Case Report

Transitional cell carcinoma of the urinary bladder in a 12-year-old Belgian Warmblood gelding

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Keywords: horse; transitional cell carcinoma; urinary; bladder; piroxicam

Summary
A 12-year-old Belgian Warmblood gelding was examined for haematuria and dysuria of 24 h duration. Cystoscopy revealed an intraluminal multinodular soft tissue mass originating from the dorsal bladder neck. Histopathological examination of biopsies identified transitional cell carcinoma. The bladder mass was surgically debulked via a temporary perineal urethrotomy. The horse commenced treatment with oral piroxicam. Follow-up examination 18 months post operatively revealed no evidence of tumour recurrence. Neoplasia of the equine bladder is uncommon and this case describes the successful short-term outcome of treatment of a transitional cell carcinoma by surgical debulking and oral piroxicam.

Case details

Case history
A 12-year-old Belgian Warmblood gelding was examined for a 24 h history of stranguria and haematuria. The owner reported that the horse had had no previous problems with urination.

Clinical findings and investigation

On examination the horse was bright, alert and responsive. All clinical parameters were within normal limits. Rectal examination revealed a partially full bladder with no palpable calculi. At the bladder neck an area of thickened soft tissue was palpable. Transrectal ultrasonography showed hyperechoic urine within the bladder and an ill-defined circular structure on the dorsal bladder wall on the left hand side. The left ureter appeared thickened, but the kidney appeared normal with no evidence of hydronephrosis indicating obstruction. The horse was sedated (500 mg xylazine i.v. and 10 mg butorphanol i.v.) and a urinary catheter was passed which yielded thick sabulous urine. The bladder failed to empty normally and was irrigated with 0.9% saline to remove the remaining sediment. Urinanalysis revealed haematuria, proteinuria and pyuria. Moderate amounts of epithelial cells, erythrocytes and bacteria were seen on urine cytology. Bacterial culture yielded no growth. Haematology and serum biochemistry profiles were within normal limits.

Cystoscopy revealed an intraluminal multinodular soft tissue mass originating from the left dorsal bladder neck (Fig 1). The left ureteral opening was obscured by the mass but urine was seen exiting the opening. The right ureteral opening appeared grossly normal. Multiple mucosal pinch biopsies of the mass were obtained via the endoscope. Histopathological examination of the biopsies revealed areas of neoplastic change consistent with TCC.

Standing radiography of the thorax showed no abnormalities of the lungs. A routine standing laparoscopic examination was performed to visualise the serosal surface of the bladder and assess the peritoneal cavity for any metastases. Prior to surgery the horse was administered phenylbutazone (4.4 mg/kg bwt i.v.), benzylpenicillin sodium (10 mg/kg bwt i.v.) and gentamicin sulfate (6.6 mg/kg bwt i.v.). The horse was sedated with 6 mg detomidine hydrochloride i.v. and 10 mg butorphanol i.v. Sedation was maintained throughout the laparoscopy via i.v. detomodine. The horse was sedated with 6 mg detomidine hydrochloride i.v. and 10 mg butorphanol i.v. Sedation was maintained throughout the laparoscopy via i.v. detomodine infusion administered to effect. Xylazine (0.22 mg/kg bwt) and lidocaine (0.35 mg/kg bwt) were administered epidurally in a 12 ml total volume of sterile saline. Routine exploratory laparoscopy via the left paralumbar fossa did not reveal any evidence of further masses, although the serosal surface of the

Introduction
Primary neoplasia of the equine urinary bladder is rare. The most commonly reported neoplasm of the bladder in the horse is squamous cell carcinoma (SCC) (Fischer et al. 1985; Gandini et al. 1998; Serena et al. 2009). Whilst transitional cell carcinoma (TCC) is the most frequently reported primary bladder neoplasm in the dog (Mutsaers et al. 2003) and man (Johansson and Cohen 1997), it has rarely been reported in the horse with only 5 previously published cases (Traub et al. 1983; Fischer et al. 1985; Servantie et al. 1986; Turner et al. 1995; Patterson-Kane et al. 2000). Other reports of neoplasia of the horse bladder include lymphosarcoma, leiomyosarcoma, fibromatous polyp and rhabdomyosarcoma (Sweeney et al. 1991; Turnquist et al. 1993; Hurcombe et al. 2008; Barrell and Hendrickson 2009; Waldrige 2010).

There are few reports of attempted treatment of bladder neoplasia in horses and in most recorded cases the affected horses were subjected to euthanasia. Chemotherapy with doxorubicin and dexamethasone was unsuccessful in treating a poorly differentiated leiomyosarcoma of the bladder in a mare reported by Hurcombe et al. (2008). Failed attempts to surgically excise a rhabdomyosarcoma and a SCC have also been previously described (Turnquist et al. 1993; Gandini et al. 1998). Monthly manual debulking and 5-fluorouracil instillation was anecdotally reported to be effective in one mare with SCC of the bladder (Cornelisse 2003) and resection cystoplasty followed by oral piroxicam therapy was effective (no recurrence within 6 months) in another mare with SCC of the bladder described by Serena et al. (2009). This report describes the successful short-term management of a TCC in the bladder of an adult gelding by surgical debulking and oral piroxicam.

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caudal bladder wall was mildly oedematous and discoloured, with oedema of the lateral ligament.

Treatment
Following completion of the laparoscopic examination and routine closure of the laparoscopic portals, a 5 cm temporary perineal urethrotomy was performed. A flexible endoscope was passed through the urethrotomy to visualise the mass at the bladder neck. The mass was surgically debulked with laparoscopy scissors and Babcock forceps via the urethrotomy. Mild haemorrhage from the excision site was observed. Samples of the mass were fixed in 10% formal saline and sent for histological examination. The urethrotomy was allowed to heal by secondary intention. Post operatively, the horse received gentamicin sulfate (6.6 mg/kg bwt i.v. q. 24 h) for 3 days, benzylpenicillin sodium (10 mg/kg bwt i.v. q. 8 h) and meloxicam (0.6 mg/kg bwt per os q. 24 h) for 5 days. On Day 6 the horse commenced oral potentiated sulfonamides (25 mg sulfadiazine and 5 mg trimethoprim/kg bwt per os q. 24 h) for 7 days.

Repeat cystoscopy performed 24 h after surgical debulking revealed a small mass of abnormal tissue remaining at the surgical site [Fig 2]. The ureteral opening was visible and urine was seen exiting the opening. Over the next 5 days, the horse remained bright, alert and responsive with only a few episodes of dysuria. Small amounts of haemorrhage were seen during urination for up to 3 days post operatively. The horse was discharged from the hospital 5 days after surgery. The urethrotomy and laparoscopy portals healed with no complications. Treatment with piroxicam (0.2 mg/kg bwt per os q. 24 h) was commenced 10 days post operatively and piroxicam continued at this dose for 4 months and then reduced to 0.1 mg/kg bwt per os q. 24 h.

Outcome
The horse was re-examined at the clinic 3 days following discharge from the hospital after the owner was concerned that he had become dysuric. Cystoscopy revealed mild inflammation within the bladder but the site of tumour excision was similar to its appearance 24 h after the surgery. The horse commenced oral phenylbutazone (2.2 mg/kg bwt per os q. 12 h) for 5 days.

At 4 weeks post surgery the horse was re-examined. Rectal palpation was unremarkable and cystoscopy showed a small, smooth swelling close to the left ureteral ostium. Mucosal pinch biopsies obtained via the endoscope showed the presence of urothelium with extensive vacuolation, glandular metaplasia, and chronic inflammation; there was no evidence of neoplastic change.

Further follow-up examinations 4, 11 and 18 months post operatively revealed no abnormalities on cystoscopy apart from mild thickening around the left ureteral opening [Fig 2]. Thirty months after treatment, the owner reported no recurrence of haematuria but had observed one episode of self-resolving dysuria approximately 9 months after treatment.

Histopathology
The mass was submitted as 4 pieces of tissue, ranging from 1.7 x 1.7 x 1 to 5 x 2.5 x 1.5 cm in size. Areas of the surface were roughened and the samples were grossly opaque, grey and gelatinous. Routine histological examination identified portions of a polypoid lesion, with an oedematous, inflamed stroma, populated by plump spindle to stellate-shaped cells with foci of mature fibrous tissue and areas of granulation tissue formation. The surface epithelium was frequently separating with foci of ulceration. The remaining surface epithelium was hyperplastic or dysplastic, with foci of neoplastic transformation showing loss of definition of the basal cell layer and/or infiltration of the underlying stroma [Fig 3]. There was also extensive intestinal epithelial differentiation (intestinal metaplasia), present either as a single layer of cells, or as a surface layer covering several layers of squamous epithelial

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cells (Figs 4 and 5). Islands of poorly differentiated squamous and glandular epithelial cells were present within the stroma, deep to the surface epithelial layer (Fig 6). The overall histopathological appearance was of a polypoid lesion with a range of changes present within the epithelial component including TCC, carcinoma in situ, Brunn's nest formation, glandular metaplasia, intestinal metaplasia and transitional cell hyperplasia and dysplasia.

Immunohistochemistry was also performed and revealed numerous cyclooxygenase-2 (COX-2) positive atypical epithelial cells that exfoliated and invaded the superficial stroma within multiple fragments of the tissue. This indicated the potential value of COX-inhibitors as a potential treatment.

A final diagnosis of TCC was made.

Discussion

Transitional cell carcinoma has been rarely reported in the equine bladder with no previously published reports of successful treatment of TCC in the horse. The combination of surgical debulking and oral piroxicam appeared to be successful in this case, although the relative efficacy of these 2 different treatments in achieving resolution of the tumour is impossible to establish. Piroxicam is commonly used in combination with chemotherapy to treat TCC in dogs (Henry 2003) and selective cyclooxygenase-2 (COX-2) inhibitors, such as celecoxib, have also been used as part of multimodal therapy for treating urothelial cell carcinoma in people (Dovedi and Davies 2009). The apparent remission of the tumour and healing of the surgical site despite the presence of a residual mass after surgical debulking is, however, suggestive that piroxicam helped to resolve the disease.

The urinary tract is lined by transitional cells that extend from the renal pelvis to the ureters, bladder and urethra and additionally includes the prostatic ducts and prostatic urethra in males. Transitional cell carcinoma may arise from any part of the urinary tract but, in horses, they have been most frequently reported in the bladder wall (Traub et al. 1983; Fischer et al.
1985; Turner et al. 1995; Patterson-Kane et al. 2000) with one report of a TCC of the renal pelvis (Servantie et al. 1986). This is similar to man where >90% cases occur in the bladder (Tanaka and Sonpavde 2011).

No breed or sex predispositions are apparent from the reported cases. All affected horses were adults, with ages ranging from 7 years to 15 years (mean 11.6 years). In dogs, studies have found that females are at higher risk than males (female: male ratio 1.7:1) with neutered individuals of both sexes at higher risk (Mutsaers et al. 2003). This is in contrast to man, where the male to female ratio is 7:1 (Tanaka and Sonpavde 2011). Risk factors identified in the dog include topical flea and tick treatments, obesity and exposure to farm insecticides (Mutsaers et al. 2003). In man, smoking remains the highest risk factor, with exposure to carcinogenic agents also identified as a cause (Tanaka and Sonpavde 2011). No risk factors have been identified to date in the horse.

Various clinical signs of TCC have been reported with haematuria being the commonest presenting sign (reported in 4/5 cases) followed by stranguria (2/5) and weight loss (2/5). Neurological deficits and fertility problems were observed in 2 cases, as a result of metastatic spread (Traub et al. 1983; Turner et al. 1995). Other clinical signs included bladder dysfunction, recurrent urinary tract infections and colic. Haematuria and stranguria of acute onset were the first signs observed in this case. This is similar to the case reported in Patterson-Kane et al. (2000), where the horse presented with acute onset of severe haematuria. All other cases report clinical signs of more chronic duration (2 months–3.5 years).

Clinical signs of bladder neoplasia are similar to that of cystic calculi. Rectal palpation and transrectal ultrasonography can be used to differentiate between these conditions. The use of cystoscopy allows direct visualisation of the bladder. It also enables biopsies of any mass to be performed. In a study of 92 dogs with histologically diagnosed TCC, cystoscopic biopsy samples were of diagnostic quality in 65% of male dogs and 96% of female dogs (Childress et al. 2011).

The case described herein had no abnormalities on haematological and serum biochemical evaluation. Other published cases reported anaemia (2/4 cases), leucocytosis with neutrophilia (3/4 cases) and hypokalaemia (1/4 cases). Urinalysis was performed in 4/5 cases. All 4 cases reported haematuria and proteinuria with 2 cases also having neutrophilia (3/4 cases) and hypokalaemia (1/4 cases). Published cases reported anaemia (2/4 cases), leucocytosis and hypokalaemia (2/4 cases). All affected horses were adults, with ages ranging from 7 years to 15 years (mean 11.6 years). In dogs, studies have found that females are at higher risk than males (female: male ratio 1.7:1) with neutered individuals of both sexes at higher risk (Mutsaers et al. 2003). This is in contrast to man, where the male to female ratio is 7:1 (Tanaka and Sonpavde 2011). Risk factors identified in the dog include topical flea and tick treatments, obesity and exposure to farm insecticides (Mutsaers et al. 2003). In man, smoking remains the highest risk factor, with exposure to carcinogenic agents also identified as a cause (Tanaka and Sonpavde 2011). No risk factors have been identified to date in the horse.

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The cyclooxygenases (COX) catalyse the conversion of arachidonic acid to prostaglandins. In most species, COX-1 is a constitutive isoform expressed in many tissues and involved primarily in homeostatic functions, whereas COX-2 is a principally inducible isofom, found at sites of inflammation (Smith et al. 2000). Epidemiological and experimental evidence indicates that dysregulated inflammation is associated with carcinogenesis in many tumours [Zhu et al. 2011]. Inflammation contributes to survival and proliferation of malignant cells, tumour angiogenesis, metastasis and reduced response to chemotherapy. In many species, including man and dogs, COX-2 is over-expressed in many different tumour types and nonsteroidal anti-inflammatory drugs can be effectively used as adjunctive therapies (Spugnini et al. 2005; Khan et al. 2011). Investigations on the expression of COX-2 in equine tumours have yielded variable results and the significance of COX-2 expression in equine neoplasia has still to be defined (Dore 2011). There have, however, been a limited number of reports, both published and anecdotal, of successful treatment of equine tumours (notably squamous cell carcinoma) by oral administration of piroxicam, a nonselective cyclooxygenase inhibitor [Moore et al. 2003; Elce et al. 2007; Iwabe et al. 2009; Serena et al. 2009]. In the current case, the TCC was shown by immunohistochemistry to have a high level of COX-2 expression and, for this reason, treatment with piroxicam was initiated. Whether or not this treatment aided in resolution or prevention of recurrence of the tumour is unclear. In conclusion, TCC is an unusual tumour of the equine bladder that can present with acute onset signs of haematuria and stranguria. The successful outcome of this case suggests that treatment by surgical debulking and use of piroxicam can be effective (assuming that no metastasis has occurred). However, further studies are required to elucidate the importance of COX-2 expression and the potential role of anti-inflammatory drugs in treatment.

Authors’ declaration of interests
No conflicts of interest have been declared.

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References


