Squamous Cell Carcinoma of the Urinary Bladder in a Horse

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A 14-year-old Hanoverian gelding was evaluated after a 10-week history of occasional straining during urination and dark red urine production after exercise. Physical examination findings were within normal limits. After 2 weeks of clinical signs, ultrasonography had found no abnormalities in the kidneys or bladder. A freely voided urine sample revealed an elevated protein concentration (500 mg/dL; reference range: <100 mg/dL) and few red blood cells. Vitamin C supplementation was suggested to acidify the urine, as was provision of a salt block to encourage water intake.

The horse returned 6 weeks later for further evaluation. The urine had remained discolored, and the horse was hesitant to move forward under saddle. The vital parameters were within normal limits. The results of physical and lameness examinations were normal. The horse was ridden for over an hour to mimic home observations and to demonstrate urine abnormalities after work. Urination after exercise demonstrated frank blood at the end of the urine stream. Transrectal ultrasonography of the apex of the urinary bladder revealed a 5 × 8–cm soft tissue mass attached to and within the bladder wall (FIGURE 1; FIGURE 2).

The horse was sedated using detomidine (0.006 mg/kg IV), and cystoscopy showed a large, irregular-surfaced mass disrupting the mucosa of the bladder at the apex (FIGURE 3). The mass was ulcerated, pink, approximately 10 cm in diameter, and attached to and within the bladder wall. The remainder of the bladder had no obvious abnormalities. The ureters were of normal size and appearance. Because of the apparent focal characteristic of the mass, partial cystectomy was recommended, and the horse's owner elected it.

Preoperatively, the horse was given procaine penicillin G (22,000 IU/kg IM), gentamicin (6.6 mg/kg IV), and flunixin meglumine (1.1 mg/kg IV). General anesthesia was induced using xylazine (0.7 mg/kg IV), diazepam (0.2 mg/kg IV), and ketamine.
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(2.2 mg/kg IV) and was maintained using sevoflurane. The horse was placed in dorsal recumbency. A 20-cm, left parainguinal incision was made using a #21 blade. The subcutaneous tissues were sharply and bluntly dissected. A #10 blade was used to make a 20-cm incision through the aponeurosis of the external abdominal oblique muscle, which was split bluntly, and the peritoneum was incised. Palpation of the abdominal viscera identified no abnormalities except for the bladder. The apex and body of the bladder were exteriorized through the incision. The apex was enlarged and firm due to the mass, which was approximately 10 × 6 cm. The serosal surface of the bladder apex was inverted and hemorrhagic (FIGURE 4).

The mass in the apex involved the full thickness of the bladder wall. The remaining bladder wall was edematous but otherwise normal. Tissue margins defining the mass seemed grossly evident. The mass was sharply excised along with a 1-cm margin of normal tissue. The mass appeared to be completely excised. The bladder was closed in two layers using #2-0 polydioxanone in a simple continuous pattern with a Lembert oversew. The body wall was closed in five layers. The rectus abdominis muscle was closed using #3 polyglactin 910 in a simple continuous pattern. The aponeurosis of the rectus abdominis muscle was closed using #3 polygastro 910 in a simple continuous pattern. The fat and subcutaneous tissues were closed in two layers using #0 polydioxanone in a simple continuous pattern. The skin was closed using #0 polydioxanone in a simple continuous pattern.

The horse recovered from anesthesia without complications. Systemic antibiotics (procaine penicillin G [22,000 IU/kg IM q12h], gentamicin [6.6 mg/kg IV q24h]) were given for 5 days; flunixin meglumine (1.1 mg/kg IV) was given q12h for 2 days followed by q24h for 2 days, and then 0.25 mg/kg IV q6h for 1 day. Starting on day 2 after surgery, the horse was hand-walked for 10 to 15 minutes once or twice per day. Some moderate ventral, perincisional edema developed 3 to 5 days after surgery. The horse was discharged on day 5 after surgery. Continued treatment included administration of trimethoprim-sulfamethoxazole (60 mg/kg PO q24h for 5 days) and piroxicam (0.2 mg/kg PO q24h for 2 weeks).

On gross pathologic examination, the mass was slightly soft and measured 10 × 6 cm. The serosal surface was pink and smooth, except for the inverted center. The mucosal surface of the bladder was rough and necrotic with foci of black indentations and sites of hemorrhagic ulceration, with raised, pink sites in between. The mass extended into the lumen approximately 4 cm (FIGURE 5).

Sections of the mass were fixed in 10% buffered neutralized formalin, prepared, and stained with hematoxylin-eosin. The mass obliterated a large portion of the mucosa and invaded the muscularis layer. Cords of squamous epithelial cells formed keratin “pearls” in the center of many nests of these cells. The neoplastic cells were large and had large, round vesicular nuclei with an average of one or two mitoses per high-power field (×400). These observations were consistent with a diagnosis of squamous cell carcinoma (SCC). Four margins (resulting from quadrant bisection) were examined. One margin had dense desmoplasia (peritumor fibroplasia) containing several small, finger-like nests of neoplastic cells. The neoplasm was variably infiltrated by lymphocytes and was moderately aggressive, with evidence of deep invasion into the urinary bladder wall to the level of the tunica muscularis. One margin had finger-like extensions of neoplastic cells that extended near the edge of the resected tissue (FIGURE 6). Close observation for local recurrence and monitoring of regional lymph nodes for evidence of metastasis were recommended.
Two weeks after surgery, a follow-up examination, ultrasonography of the bladder and abdomen, and cystoscopy were performed. Ultrasonography demonstrated a focal, extraluminal, echodense nodule in the urinary bladder; this was likely tissue folding from the sutured bladder closure and smooth mucosa. Endoscopy of the bladder revealed mucosal folding from the surgical site at the apex and slight hyperemia. Administration of piroxicam (0.2 mg/kg PO q24h) was continued and reevaluation scheduled to take place in 30 days.

At reevaluation 6 weeks after surgery, the physical examination findings were within normal limits. Per-rectum ultrasonography of the left iliac lymph node revealed a heterogenous appearance with hyperechoic nodules (FIGURE 7). The urinary bladder wall had mounding tissue at the previous surgical site, with echodense tissue of approximately 2 × 3 cm under the wall. After the horse was sedated with xylazine (0.5 mg/kg IV) and acepromazine (0.02 mg/kg IV), cystoscopy showed hyperemic mucosa at the apex of the bladder and raised, rough tissue along the previous incision line. Samples were taken for cytology and histopathology, which confirmed the raised tissue to be SCC. Despite the guarded long-term prognosis due to the heterogenous lymph node, the owner elected a second partial cystectomy.

For the second partial cystectomy, the preoperative medication, induction and maintenance of anesthesia, and surgical approach were similar to those for the first surgery. The apex and the body of the bladder were exteriorized through the incision. The previous incision was identified, as well as a firm, approximately 6-cm mass that was palpable on the mucosal surface of the bladder at the apex. The mass involved the full thickness of the bladder wall. The remaining bladder wall was edematous but otherwise seemed normal. Stay sutures were placed, and the bladder was packed with laparotomy sponges. A 3- to 4-cm margin was used to excise the previous incision line and the mass in total, which comprised approximately one-half of the bladder volume. The bladder was closed in two layers using #2-0 polydioxanone in a simple continuous pattern with a Lembert oversew. The body wall was closed in five layers, similar to the first procedure.

The horse recovered from anesthesia without complications. Systemic antibiotics were continued: procaine penicillin G (22,000 IU/kg IM q12h for 5 days), gentamicin (6.6 mg/kg IV q24h for 5 days), and flunixin meglumine (1.1 mg/kg IV q12h for 5 days). Some moderate, ventral, periincisional edema developed 3 days after surgery, as did mild serous incisional drainage, which resolved the next day. The horse was discharged on day 5 after surgery. Continued treatment included flunixin meglumine (1.1 mg/kg PO q24h for 3 days), trimethoprim-sulfamethoxazole (60 mg/kg PO q24h for 7 days), and piroxicam (0.2 mg/kg PO q24h).

Sections from the anterior aspect of the mass, the single nodule along one margin, and the corrugated, ulcerated mucosal region from the previous surgical site were fixed in 10% buffered neutralized formalin, prepared, and stained with hematoxylin-eosin. All of the sections showed a margin of normal urinary bladder mucosa next to a recurrence of the original neoplasm. Nests of various sizes had neoplastic squamous cells with large, vesicular nuclei and keratinized central regions that penetrated to the submucosa and muscularis. One section had a vessel containing a cluster of cohesive neoplastic cells, some of which were keratinized, within the lumen. There were scattered infiltrates of moderate numbers of lymphocytes along the mucosa and margins of the neoplasm (FIGURE 8). These findings confirmed recurrence of SCC along the original incision site, with possible metastasis due to the presence of an intravascular lesion. Close monitoring for local regrowth and metastasis was recommended.

The horse recovered well and returned for reevaluation 2 weeks after surgery. Transrectal ultrasonography found multiple small regions of echodense material surrounding suture material, which was likely consistent with normal tissue healing. The iliac lymph node that was abnormal on the previous examination had not changed.
One month later, the horse returned for reevaluation and was sedated using xylazine (0.4 mg/kg IV) and detomidine (0.006 mg/kg IV). Transrectal ultrasonography showed no bladder abnormalities, with a small amount of sediment in the ventral urinary bladder. The abnormal iliac lymph node from the previous examination could not be identified. Urinary cystoscopy showed some mucosal hemorrhage after the catheterization and some sediment, but results of cystoscopy of the bladder were within normal limits. Continued administration of piroxicam was recommended to inhibit regrowth and metastasis.

At reevaluation 10 weeks after surgery, the owner reported good progress: the horse had returned to light activity and was moving well. The horse was sedated using xylazine (0.4 mg/kg IV) and detomidine (0.006 mg/kg IV). The findings of per-rectum palpation were within normal limits. Ultrasonography of the bladder demonstrated excess sediment in the ventral bladder. Visualization of the regional lymph nodes revealed no abnormalities. Endoscopy of the urinary bladder revealed normal mucosa at the bladder apex and no evidence of abnormal tissue. Endoscopy confirmed the presence of crystalline sediment in the ventral bladder. Continued administration of piroxicam was recommended. The incision had healed well, and the horse returned to normal exercise over the following weeks.

At reevaluation 6 weeks later, the owner reported that the horse had been hesitant to finish feed off the ground. A full physical examination demonstrated some muscle soreness in the croup and neck, which was likely secondary to the return to exercise. The horse was sedated in a manner similar to that in previous examinations. Rectal palpation revealed no abnormalities. Transrectal ultrasonography of the urinary bladder demonstrated some excess sediment in the ventral bladder but less than in previous examinations. Findings from ultrasonography of the regional lymph nodes were within normal limits. Cystoscopy revealed normal mucosa at the bladder apex, with no evidence of irritation. Administration of piroxicam was continued, and flunixin meglumine (1.1 mg/kg IV) was given as needed by the owner for the horse’s mild muscle soreness.

Approximately 3 weeks later, the horse returned to the hospital for evaluation of acute swelling of the left hindlimb. The owner noticed mild swelling in the left hindlimb 1 week before presentation and had been treating it with hydrotherapy and flunixin meglumine (1.1 mg/kg IV q24h). On presentation, the horse was bright, alert, and responsive. All vital parameters were within normal limits. There was some pitting edema from the fetlock to the stifle on the left hindlimb and in the prepuce and the ventral abdomen. The horse was slightly stiff on the left hindlimb but not appreciably lame. The diagnosis was nonseptic cellulitis with poor lymphatic return, possibly due to previous surgical procedures. Treatment with dimethyl sulfoxide (1 mg/kg IV q12h) and trimethoprim-sulfamethoxazole (30 mg/kg PO q12h) was started, and administration of flunixin meglumine (1.1 mg/kg IV q12h) and warm-water hydrotherapy with hand-walking were continued. The edema readily responded to treatment, and the horse was sent home the following day with trimethoprim-sulfamethoxazole (30 mg/kg PO q12h for 10 more days) and flunixin meglumine (1.1 mg/kg PO q24h for 7 more days).

When the horse returned 20 days later for reevaluation, the owner reported a good recovery from the cellulitis on the left hindlimb but had recently noticed a swelling behind the left caudal-most rib. On initial examination, the epaxial muscles above the ribs on the left side were atrophied. There was some contracture of the intercostal muscles in the flank region. No lymph node enlargement was noted. Due to the unusual presentation, ultrasonography of the bladder was performed. The transrectal findings were within normal limits, and no mass effect was evident in the bladder wall. Percutaneously, on the left body wall, there was possible retroperitoneal fluid deep to the caudal ribs; this was likely due to trauma and a possible seroma because no other abnormalities were found. It was recommended to restart administration of flunixin meglumine (0.5 mg/kg PO q12h for 5 days), stall rest and daily hand-walk the horse, and administer hydrotherapy to the whole left hindquarters to encourage lymphatic return.

Approximately 2 weeks later, the horse returned with signs of mild discomfort, and the left hindlimb was swollen again. On physical examination, the vital parameters were within normal limits. Marked atrophy was noticed in the epaxial muscles, more so on the left side. The left hindlimb had pitting edema from the fetlock to the hock, and the prepuce had mild pitting edema. Abdominal ultrasonography found no abnormalities. On per-rectum palpation, there was a large, cobble-stoned, plaque-like mass in the dorsal retroperitoneal region cranial to the large vessel bifurcation and caudal to the left kidney. Transrectal ultrasonography confirmed the presence of a large, irregular mass between the vascular branches (Figure 9). The findings from examining the bladder were within normal limits. Blood work revealed mild hyperalbuminemia (3.3 g/dL) and hypercalcemia (13.6 mg/dL), which could be consistent with recurrence of SCC. The owner elected to take the horse home and give flunixin meglumine (1.1 mg/kg PO q12–24h) as needed and declined to have the mass biopsied because of the risk associated with the location of the mass and the high likelihood that it was a recurrence of SCC. The owner also declined retreatment with intralesional cisplatin because of the risk associated with the location of the mass and because of the cost.

The horse returned 3 weeks later to be euthanized because it was showing signs of mild to moderate discomfort despite administration of flunixin meglumine (1.1 mg/kg PO q12h) and had become anorectic. Euthanasia was performed using pentobarbital (65 mg/kg). Necropsy was declined by the owner.
Discussion

Primary urinary bladder neoplasia in horses is uncommon.1–3 The most common bladder neoplasm is SCC.1,3 Transitional cell carcinoma has also been described in horses.1,4–6 Lymphosarcoma, hemangiosarcoma, and melanoma rarely metastasize to the bladder.2,3 Horses with bladder tumors typically have signs of weight loss and hematuria and may also have polakiuria and stranguria.1–3 The mass may be palpated on rectal examination and can be confirmed by transrectal ultrasonography and cystoscopy.2,3 Urinalysis usually shows hematuria and occasionally reveals exfoliated neoplastic cells.2,3 Historically, treatment of bladder neoplasia includes surgical excision combined with topical chemotherapy using 5-fluorouracil, triethylenethiophosphoramide,1 or cisplatin.5

SCC is one of the most common tumors in horses but is more common in anatomic locations other than the bladder, such as the external genitalia, the skin, the stomach, and the eye. Presentation and diagnosis of SCC vary with the location. Masses on the skin, genitalia, and ocular structures are grossly evident, and diagnosis can easily be made using biopsy and histopathology. Horses with gastric SCC present with clinical signs including anorexia, emaciation, colic, dysphagia, and neutrophilia. Either gastroscopy with biopsy and histopathology or exploratory laparotomy can yield a diagnosis in most horses.6,7 Management of equine SCC depends on the location and size of the tumor, the available equipment, and the cost of treatment. With penile and preputial SCCs, tumor grading can help select the treatment and determine the prognosis. Complete phallectomy and preputial resection with penile retroversion and removal of inguinal lymph nodes can result in the lowest rate of tumor recurrence compared with other therapies, such as cryosurgery and partial phallectomy and sheath ablation.9 Potential therapies for ocular SCC include surgical resection, strontium 90 irradiation, interstitial radiotherapy, external beam radiotherapy, radiofrequency hyperthermia, intratumoral or topical chemotherapy, carbon dioxide laser ablation, and cryotherapy.9 Adjuvant radiation therapy for ocular and adnexal SCCs has produced a much lower recurrence rate than that of tumors treated without it.10 The high risk of recurrence makes successful therapy difficult.1,10

Recently, NSAIDs have been shown to (1) reduce the recurrence rate and stabilize or reduce the size of tumors of the colon and (2) decrease angiogenesis in tumor models.11 Cyclooxygenase-2 (COX-2) is an inducible enzyme involved in prostaglandin production during pathologic events. COX-2-derived prostaglandins have been linked to tumor growth, metastasis, and angiogenesis.11 Many types of tumors, including some SCCs, upregulate COX-2 in their tissues. A link between COX immunoreactivity in canine SCC and NSAID sensitivity12 has been described. Several studies have demonstrated that equine SCCs have increased expression of COX-1 and COX-2.9,13–16 This has led to some new therapies for equine SCC. Piroxicam, a nonspecific COX blocker, has been used to successfully treat canine SCC.12,13 Although equine SCC appears to have less specific immunoreactivity to COX than canine SCC,9,14 piroxicam may still be a valid treatment for horses because it reduces direct DNA damage, prevents malignant transformation of cells, and stimulates immunity by reducing prostaglandin E2 production by neoplastic and other effector cells. Piroxicam also suppresses cellular proliferation by reducing prostaglandin E2 production, inhibits angiogenesis, interacts with growth factors, and induces apoptosis.11,12,16 Anecdotal and clinical evidence has indicated that piroxicam alone or with adjunct therapy, such as surgical excision or administration of chemotherapeutic agents, can provide long-term control of SCC in horses.17 Further research is needed to fully assess the long-term and adverse effects of piroxicam in horses, but this drug may have fewer gastrointestinal and renal effects than other nonselective NSAIDs, as suggested by use in dogs.12

The long-term prognosis for horses with SCC depends on the tumor location. As demonstrated in this case, even with aggressive treatment such as full resection and administration of COX-2 inhibitors, recurrence is likely. With superficial tumors (e.g., ocular, external genitalia, and skin tumors), resection and intralesional therapy are easier to perform, possibly improving the likelihood of successful therapy. Diagnosis and treatment of intraabdominal SCC are associated with more difficulties, which can lead to a poor prognosis.

References