence, chronic weight loss, ventral sternal edema, and pyrexia were common clinical findings in horses affected by carcinoma [23]. Lymphadenopathy and self-mutilation have also been observed previously in one llama [24] and two horses [9,11] with Marjolin's ulcer. Abnormal laboratory findings were not particularly helpful in establishing the diagnosis of Marjolin's ulcer; however, nonspecific findings such as anemia, leukocytosis, and neutrophilia are commonly observed in horses with neoplasia [23]. Although neoplastic cells were not observed during peritoneal fluid analysis of the first mare, the absence of these cells does not rule out a diagnosis of primary neoplasia or metastasis in the peritoneal or pleural cavities [23,25].

Definitive diagnosis of Marjolin's ulcer was based on postmortem and histopathological examination. Necropsy and histopathological findings indicated that the tumor was locally invasive and had metastasized to the regional inguinal lymph node (case 1) and thoracic cavity (both cases). Previous reports in a llama [24] and in a horse [11] with Marjolin's ulcer also demonstrated that these tumors are locally invasive and metastasize to local lymph nodes. Lymph node metastasis is also commonly observed in humans affected by Marjolin's ulcer and is correlated with a poor prognosis [12,16]. A thorough review of the literature indicates hundreds of cases of SCC involving genital and ocular structures in the horse [26-32]. Although a small percentage of these horses had local or lymph node metastasis, lung metastasis was quite rare. [26-32].

Cyclophilin B contributes to the regulation of integrin-mediated adhesion of T lymphocytes into an inflammatory site [33]. Thus, the lung metastasis described in this study could possibly be associated with the failure of immune surveillance due to T cell malfunction as a result of the cyclophilin B missense mutation of HERDA horses.

Alternatively, the increased metastatic potential of the SCC in these two cases may be because of increased vulnerability to matrix metalloproteinase digestion due to the increased solubility of collagen in HERDA horses [34] to increase angiogenesis and tumor invasiveness. The metastatic phenotype is also associated with downregulation of cell adhesion or cell matrix molecules and may play a role in cell migration, invasion, and metastasis creation. Chronic inflammation and tumor-associated macrophages have previously been shown to contribute to tumor formation and development by effects on tumor growth and angiogenesis, tumor progression, metastasis, and immunosuppression [35].

The Ki-67 and p53 biomarkers were previously used to assess the proliferation index and abnormal protein expression of SCC in domestic animals [14,36]. In humans with SCC of the oral cavity and tongue, increase in p53 and Ki-67 expression was associated with larger tumors, metastasis to lymph nodes, and a worse prognosis [37]. Additionally, pseudocarcinomatous hyperplasia (PCH) is a common histopathological finding at the margins of chronic, nonhealing ulcers [38]. In humans, immunopositivity for p53, unlike Ki-67, has been useful for the differentiation of SCC and PCH, because p53 staining is observed only in SCC arising from chronic ulcers. This feature distinguishes between benign and malignant processes arising in squamous epithelium [39]. Because chronic ulcerated wounds are a common problem in equine

medicine, these immunohistochemistry findings may be useful for differentiating SCC from PCH in horses as well. Despite its usefulness, immunohistochemistry for these biomarkers was not performed previously in cases of equine Marjolin's ulcer. The moderately differentiated SCC lesion in case 1 exhibited 34% positive cells for p53. In humans, >10% immunopositivity for p53 indicates a mutation in the p53 gene and is associated with negative prognosis [40]. Because p53 mutation is associated with ultraviolet light, and HERDA horses may be more sensitive to ultraviolet light, it is reasonable to think that HERDA horses may be more susceptible to actinic skin damage including SCC [4]. Interestingly, the mean labeling index values for Ki-67 in the primary neoplasia and lung metastasis samples in this study were found to be 35% and 50%, respectively. Both of these values were much higher than those previously reported in ocular SCC study in cattle (4.5%-26% of moderately differentiated SCC cells were positive for Ki-67) [14].

4. Conclusions

These cases represent the first report to describe SCCs consistent with Marjolin's ulcers in horses with HERDA. Ultraviolet light, chronic inflammation, T cell suppression, and poorly formed dermal collagen due to the cyclophillin B mutation associated with HERDA are believed to be responsible for the development of SCC at the wound sites and subsequent pulmonary metastasis. Neither wound site SCC nor pulmonary metastasis are commonly seen or reported in equine patients. Malignant transformation must always remain on the differential diagnosis list for any chronic nonhealing wound, and biopsies should be taken to rule out SCC, equine sarcoid, or other neoplasia.

Acknowledgments

The authors acknowledge Luis Emiliano Cisneros-Álvarez for the critical review of the manuscript and the assistance of Dr Renée Laufer Amorim for the immunohistochemistry procedures. This work was partially supported by grants from the American Quarter Horse Association (to A.R.R.) and Fundação de Amparo a Pesquisa do Estado de São Paulo FAPESP (to A.S.B.).

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