

Equine Penile Squamous Cell Carcinoma

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Introduction:

Penile and preputial tumors are commonly found in the horse.^{3,4} These areas are covered by skin and mucosa, therefore, tumors can be of epithelial or mesenchymal origin.^{3,4} Squamous cell carcinoma (SCC) is the most common tumor affecting the penis and prepuce in the horse.^{3,4,5} Neoplasia in this region often leads to discomfort, and it can progress to even more severe sequelae, even resulting in death of the animal.^{3,4} Staging and classification of the primary tumor are vital for ascertaining prognosis, selection of proper treatment, and recurrence rate.^{2,4} Treatments range from minimally invasive nonsurgical interventions to radical surgery.³ Post-operative histopathological evaluation is key to determining the presence of complete or incomplete margins.^{3,4}

History and Presentation:

Jaxon is an approximately 19-year-old Mustang gelding who presented to MSU-CVM on March 28, 2017 for assessment and treatment of a penile tumor. Jaxon was rescued 6 weeks prior to presentation and was residing in foster care. The foster reported that the patient would sprinkle while trying to urinate and failed to extend his penis. She attempted to clean his sheath after administering acepromazine, but the original problem persisted. She cleaned the penis as thoroughly as possible, however the foul odor and debris persisted as well. About a week later, preputial and ventral midline swelling was noted and progressively worsened over the weekend. His regular veterinarian, Dr. Rebecca Longoria, assessed him on March 24th and suggested that Jaxon be brought to MSU-CVM for a surgery consultation.

Upon admission, Jaxon was bright, alert, and responsive. He weighed 725 pounds with a body condition score of 3.5/9. He had a heart rate of 60 beats per minute, respiratory rate of 40

breaths per minute, and temperature at 99.7 Fahrenheit. Thoracic auscultation revealed no abnormalities. He had a moderate sized plaque of ventral edema and moderate preputial edema. After being sedated with a total of 7 mg of detomidine and 7 mg of butorphanol, he relaxed sufficiently to allow a thorough penile and preputial exam. The glans and most of the free portion of the penis were firm. He had both proliferative tissue and severe erosion of the midshaft of his penis. The prepuce was mildly edematous, but was free of gross lesions. The external inguinal lymph nodes were both moderately enlarged and very firm. Rectal exam revealed no abnormalities.

Pathophysiology:

Approximately 6-10% of neoplasia in the horse affect the external genitalia.^{3,4} Squamous cell carcinoma occurs the most with an incidence of 49-82.5%.³ This tumor is commonly found in older horses with many studies suggesting the average age is 17.4-19.5 years.^{3,4} Ponies have been found to be more susceptible than their horse counterparts, but this could be attributed to their higher average life expectancy.^{3,4} Breeds such as Appaloosas and American Paint horses with nonpigmented genitalia are believed to have a predilection for the development of SCC.^{3,4}

In many equine histopathological reports on penile tumors, papillomas have been found undergoing transition to SCC.^{3,4} Recently, a novel papillomavirus termed *Equus caballus* papillomavirus-2 (EcPV-2) has been identified in penile papillomas and SCC.^{3,4} The viral DNA and RNA was present in genital tumors, but not found in adjacent histologically normal tissue.^{3,4} EcPV-2 DNA was not detected in scrotal tissue and most smegma from tumor-free horses.^{3,4} The papilloma virus is believed to be the initiator of SCC development, but smegma may act as a promoter in the disease process.^{3,4}

Diagnostic Approach/Considerations:

A thorough history and physical exam along with clinical signs and diagnostic tools can aid in the diagnosis of SCC, but definitive diagnosis is declared on histopathology. Clinical signs can manifest from the primary tumor or arise from the secondary inflammatory processes. There is a vast array of clinical signs including depigmented plaques, nonhealing erosions with or without granulation tissue, and in more advanced stages, the tumor may have the proliferative cauliflower-like appearance or exist as a solid mass.^{3,4} Other common signs include interference with protrusion or extraction, intense, pungent odor due to infection or even secondary necrosis, edema of the prepuce and disturbed micturition.^{3,4} In 53-84% cases with equine penile and preputial SCC the glans penis is involved.^{3,4} Sedative administration aids in relaxation of the retractor penis muscle allowing thorough visual inspection and palpation of the prepuce and penis for tumor evaluation. Ultrasonographical examination may aid in analyzing the gross extent of the tumor and degree of involvement in various structures.^{3,4} Pathological evaluation of the primary tumor is necessary to classify the tumor and establish a treatment plan.^{3,4} This can be achieved by fine needle aspiration biopsy (FNAB) or by a punch or excisional biopsy. For SCC a full thickness biopsy to evaluate tumor architecture and depth of lesion invasion is more reliable than FNAB.^{3,4} Histopathological features of invasive SCC are comprised of small aggregates, irregular islands, nests, or cords of neoplastic keratinocytes that propagate downward from the epidermis and invade the subepithelial stroma of the dermis.^{3,4}

In evaluating horses with preputial and penile SCC metastasis is a major concern. The superficial and deep inguinal lymph nodes are affected first, followed by the medial iliac lymph nodes which can be evaluated per rectum by palpation and ultrasonographically.^{3,4} Enlarged

lymph nodes should have samples collected by FNAB and examined cytologically.^{3,4} False negatives have an incidence of 29% and the absence of lymph node enlargement does not exclude metastasis.^{3,4} Distant metastasis to the lung is relatively rare in the horse, but if SCC has invaded the corpus cavernosum or spongiosum, neoplasia can spread to other areas of the body through circulation.^{2,3,4}

Treatment and Management:

Histopathological grading and tumor staging using the TNM classification system, commonly used in human medicine for malignant tumors, is essential in helping veterinarians evaluate prognostic factors and select an appropriate treatment plan for the patient.^{2,3,4} Using the TNM classification system, the 'T' denotes the size of the tumor and invasion of adjacent tissue, the 'N' defines the extent of regional lymph node, and the 'M' signifies the presence of distant metastasis.^{2,3,4} Histopathological grading is determined by examining a representative biopsy of the tumor. Malignant tumors are divided into Grade 1 (G1) as well differentiated SCC, Grade 2 (G2) as moderately differentiated SCC, and Grade 3 (G3) as poorly differentiated SCC.^{2,3,4} Although SCC can be heterogeneous,^{2,3,4} Van den Top et al. found a positive correlation between a higher grade tumor and the incidence of metastasis.^{2,3} Multiple studies suggest that horses with SCC invasion into the corporeal bodies and urethra are at higher risk for metastasis.^{2,3} Increased risk of recurrence has been shown with regional lymph node involvement.³ No successful treatment has been established for cases with pelvic lymph node involvement or presence of distant metastasis.³

The main goal of treatment is to eliminate the tumor while preserving the natural function of the external genitalia, although this goal is not always attainable.^{3,4} Nonsurgical techniques

including hyperthermia, cryotherapy, radiotherapy, and topical use of 5-fluorouracil and cisplatin intratumor injection have been used, but the major limiting factor for these methods is the size and stage of the tumor.^{3,4} Many of these noninvasive techniques require surgical debulking prior to treatment, or they are used in conjunction with surgery.^{3,4} Surgical intervention is directed at removing the primary malignant lesion with sufficient margins, therefore minimizing the risk of reoccurrence.^{3,4} There are many surgical techniques, including simple excision, segmental posthioplasty, partial phallectomy, partial phallectomy combined with sheath ablation, and en bloc penile and preputial resection with penile retroversion. In cases with well or moderately differentiated (G1 or G2) tumors that do not invade surrounding structures, local excision, cryotherapy, and posthioplasty can be considered.^{3,4} Tumors that are relatively confined but invasion of subepithelial tissue is suspected and/or anatomical reconstruction after excision is not achievable, a partial phallectomy is indicated.^{3,4} More radical procedures such as partial phallectomy with sheath ablation or en bloc penile and preputial resection with penile retroversion are needed with more extensive or poorly differentiated tumors, and this is the treatment of choice for tumors with metastasis to the regional lymph nodes without distant metastasis.^{3,4} Tumor reoccurrence is the main factor influencing prognosis with an overall reoccurrence incidence of 11-30% within the first year regardless of treatment choice.^{3,4} Less invasive treatment modalities, such as local excision and partial phallectomy have a relatively high rate of recurrence of 54-67% likely due to insufficient surgical margins.^{3,4} More invasive treatment therapies including en bloc penile and preputial resection with penile retroversion had a lower recurrence of 12.5%.^{3,4,5} Even with metastasis to the regional lymph nodes, success rates of the surgical techniques were as high as 86-100%.²

Case Outcome:

Based on our physical exam findings, treatment options discussed with the owner included standing modified Vinsot's technique for partial phallectomy or penile amputation with lymph node removal under general anesthesia. Due to financial concerns and the less invasive nature of the procedure, the standing procedure without lymph node removal was chosen for Jaxon. This procedure is effective for horses who are unsuitable candidates for general anesthesia based on medical or financial constraints.¹

Complete blood count and serum chemistry were performed and analyzed prior to the procedure. These diagnostics were unremarkable apart from mild anemia that was attributed to chronic disease. Jaxon was then placed in the stocks and sedated. A stallion catheter was inserted into the penis to the bladder. A subischial urethrostomy was performed by making a vertical incision that extended through the retractor penis muscles, bulbospongiosus muscle, the corpus spongiosum penis and urethral mucosa overlying the catheter. A permanent urethral stoma was created and the stallion catheter was removed. A ring block with carbocaine was placed at the proximal penis. A partial phallectomy was performed using a tourniquet placed by a Callicrate Bander™ 2 cm proximal to the site of penile transection. The procedure was unremarkable and upon returning to his stall Jaxon urinated a strong stream through his perineal urethrostomy. The penis was submitted for histopathology and results revealed locally extensive and infiltrative squamous cell carcinoma with intralymphatic tumor embolus. In hospital Jaxon received his Encevac-T vaccine, Procaine Penicillin-G as a prophylactic antibiotic and flunixin meglumine for pain and inflammation. Jaxon was sent home on exercise restriction for 4 weeks and prescribed Tucoprim and phenylbutazone. His foster reported that he was doing well at home

after his surgery. Unfortunately, approximately 6 months after surgery Jaxon's condition deteriorated and he was humanely euthanized.

REFERENCES:

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Penile squamous cell carcinomas (SCCs) are common tumors in older horses, with poor prognosis mostly due to local invasion and recurrence. These tumors are thought to be mainly caused by Equus caballus papillomavirus type 2 (EcPV-2). The aim of this study is to characterize the tumor immune environment (TIME) in equine penile tumors. *Equine Penile Squamous Cell Carcinomas as a Model for Human Disease: A Preliminary Investigation on Tumor Immune Microenvironment.* by Ilaria Porcellato. After sarcoids, squamous cell carcinomas are considered the most common equine neoplasm¹⁻³. Around one tenth of all equine neoplasms are diagnosed in the penis, vulva and ocular adnexa^{4,5} of which EpSCC is the most common. Incidence rates of EpSCC, reported more in ponies compared to horses⁶, vary and no specific breed predilection has been ascertained⁶. However, it is difficult to separate cause from effect from these findings. The diagnostic and prognostic indicators rely on histopathological interpretation, whilst mechanisms of molecular carcinogenesis are not yet known. We recently discovered that the activation of the Wnt pathway is an important feature of human penile squamous cell carcinoma¹⁸. 3 Bell Equine Veterinary Clinic, Maidstone, UK. 4 Queen's Medical Research Institute, University of Edinburgh, Edinburgh, United Kingdom. 5 Research Department of Cell and Developmental Biology, The Centre for Cell and Molecular Dynamics, Rockefeller Building, University College London, London, United Kingdom. 6 Prostate Cancer Research Centre at the Centre for Stem Cells and Regenerative Medicine, King's College London, London, United Kingdom. aamir.ahmed@kcl.ac.uk.