Case report: focal squamous cell carcinoma, extensive squamous dysplasia and balanitis of the penis in a stallion

Kristen D. Loncar, Patrick M. McCue, Dean A. Hendrickson, Ryan A. Ferris
Department of Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO

Summary

An 18 year old Quarter Horse stallion was presented with a copious amount of dried purulent debris adhered to his penis. Removal of the surface debris revealed a focal squamous cell carcinoma lesion on the glans penis and extensive squamous dysplasia along the shaft of the penis. The focal lesion was removed surgically. Additional therapeutic options were discussed.

Keywords: Stallion, penis, squamous cell carcinoma, tumor

Background

An 18 year old American Quarter Horse stallion had been turned out with a band of mares for three months in 2013 in a pasture breeding program. The owner noticed at the time of turn-out that the horse had a significant amount of debris and areas of discoloration on the shaft of the penis.

The stallion was presented to the Equine Reproduction Laboratory at Colorado State University prior to the onset of the 2014 breeding season for evaluation of his penis and a concern about the ability of the horse to continue to live cover mares. No difficulties in breeding were observed by the owner during the previous (2013) breeding season. Pregnancy rate for the 2013 breeding was not available.

Case presentation

The stallion was in good body condition and weighed 577 kg at presentation. He showed good libido when teased to a mare in estrus. He dropped his penis and gained an erection which allowed for examination of the suspected penile lesions. A layer of dried purulent material was present along the shaft of the penis (Figure 1). The exudate was gently rinsed off with warm water and multiple areas of depigmentation and thickening were noted scattered along the penis distal to the preputial ring (Figure 2). In addition, a proliferative, raised red mass approximately 1 cm in diameter was visible on the dorsal aspect of the glans penis (Figure 3).

Several unsuccessful attempts were made to collect semen from the stallion using a Colorado model artificial vagina. However, the stallion would mount the jump mare, thrust into the artificial vagina several times, but dismount without ejaculation during each collection attempt.

Pharmacologically induced *ex copula* ejaculation (commonly called‘chemical ejaculation’) was subsequently performed. The stallion was administered a dose of imipramine hydrochloride orally (3 mg/kg) followed two hours later by intravenous administration of xylazine hydrochloride (0.26 mg/kg).[1] The stallion ejaculated into a collection bottle approximately 12 minutes after administration of the xylazine.

Semen analysis revealed a volume of 53 ml and a spermatozoal concentration of 163 million/ml, for a total of 8.64 billion spermatozoa. Sperm motility was analyzed using a computer-assisted sperm analysis (CASA) system (SpermVision®; Minitube USA, Delavan, WI) and was determined to consist of 74% total motility and 63% progressive motility. Sperm morphology was evaluated using an eosin-nigrosin stain.[2] A total of 100 spermatozoa were evaluated on each of two stained slides and 73% of the spermatozoa were noted to be morphologically normal.

The owner declined further diagnostic tests to evaluate the lesions on the penis. The stallion was initially turned out on pasture with four mares in the month of April and then turned out with a different group of 14 mares in early May and removed from pasture after approximately 90 days.

Pregnancy evaluation

Transrectal ultrasonic pregnancy examinations were performed at the ranch on the group of 14 mares three weeks after the stallion was removed from the pasture. Nine of the 14 mares were determined to be pregnant. Three of the five non-pregnant mares were two years old. The owner reported that all four other mares were confirmed by ultrasonography to be pregnant by another veterinarian. Overall, the stallion achieved pregnancies in 13 of the 18 (72.2%) mares he was turned out with in 2014.

Further diagnostic tests

The stallion was returned to the clinic in early January 2015 for additional diagnostic tests on the penile lesions. He was sedated with a combination of 5 mg detomidine hydrochloride and 5 mg butorphanol tartrate, administered intravenously, and placed in examination stocks. Culture swabs were collected from the shaft of the penis and urethral fossa and submitted for microbial culture.

The penis was washed with a non-residual soap (Ivory® Liquid; Procter and Gamble, Cincinnati, OH) and rinsed with warm water. Lidocaine hydrochloride was infused subcutaneously and biopsy samples were collected using a scalpel blade from the raised red lesion on the glans penis and three sites along the shaft of the penis in areas that appeared thickened and depigmented. All biopsy sites were subsequently closed with 3-0 monofilament absorbable suture on a taper needle (Biosyn™, Coviden, Dublin, Ireland). Samples were submitted to the Colorado State University Veterinary Diagnostic Laboratory for histopathologic evaluation.

The stallion was administered a single 6.6mg/kg dose of ceftiofur crystalline free acid (CCFA) (Excede®; Zoetis, Florham Park, NJ), intramuscularly and 500 mg flunixin meglumine, intravenously, after the biopsy procedures.

Microbial culture of samples collected from the penile shaft and urethral fossa yielded moderate growth of beta hemolytic *Streptococcus equi* subspecies *zooepidemicus* and heavy growth of *Trueperella pyogenes* (formerly known as *Corynebacterium pyogenes* and *Actinomyces pyogenes*).

Histopathologic evaluation of the three penile shaft biopsies indicated moderate to severe lymphoplasmacytic and eosinophilic balanitis with marked acanthosis and dysplasia which were interpreted as pre-neoplastic changes.

The biopsy of the glans penis lesion revealed epithelial cells that formed clumps, masses and areas of squamous differentiation with formation of squamous pearls (Figures 4 and 5). Nuclei were mildly pleomorphic, round and had prominent nucleoli. Mitoses were noted in two to three cells per high-powered field (Figure 6). The histopathologic diagnosis for the glans penis lesion was squamous cell carcinoma (SCC).

Treatment

The first step in the treatment plan was to reduce the chronic infectious and inflammatory processes within the sheath and on the surface of the penis and the second step was to remove the tumor on the glans penis. The stallion was administered trimethoprim-sulfamethoxazole at a dose of 30 mg/kg orally twice daily for ten days. He was also administered prednisolone, starting with a dose of 1.0 mg/kg orally once daily for four days, which was subsequently tapered to 0.5 mg/kg for four days and then 0.25 mg/kg for two additional days. The horse was also administered a dose of ceftiofur crystalline free acid (6.6 mg/kg, intramuscularly) followed by an additional dose four days later.

The stallion was sedated with xylazine hydrochloride (0.3 mg/kg) every second day and his penis was gently washed with warm water, rinsed with hypertonic saline and then coated with a layer of silver sulfadiazine cream.

After ten days of therapy, the stallion was sedated with a combination of 5 mg detomidine hydrochloride and 5 mg butorphanol tartrate administered intravenously, and restrained in examination stocks. A ring block was performed using a 22 gauge 1.5 inch needle inserted at six separate sites to infuse a total volume of 20 mls of lidocaine subcutaneously in a circumferential ring around the penile shaft midway between the preputial ring and the glans penis (Figure 7). Three mls of lidocaine

hydrochloride was infused around and beneath the lesion on the glans penis. The lesion was removed using an elliptical incision approximately 5 mm from the margin of the mass and sufficiently deep to remove the entire mass (Figure 8). The incision was closed in two layers using 3-0 monofilament absorbable suture (Figure 9). The horse was subsequently administered 500 mg flunixin meglumine and maintained on 1 gram of phenylbutazone orally for an additional two days.

Outcome

Two days after the initial procedure, the stallion was again sedated with xylazine hydrochloride to evaluate the surgical area. There was no evidence of swelling, hemorrhage or dehiscence, and the stallion was sent home with instructions to remain on stall rest for two weeks and to remain isolated away from mares to minimize sexual stimulation and development of an erection in order to prevent complications at the surgery site.

Histopathology of the glans penis mass confirmed the initial diagnosis of squamous cell carcinoma. It was also noted that the tissue margins were comprised of normal tissue, indicating that the tumor had been excised completely.

Additional therapeutic options were discussed for management of the multiple and extensive dysplastic skin lesions on the shaft of the penis. Practical options included topical administration of a chemotherapeutic agent, such as 5-fluorouracil, and long-term oral administration of a cyclooxygenase-2 (COX-2) inhibitor, such as peroxicam or firocoxib. The owner elected to not treat the penile shaft lesions at the current time. The primary factors that led to the decision were that the lesions had been determined histologically to be dysplastic and had not as yet progressed to actual squamous cell carcinoma (even though dysplasia is considered to be a precursor stage to SCC), and the stallion was housed on a large pasture and daily administration of an oral medication would be challenging to accomplish.

Ultimately the owner decided to use the stallion in a pasture breeding program again this year and return him to the clinic for re-examination at the end of the breeding season with the possibility of starting additional therapies at that time.

Discussion

The most commonly reported neoplasms of the penis and prepuce are sarcoids, squamous cell papillomas, carcinomas and melanomas.[3] Squamous cell carcinoma is a tumor arising from squamous epithelial cells. The penis, prepuce and urethral process are considered to be predisposed sites for development of squamous cell carcinoma.[3-5] More specifically, the glans penis has been reported to be involved in 53 to 84% of cases of equine penile and preputial squamous cell carcinoma.[6-8] Penile SCC lesions in horses less than eight years of age tend to be aggressive and commonly metastasize to regional lymph nodes.[9,10]

Factors that predispose horses to development of SCC of the penis and prepuce include lack of pigmentation on the genitalia, exposure to the ultraviolet component of solar radiation, infection with *Equus caballus* papillomavirus 2 (EcPV-2),[11-13] smegma,[14] and poor hygiene which leads to chronic irritation and balanoposthitis.[15] Infection with EcPV-2 is currently thought to be the main cause for development of SCC of the penis and prepuce in the horse.[16,17]

The condition primarily affects adult horses,[6,15,18] with an average age of 18.9 years (range 13 to 30) noted in one report.[3] Other commonly affected areas include the periorbital and perineal regions.

Squamous cell carcinoma lesions are often locally invasive and multicentric, metastasize slowly to regional lymph nodes and occasionally metastasize to distant sites such as lung, liver and thoracic lymph nodes.[3,7] Metastasis to the inguinal lymph nodes for cases of SCC of the equine genitalia has been reported to range from 12.5 % to 16.9 %.[6,19]

Clinical signs of SCC range from hemospermia to depigmented plaques or non-healing erosive lesions to solid masses with a cauliflower-like appearance.[19] Diagnosis may be based on physical examination, visual inspection, ultrasonography to determine extent and invasiveness of the tumor, fine needle aspiration or, preferably, a full thickness biopsy. Ideally, the biopsy should include the lesion and

interface with normal appearing skin. Transrectal palpation and possibly thoracic ultrasonography and radiography are also recommended in malignant cases to ascertain metastasis.[9]

Differential diagnoses for SCC lesions include sarcoid, papilloma, mast cell tumor, exuberant granulation tissue ('proud flesh'), habronemiasis, phycomycosis, cutaneous lymphoma, adenocarcinoma/adenoma, neurofibroma, posthitis/balanoposthitis, foreign body reactions and melanoma.[9,10]

Treatment options include surgical procedures, non-surgical interventions or a combination of surgical debulking or debridement followed by a non-surgical therapy. Non-surgical interventions include cryotherapy, radiofrequency hyperthermia, radiation therapy, photodynamic therapy, topical or intratumoral chemotherapy, immunomodulators, and other treatments. Local or intralesional therapy may be beneficial in reducing systemic side effects of treatments.

Surgical options are often dictated by the size, anatomic location, invasiveness and local or regional extent of the tumor. A surgical margin of at least 0.5 to 1.0 cm between the tumor and normal tissue is recommended.[10] Small tumors may only require local resection, but there is a risk of recurrence with local excision.[18] Larger or more invasive tumors, such as a tumor that has invaded the urethra, tunica albuginea, corpus cavernosum or corpus spongiosum of the penis may require segmental posthioplasty ('reefing'), partial phallectomy or *en bloc* penile and preputial resection with penile retroversion.[8,20] Mair and colleagues[6] reported that four of 24 horses that underwent penile amputation for lesions on the glans penis were ultimately euthanized due to recurrence of the tumor. An overall success rate of 55.7 % was reported for stallions with penile and preputial SCC.[8]

Small SCC lesions can be eliminated by laser ablation[3] with a neodymium:yttrium-aluminum garnet, gallium-aluminum-arsenide diode or carbon dioxide laser. Lasers vaporize cells along the incision site as well as cause coagulation of small blood vessels, lymphatic vessels and nerves[21,22] which leads to less hemorrhage and post-operative pain. McCauley[23] reported the use of a carbon dioxide laser in nine horses with squamous cell carcinoma, of which two cases resulted in recurrence of the tumor.

Cryotherapy involves direct application of liquid nitrogen (-196°C) by spray or probe to the tumor to cool the cells to tumoricidal temperatures of -20 to -40°C for a period of one minute.[24,25] Repeated cycles of quick freezing and slow warming leads to cellular injury, vascular damage and eventually cell death. In human medicine, a cure rate of 97.3% has been reported following the use of cryotherapy if the tumor is small.[26] Cryotherapy can be used alone or after surgical debulking of the tumor.

Radiofrequency hyperthermia involves use of a probe that emits radio waves which create heat inserted directly into a tumor. Grier et al[27] reported that 80% of bovine and equine ocular squamous cell carcinomas had complete regression and 16% had partial regression of the tumor. The authors concluded that radiofrequency hyperthermia was easy to administer, but not as effective for large tumors as compared with small tumors. Hyperthermia can be used as an adjunctive therapy after surgical debulking a SCC tumor.

Radiation therapy has been used extensively in cancer therapy in humans and animals. Brachytherapy involves the use of a sealed radiation source such as iridium-192, iodine-125 or strontium-90 enclosed in a protective capsule, beads, seeds, pins or wires implanted directly within the target tissue to delivery continuous radiation to the site.[28,29] Ionizing radiation from the source only effects cells in the local surrounding tissue. Brachytherapy can be used alone for small SCC lesions or as an adjunctive therapy following surgical debulking of a tumor. Wyn-Jones[30] reported a 100% success rate when using iridium pins to treat a variety of tumors in the horse. Mosunic and colleagues[31] noted that adjuvant radiation therapy along with the primary treatment was associated will less recurrence of ocular and adnexal SCC than primary treatments alone.

In contrast, teletherapy or external beam radiotherapy refers to the use of an external radiation source, such as strontium 90, cobalt 60 or other source, to deliver a controlled amount of radiation from a remote source to the affected tissue for a selected period of time.[28] Radiation has been used in the horse to treat many types of neoplasia, including squamous cell carcinoma, fibrous connective tissue tumors,

sarcoids, nerve cell tumors, and solitary lymphomas.[32] Side effects noted with various types of radiation therapy in the horse have included alopecia, delayed healing and infection.

Photodynamic therapy involves the activation of a photosensitizer drug (a porphyrin compound) with light which results in the formation of reactive and cytotoxic singlet oxygen.[33] Photosensitizers are preferentially absorbed by proliferating tumor cells, which can then be destroyed when light is delivered to a highly specific area.[10] Photodynamic therapy is advantageous in that it is non-invasive and effective when treating a large surface area. Giuliano and colleagues[34] reported that horses with periocular squamous cell carcinoma treated with excision and photodynamic therapy did not exhibit recurrence of the tumor, while 78.5% of horses treated with cryotherapy after excision exhibited recurrence of the tumor.

Cisplatin (cis-diammine dichloroplatinum) is a broad spectrum chemotherapeutic drug that works by crosslinking DNA and interfering with mitotic cell division. Damaged cells undergo apoptosis once repair mechanisms fail.[35] Cisplatin can be mixed with purified medical grade sesame oil to a concentration of 3.3 mg/ml and injected directly into the tumor once every two weeks for a total of four treatments.[36] Alternatively, biodegradable beads containing cisplatin has also been used in the treatment of equine SCC as a slow-release delivery system.[37] Results often depend on initial size of the tumor and larger tumors (i.e. > 1.5 cm) should be debulked prior to cisplatin treatment. Cisplatin can be injected or implanted along the margins of the excision site after debulking or tumor removal. Théon and others[38] reported a success rate of 88% for horses with squamous cell carcinoma lesions treated with one course of intralesional cisplatin. Hewes and Sullins[37] recommended three applications of cisplatin beads at one month intervals for equine SCC.

5-fluorouracil (5-FU) is a fluoropyrimidine that works by incorporation of its metabolites into DNA and RNA, which leads to improper replication and inhibition of the nucleotide synthetic enzyme thymidylate synthase[39] Disruption of DNA synthesis causes rapidly dividing cancer cells to undergo cell death, whereas normal epithelium adjacent to the tumor remains intact with minimal inflammation. 5-FU is available as a topical cream and a sterile injectable solution and is an alternative to other forms of local chemotherapy.[10] Paterson[40] reported that two horses with facial SCC remained in remission after a 30-day course of topical 5-FU, while a third horse was controlled by topical administration of 5-FU for seven days every six weeks. Fortier and MacHarg[41] described the use of 5-FU cream topically as a treatment for non-metastasized SCCs. Penile lesions were treated every 14 days with a mean number of five treatments (range two to seven) and treatment was noted to result in complete regression of the lesions. Debulking or laser surgery is recommended on large SCC tumors prior to 5-FU treatment.

Mitomycin C is an antimicrobial agent with anti-tumor properties that inhibits DNA synthesis and replication.[42,43] It has the potential to selectively attack the hypoxic cell component of tumors, which can be advantageous against larger tumors.[44] It has been used topically to treat ocular squamous cell carcinoma in the horse, with curative rates reported to be 75% when used alone[45] or 90% when used in conjunction with carbon dioxide laser ablation.[43]

Bleomycin is a glycopeptide antitumor agent produced by the bacterium *Streptomyces verticillus*. The mechanism of action is breakage of DNA strands. Bleomycin has been evaluated in the treatment of periocular SCC in horses, but was not as effective when compared to cisplatin.[46]

Piroxicam is a non-steroidal anti-inflammatory drug (NSAID) which suppresses prostaglandin production by inhibiting the cyclooxygenase (COX) pathway. Most equine SCC tumors express COX-2[47] and it has been suggested that COX-2 derived prostaglandins may be responsible for tumor growth, angiogenesis and metastasis.[48,49] Consequently, administration of piroxicam or other COX-2 inhibitors may be beneficial in management of tumors through induction of apoptosis in tumor cells, inhibition of angiogenesis or inhibition of prostaglandin E_2 production.[47,50-51] Piroxicam has been used in the management of squamous cell carcinomas of the lip, face and third eyelid of horses.[50-52]

Immunotherapy involves stimulation of the immune system to reject or destroy cancer cells. Bacillus Calmette-Guerin (BCG), a cell wall extract developed from *Mycobaterium bovis*, has been the most commonly used immunotherapy agent in large animal veterinary medicine. In the horse, BCG has been used in the treatment of sarcoids[11] and periocular squamous cell carcinoma in a pony.[53] Bacillus

Calmette-Guerin has also been used in the treatment of bovine ocular SCC, with complete regression of the primary tumor noted in 70% of cases treated with BCG cell wall and 60% regression in cases treated with a live BCG vaccine.[54] Chemotherapeutic drugs have largely replaced BCG therapy in the horse for the treatment of SCC.[55]

Tumor location, size, extent of lymph node involvement, presence of metastases, degree of invasiveness and histopathologic appearance combine to dictate grade and stage of an equine SCC. Prognosis for a case of SCC in a horse is based on the aforementioned features and recurrence of the tumor if it had been treated. A majority of tumors that recur do so within a year and the overall rate of recurrence ranges from 11 to 30%.[17] Overall, the prognosis is guarded in all cases other than small lesions detected early.

In general, penile SCC lesions are usually managed by a combination of surgical excision, debulking or amputation potentially in combination with cryotherapy or topical application of 5-FU. A majority of the other treatments described have been used in other anatomical sites (i.e. periocular region) or have not been reported for management of penile SCC.

In the present case, surgical excision was chosen for treatment because of the location and small size of the tumor. Overall a guarded to poor prognosis was given for long-term health of the stallion. It is anticipated that additional squamous cell carcinoma lesions will be identified in this horse in the next few years due to the extensive pre-cancerous squamous dysplasia lesions identified on the penile shaft.

The immediate goal of the stallion manager was to be able to utilize the stallion in a pasture breeding program during the upcoming summer months. The future goal is to collect semen for cryopreservation in the event that the stallion is not able to live cover mares.

Summary

An aged stallion was presented with a focal squamous cell carcinoma lesion glans penis, multiple squamous dysplasia lesions on the penile shaft and a secondary balanitis associated with a mixed infection of *Streptococcus equi* subspecies *zooepidemicus* and *Trueperella pyogenes*. The infection was treated with a combination of local cleansing, topical antiseptics and systemic antibiotics. The SCC lesion on the glans penis was completely surgically excised. Other options for continued future therapy are discussed.

Learning points

- Squamous cell carcinoma is one of the most common neoplasms affecting the penis and prepuce of the adult horse.
- Tumors are usually locally invasive and metastasize slowly to the inguinal lymph nodes
- Medical management options include cryotherapy, radiofrequency hyperthermia, radiation therapy, photodynamic therapy, topical or intratumoral chemotherapy, and immunomodulators
- Tumor recurrence ranges from 11-30% and prognosis is usually guarded unless lesion is small and detected early

References

1. McDonnell SM: Oral imipramine and intravenous xylazine for pharmacologically-induced ex copula ejaculation in stallions. Anim Reprod Sci 2001;68:153-159.
2. Cecere JT: Eosin-nigrosin staining in the evaluation of sperm. In: Dascanio J, McCue P, editors. Equine reproductive procedures. Ames (IA): Wiley Blackwell; 2014. p. 373-376.
3. Edwards JF: Neoplasia of the reproductive tract. In: McKinnon AO, Squires EL, Vaala WE, et al, editors. Equine reproduction. Ames (IA):Blackwell Publishing Ltd, 2011. p. 1166-1171.
4. Schaffer PA, Wobeser B, Martin LER, et al: Cutaneous neoplastic lesions of equids in the central United States and Canada: 3,351 biopsy specimens from 3, 272 equids (2000-2010). J Am Vet Med Assoc 2013;242:99-104.
5. Bedford SJ, McDonnell SM, Tulleners E, et al: Squamous cell carcinoma of the urethral process in a horse with hemospermia and self-mutilation behavior. J Am Vet Med Assoc 2000;216:551-553.
6. Howarth S, Lucke VM, Pearson H: Squamous cell carcinoma of the equine external genitalia: A review and assessment of penile amputation and urethrostomy as a surgical treatment. Equine Vet J 1991;23:53-58.

7. Mair TS, Walmsley JP, PhillipsTJ: Surgical treatment of 45 horses affected by squamous cell carcinoma of the penis and prepuce. Equine Vet J 2000;32:406-410.
8. Van den Top JGB, De Heer N, Klein WR, et al: Penile and preputial tumors in the horse: a retrospective study of treatment of 77 affected horses. Equine Vet J 2008;40:533-537.
9. Knottenbelt DC, Patterson-Kane JC, Snalune KL: Tumors on the male and female reproductive systems and mammary gland. In: Clinical equine oncology, Edinburgh:Elsevier; 2015. p. 629-651.
10. Taylor S, Haldorson G: A review of equine mucocutaneous squamous cell carcinoma. Equine Vet Educ 2013;25:374-378.
11. Martens A, De Moor A, Vlaminck L, et al: Evaluation of excision, cryosurgery and local BCG vaccination for the treatment of equine sarcoids. Vet Rec 2001;149:665-669.
12. Scase T, Brandt S, Kainzbauer C, et al: *Equus caballus* papillomavirus-2 (EcPV-2): an infectious cause for equine genital cancer? Equine Vet J 2010;42:738-745.
13. Knight CG, Munday JS, J Peters, et al: Equine penile squamous cell carcinomas are associated with the presence of equine papillomavirus Type 2 DNA sequences. Vet Pathol 2011;48:1190-1194.
14. Edwards JF: Pathologic conditions of the stallion reproductive tract. Anim Reprod Sci 2008;107:197-207.
15. Brinsko SP: Neoplasia of the male reproductive tract. Vet Clin North Am Equine Practice 1998;14:517-533.
16. Lange CE, Tobler K, Lehner A, et al: EcPV2 DNA in equine papillomavirus and in situ and invasive squamous cell carcinomas supports papillomavirus etiology. Vet Pathol 2013;50:686-692.
17. Van den Top G: Squamous cell carcinoma of the penis and prepuce. In: Sprayberry KA, Robinson NE, editors. Robinson's current therapy in equine medicine. St. Louis: Elsevier 2015; p. 418-423.
18. Straffus AC: Squamous cell carcinoma in the horse. J Am Vet Med Assoc 1976;168: 61-62.
19. Van den Top JGB, Ensink JM, Barneveld A, et al: Penile and preputial squamous cell carcinoma in the horse and proposal of a classification system. Equine Vet Educ 2011;23:636-648.
20. Markel MD, Wheat JD, Jones K: Genital neoplasms treated by en bloc resection and penile retroversion in horses: 10 cases (1977-1986). J Am Vet Med Assoc 1988;192:396-400.
21. Palmer SE: Clinical use of a carbon dioxide laser in equine general surgery practice. Proc Annu Meet Am Assoc Equine Pract 1990;35:319-329.
22. Palmer SE: Instrumentation and techniques for carbon dioxide laser in equine surgery. Vet Clin North Am Equine Pract 1996;12:397-414.
23. McCauley CT, Hawkins JF, Adams SB, et al: Use of a carbon dioxide laser for surgical management of cutaneous masses in horses: 32 cases (1993-2000). J Am Vet Med Assoc 2002;220:1192-1197.
24. Alam M, Ratner D: Cutaneous squamous cell carcinoma. NE J Med 2001;344:983.
25. Theodorescu D: Cancer cryotherapy: evolution and biology. Rev Urol 2004;6(Suppl 4):S9-S19.
26. Graham G, Clark L: Statistical analysis in cryosurgery of skin cancer. Clin Dermatol 1990;8:101-107.
27. Grier RL, Brewer WG, Paul SR, et al: Treatment of bovine and equine ocular squamous cell carcinoma by radiofrequency hyperthermia. J Am Vet Med Assoc 1980;177:55-61.
28. Henson FMD, Dobson JM: Use of radiation therapy in the treatment of equine neoplasia. Equine Vet Educ 2004;16:315-318.
29. Théon AP, Pascoe JR: Iridium-192 interstitial brachytherapy for equine periocular tumours; treatment results and prognostic factors in 115 horses. Equine Vet J 1995;27:117–121.
30. Wyn-Jones G: Treatment of equine cutaneous neoplasia by radiotherapy using iridium 192 linear sources. Equine Vet J 1983;15:361-5.
31. Mosunic CB, Moore PA, Carmicheal KP, et al: Effects of treatment with and without adjuvant radiation therapy on recurrence of ocular and adnexal squamous cell carcinoma in horses: 157 cases (1985–2002). J Am Vet Med Assoc 2004;225:1733-1738.
32. Blackwood L, Dobson JM: Radiotherapy in the horse. Equine Vet Educ 1994;6:95-99.
33. Ericson MB, Wennberg A, Larko O: Review of photodynamic therapy in actinic keratosis and basal cell carcinoma. Ther Clin Risk Manag 2008;4:1-9.
34. Guiliano EA, Johnson PJ, Delgado C, et al: Local photodynamic therapy delays recurrence of equine periocular squamous cell carcinoma compared to cryotherapy. Vet Ophthal 2014;17(Suppl 1):37-45.
35. Eastman A: The mechanism of action of cisplatin: from adducts to apoptosis. In: Lippert B, editor. Cisplatin: chemistry and biochemistry of a leading anticancer drug. Wiley Online Library; 1999. Chapter 4.
36. Théon AP, Pascoe JR, Carlson GP, et al: Intratumoral chemotherapy with cisplatin in oily emulsion in horses. J Am Vet Med Assoc 1993;202:261-267.
37. Hewes CA, Sullins KE: Use of cisplatin-containing biodegradable beads for treatment of cutaneous neoplasia in equidae: 59 cases (2000–2004). J Am Vet Med Assoc 2006;229:1617-1622.
38. Théon AP, Wilson WD, Magdesian KG, et al: Long-term outcome associated with intratumoral chemotherapy with cisplatin for cutaneous tumors in equidae: 573 cases (1995-2004). J Am Vet Med Assoc 2007;230:1506-1513.
39. Longley DB, Harkin DP, Johnston PG: 5-Fluorouracil: mechanisms of action and clinical strategies. Nat Rev Cancer 2003;3:330-338.
40. Paterson S: Treatment of superficial ulcerative squamous cell carcinoma in three horses with topical 5-fluorouracil. Vet Rec 1997;141:626-628.

41. Fortier LA, MacHarg MA: Topical use of 5-fluorouracil for treatment of squamous cell carcinoma of the external genitalia of horses: 11 cases (1988-1992). J Am Vet Med Assoc 1995;205:1183-1185.
42. Nakata Y, Nakata K, Sakamoto Y: On the action mechanism of mitomycin C. Biochem Biophys Res Commun 1961;6:339-343.
43. Rayner SG, Van Zyl N: The use of mitomycin C as an adjunctive treatment for equine ocular squamous cell carcinoma. Aust Vet J 2006;84:43-46.
44. Kennedy KA, Rockwell S, Sartorelli AC: Preferential activation of mitomycin C to cytotoxic metabolites by hypoxic tumor cells. Cancer Res 1980;40:2356-2360.
45. Malalana F, Knottenbelt D, McKane S: Mitomycin C, with or without surgery, for the treatment of ocular squamous cell carcinoma in horses. Vet Rec 2010;167:373-376.
46. Théon AP, Pascoe JR, Madigan JE, et al: Comparison of intratumoral administration of cisplatin versus bleomycin for treatment of periocular squamous cell carcinomas in horses. Am J Vet Res 1997;58:431-436.
47. Thamm DH, Ehrhart EJ, Charles JB et al: Cyclooxygenase-2 expression in equine tumors. Vet Pathol 2008;45:825-828.
48. Leahy KM, Ornbert RL, Wang Y et al: Cyclooxygenase-2 inhibition by celecoxib reduces proliferation and induces apoptosis in angiogenic endothelial cells *in vivo*. Cancer Res 2002;62:625-631.
49. Masferrer JL, Leahy MK, Koki AT et al: Antiangiogenic and antitumor activities of cyclooxygenase-2 inhibitors. Cancer Res 2000;60:1306-1311.
50. Moore AS, Beam SL, Rassnicks KM, et al: Long-term control of mucocutaneous squamous cell carcinoma and metastases in a horse using piroxicam. Equine Vet J 2003;35:715-718.
51. Iwabe S, Ramírez-López L, Juárez-Sánchez, M: The use of piroxicam as an adjuntive treatment for squamous cell carcinoma in the third eyelid of a horse. Vet Méx 2009;40:389-395.
52. Dória RGS, Laskoski LM, Carvalho MB, et al: Use of chemotherapy as treatment of squamous cell carcinoma with metastasis in the face of a horse - case report. Rev Bras Med Vet 2012;34:336-340.
53. McCalla TL, Moore CP, Collier LL: Immunotherapy of periocular squamous cell carcinoma with metastasis in a pony. J Am Vet Med Assoc 1992;200:1678-1681.
54. Klein WR, Ruitenberg J, Steerenberg PA, et al: Immunotherapy by intralesional injection of BCG cell walls or live BCG in bovine ocular squamous cell carcinoma: a preliminary report. J Natl Cancer Inst 1982;69:1095-1103.
55. Hendrix DVH: Equine ocular squamous cell carcinoma. Clin Tech Equine Pract 2005;4:87-94.

Figure 1. Shaft of the penis prior to washing.

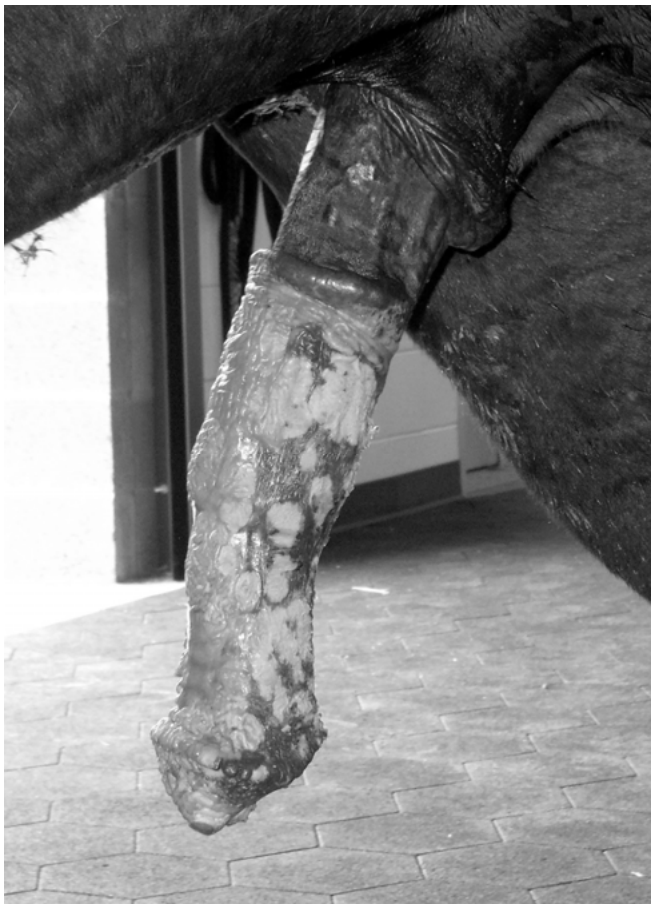

Figure 2. Shaft of the penis after washing showing with multiple areas of depigmentation.

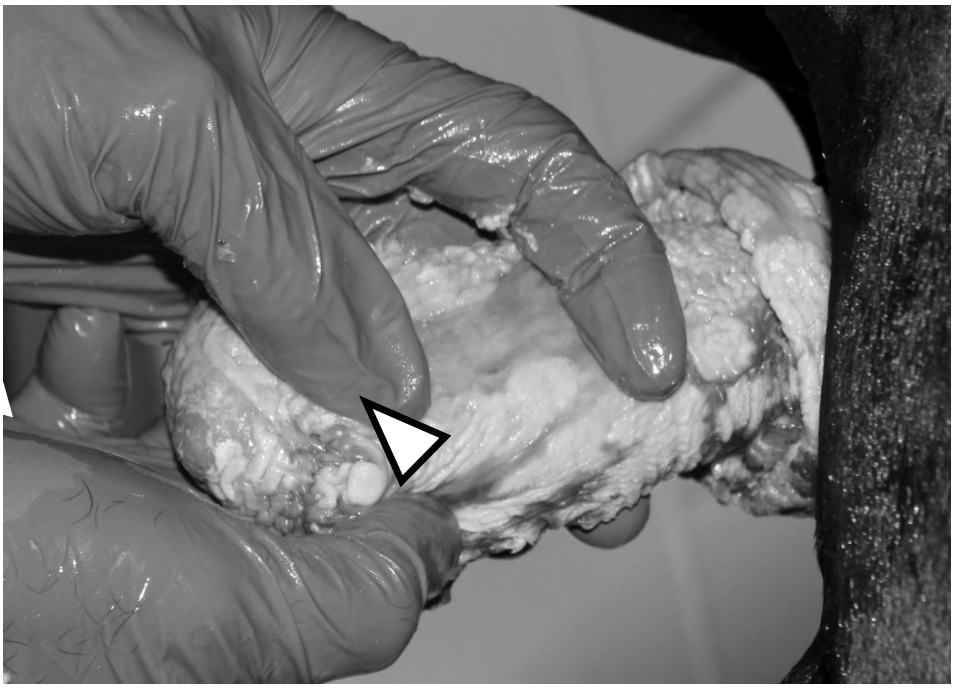

Figure 3. Raised proliferative lesion on glans penis (arrow) and areas of thickened and discolored epithelium (arrowhead).

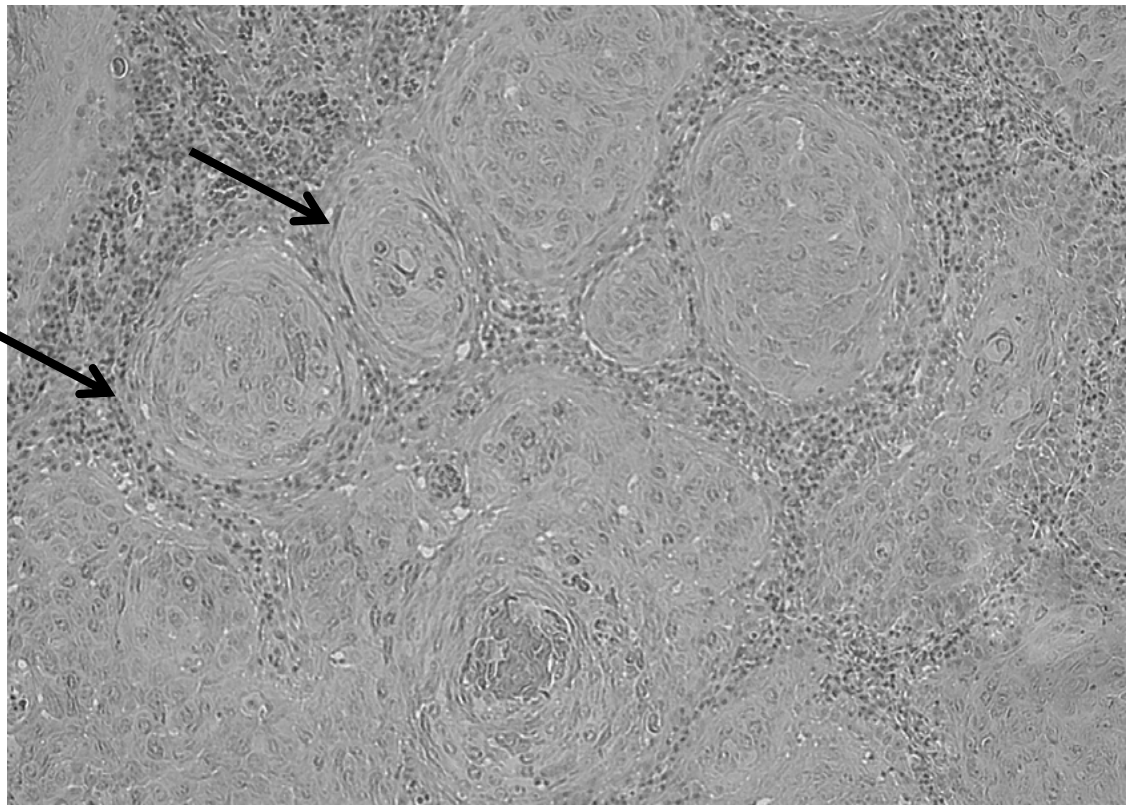

Figure 4. Histology of the squamous cell carcinoma lesion on the glans penis showing characteristic nesting of tumor cells and invasion into the submucosa.

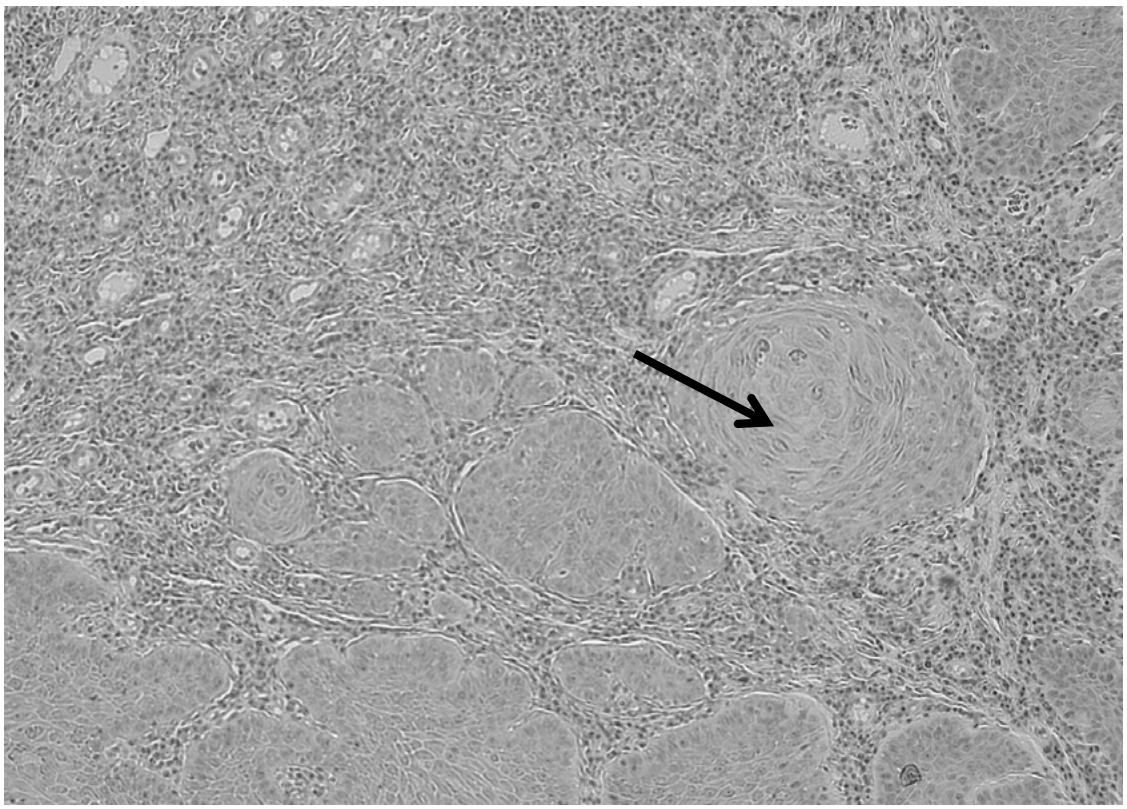

Figure 5. Squamous pearl.

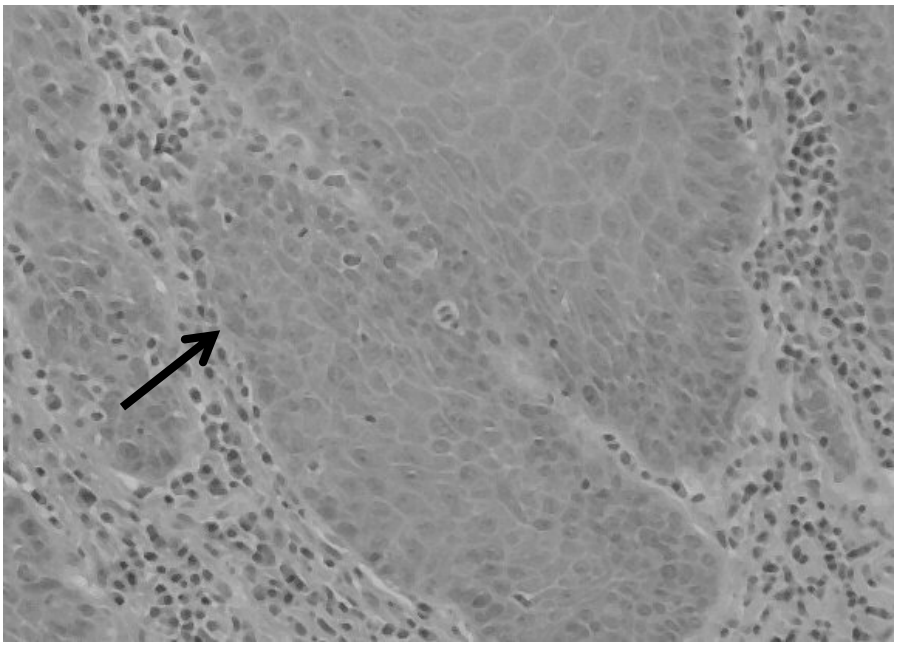

Figure 6. Cell undergoing mitosis in the squamous cell carcinoma.

Figure 7. Placing a ring block around distal end of penis.

Figure 8. Surgical excision of the tumor mass on the glans penis.

Figure 9. Suturing the defect in the glans penis after removal of the tumor mass.