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Polypoid cystitis as a cause of haematuria in a pony mare

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Summary

A 15-year-old pony mare was presented for investigation of haematuria of two weeks' duration. On cystoscopy, multiple small pedunculated soft tissue structures were observed on the bladder mucosa. Histopathological analysis of the masses was consistent with chronic polypoid cystitis. The polypoid lesions and associated haematuria resolved following prolonged antibiotic treatment. Polypoid cystitis has not previously been described in horses. This condition should be considered a differential for haematuria, requiring cystoscopy and biopsy to confirm a diagnosis.

Introduction

Haematuria can arise from haemorrhage anywhere along the urinary tract. Commonly recognised causes of haematuria in horses include urethral defects (Schumacher *et al.* 1995), uroliths (Lund *et al.* 2013), various forms of neoplasia (Fischer *et al.* 1985; Voeroes *et al.* 1993; Hurcombe *et al.* 2008)

and urinary tract infections (pyelonephritis and cystitis) (Kisthardt *et al.* 1999; Saulez *et al.* 2005). Less commonly, haematuria has been associated with exercise (Schott *et al.* 1995), idiopathic renal haemorrhage (Schott 2009; Gracia-Calvo *et al.* 2014), certain toxicoses including Blister beetle (cantharidin) ingestion (Schoeb and Panciera 1978; Schmitz 1989), gentamicin toxic nephropathy (Riviere *et al.* 1982) and long-term or excessive NSAID administration (Aleman *et al.* 2011).

The term 'polypoid cystitis' is used to describe a condition of the urinary bladder featuring reversible, outward-growing (polyp-like) inflammatory lesions (Kiliç *et al.* 2002). The condition is a rare cause of gross haematuria in humans that is often mistaken as an indicator of neoplastic bladder disease (Lane and Epstein 2008). Histologically, polypoid cystitis is characterised by urothelial hyperplasia with microabscess formation within the urothelium (Ekelund 1983). Oedema of the submucosa, infiltration with lymphocytes and granulocytes, increased vascularity and evidence of haemorrhage are also described. In humans, polypoid cystitis commonly occurs as a result of bladder mucosal injury secondary to urolithiasis (Martinez *et al.* 2003) or urethral catheterisation (Ekelund 1983), but in some cases an underlying aetiology is not identified (Kiliç *et al.* 2002). For humans, the reasons for presentation are usually related to bladder obstruction or haematuria (Kiliç *et al.* 2002; Lane and Epstein 2008). Polypoid cystitis has been documented in dogs for which the most common reason for presentation is gross haematuria, with abnormal urination behaviour also common (Moses *et al*. 2002; Martinez *et al*. 2003; Eo Jin *et al.* 2009). The condition has also been reported in domestic cattle associated with bracken fern toxicosis (Carvalho *et al.* 2006). Polypoid cystitis has not been documented in horses and this report describes haematuria related to the condition in an otherwise healthy pony.

Case details

Case history

A 15-year-old Australian Riding Pony mare presented to the University of Melbourne's Veterinary Teaching Hospital (VTH) with a history of discoloured (red-tinged) urine present throughout urination. The discoloured urine was first noticed by the owners 2 weeks previously and was not associated with exercise. The owners reported neither signs of abdominal discomfort nor signs of dysuria, stranguria or pollakiuria. The mare did not have access to known noxious plants, including bracken fern. On initial evaluation by the referring veterinarian, the pony appeared to be in good health with a normal heart rate, respiratory rate and rectal temperature. Following sedation with detomidine (Dormosedan[1]; 0.01 mg/kg bwt i.v.), a speculum examination of the vagina and cervix was performed and was considered normal. A urine sample collected at the same visit had a specific gravity of 1.015, with dipstick evaluation revealing a pH of 8.0 and moderate proteinuria. On sediment examination, greater than 200 erythrocytes per high powered field (HPF) were observed although the white cell count of the sample was normal (<5 per HPF) and there was no evidence of casts or crystals. Culture of the urine sample was not performed based on the absence of pyuria.

Haematology and plasma biochemistry profiles collected at the time of this initial evaluation were normal. Based on these findings, the pony was referred to the VTH for further evaluation.

Clinical findings

On presentation to the VTH, the mare was bright and alert and in good condition (BCS 6 out of 9) (Henneke *et al.* 1983). Resting heart (44 beats/min) and respiratory (14 breaths/min) rates were normal with no abnormalities appreciated on thoracic auscultation. Rectal temperature was 37.7°C. Oral mucous membranes were pink with a capillary refill time of less than two seconds. No evidence of mucosal haemorrhage suggestive of primary haemostatic dysfunction was present. Hydration, based on skin turgor, jugular refill and mucous membrane character, was considered adequate. The pony showed no signs of abdominal discomfort or evidence of urinary incontinence or stranguria during evaluation at the VTH.

The mare was sedated with detomidine (Dormosedan[1]; 0.01mg/kg bwt i.v.) and butorphanol (Torbugesic[1]; 0.01mg/kg bwt i.v.). Vaginoscopy was unremarkable and the external *os* of the cervix was closed with no discharge evident. Cystoscopy revealed grossly red-tinged urine that was evacuated using gentle suction. There was no evidence of sabulous material accumulation within the bladder. The majority of the bladder mucosa appeared grossly normal; however, there were multiple small, polypoid structures projecting from the mucosa throughout the bladder (Fig 1). Haemorrhage from the mucosal attachment of several of these lesions was evident. Several pinch biopsies were collected from lesions and the adjacent (grossly normal) bladder mucosa and submitted for histopathology. Urine expelled from both ureters appeared grossly normal.

Following cystoscopy, palpation of the bladder *per rectum* was performed with no abnormalities appreciated. Transrectal ultrasonography revealed focal thickening of the bladder wall and focal irregularities of the bladder mucosa. Transcutaneous ultrasonography of the kidneys was considered normal.

Histopathology Results

Histologic examination of the pinch biopsy samples identified intracellular swelling and cystic vacuolation of epithelial cells and there was accumulation of mildly degenerate neutrophils forming microabscesses (Fig 2A). The urothelium was hyperplastic with neutrophilic infiltration accompanied by diffuse oedema of the submucosa and dilation of submucosal vessels (Fig 2B). Superficially, the epithelium was intact with fibrinosuppurative exudation. There were moderate numbers of gram positive cocci located within fibrinosuppurative exudate in one (the largest) sample but this was not observed in others. Histopathology of the apparently normal mucosa revealed mildly oedematous epithelium with minimal evidence of inflammation. No evidence of atypical cells or mitotic figures to suggest a neoplastic process was present in any of the sections examined. Based on the histologic findings, a diagnosis of chronic polypoid cystitis was made.

Differential diagnoses

Neoplasia of the urinary tract was considered most likely at the time of initial evaluation at the VTH, although the appearance of the bladder mucosa was not consistent with previously described bladder neoplasms. Squamous cell carcinoma (Fischer *et al*. 1985; Serena *et al.* 2009), transitional cell carcinoma (Lisowski *et al.* 2015), lymphosarcoma (Sweeney *et al.* 1991; Meyer *et al.* 2006) and leiomyosarcoma (Hurcombe *et al.* 2008) have been reported as causes of haematuria in horses, although they are typically associated with difficulty urinating and/or systemic illness which was not evident in this patient. Other differentials included benign fibromatous/fibroepithelial polyps (Fischer *et al.* 1985), urothelial papilloma or polypoid formation secondary to cystitis although the latter two have not been previously described in horses (Tsuzuki and Epstein 2005). Pyelonephritis as a cause of the haematuria was considered unlikely given the pony's good health and the absence of signs of a systemic illness on physical examination, haematological analysis and urinalysis.

Treatment

Based on reports in dogs with polypoid cystitis, a 2-week treatment trial of trimethoprim sulfadimidine (Trimidine[2]; 30mg/kg bwt *per os* q12h) was initiated. The significance of the bacteria observed histologically was unclear; however, based on the clinical course (see below), it was assumed that a bacterial infection was at least a component of the aetiology. The mare was discharged from hospital the same day of examination. Repeat cystoscopy was scheduled for 2 weeks' time, with view to perform urine culture if there was no evidence of clinical improvement following empirical antibiotic treatment.

Outcome and follow-up

Two weeks after the initial presentation, communication via a telephone conversation with the owners indicated that the haematuria had resolved and that the mare remained otherwise healthy. Cystoscopy was postponed and treatment with the potentiated sulphonamide continued. Repeat cystoscopy was performed approximately 3 weeks after presentation to the VTH to monitor the response to treatment. Subjectively, the appearance of the urine was much improved although there had been little or no change in the appearance of the mucosal polypoid lesions. Urine collected from both ureters was grossly normal in appearance; white cell counts estimated from a haemocytometer were 11 leukocytes/μL from the left ureter and 10 leukocytes/μL from the right. Both samples also had increased red cell counts (19,800-29,621 erythrocytes/μL); this was thought to be a result of trauma associated with sample collection or perhaps vesicoureteral reflux. Renal haemorrhage was considered unlikely based on the overall clinical picture but could not be completely excluded. No bacteria or neoplastic cells were identified in either sample. Due to the clinical improvement, urine culture was not performed and antibiotic treatment was continued for a further 2 weeks.

One week after discontinuing antibiotics (6 weeks after initial evaluation), cystoscopy revealed grossly normal urine and both ureters were observed to expel urine that was grossly normal. There was a marked reduction in the number and size of the polypoid lesions with only a few areas of slightly raised, irregular bladder mucosa and no evidence of haemorrhage. Biopsies were not collected nor were further urinalyses performed due to the clinical improvement. No further treatment was prescribed and the owner was advised to revisit in 4-6 weeks' time unless the haematuria re-occurred.

Prior to the final cystoscopy and 8 weeks after discontinuing antibiotic therapy, the owners had not observed the pony to urinate. Red-tinged urine was found upon bladder catheterisation and 2 small, slightly raised areas of mucosa were present on cystoscopy. Another larger, more pedunculated mass was also noted. Urine expelled from both ureters appeared grossly normal. Histopathological evaluation of a pinch biopsy collected from the larger mass confirmed polypoid cystitis. Given the clinical improvement previously achieved with potentiated sulphonamide treatment, a 4-week course of trimethoprim sulphadimidine (30 mg/kg bwt *per os* q12h) was re-instigated. Telephone follow-up with the owners one and 5 months after discontinuing medication revealed that the pony's haematuria had resolved.

Discussion

Polypoid cystitis is a non-neoplastic condition affecting the bladder mucosa that is associated with gross haematuria in humans and dogs but, as far as the authors are aware, has not previously been reported in horses. A fibromatous polyp characterised by fibrous tissue covered by transitional epithelium has been described in one horse (Fischer *et al.* 1985). However, that case lacked the histological signs of inflammation of the lesions observed in this case, and did not display the hyperplastic transitional epithelium with associated inflammation and oedema. In this case, a diagnosis of polypoid cystitis was made in an otherwise healthy middle-aged pony based on histological findings. Although surgical removal of polypoid lesions is the recommended treatment in human patients, resolution of haematuria and a marked regression of the lesions were achieved in this case with prolonged, broad-spectrum antimicrobial therapy.

Polypoid cystitis is suggested to arise from chronic irritation of the bladder mucosa. In humans the condition is most commonly associated with an indwelling urinary catheter, although the condition has been reported in the absence of urinary catheterisation (Kiliç *et al.* 2002; Young 1988). In dogs, polypoid cystitis has been associated with bacterial urinary tract infections and uroliths (Martinez *et al.* 2003). However, a definitive aetiology has not yet been determined for dogs and it is unclear whether the associated bacterial infection is a cause or a consequence of the polypoid lesions. In the medical literature, the terms polypoid and papillary cystitis have historically been used interchangeably. However, while the two conditions represent a continuum and both are characterised by inflammation and proliferation of the bladder mucosal epithelium, polypoid and papillary cystitis can be distinguished grossly and on their histological appearance. Grossly, polypoid lesions appear as

oedematous, broad-based outgrowths of the epithelium while papillary lesions appear as thin frond-like projections (Young 2009). Polypoid cystitis is frequently confused with urinary tract neoplasia based on both gross inspection at cystoscopy and, in some cases, histology. A human study reported that 26% (41/155) of cases of polypoid cystitis were initially incorrectly diagnosed as papillary urothelial neoplasms (Young 1988; Lane and Epstein 2008). The prevalence of haematuria in humans with polypoid cystitis has not been reported, but 82% of canine cases reportedly present with gross haematuria (Martinez *et al.* 2003). Simultaneous regression of the polypoid lesions and resolution of the gross haematuria in combination with the overall clinical picture suggests that, in this mare, haematuria resulted from bladder mucosal bleeding. However, it can often be difficult to definitively exclude other sources of haemorrhage.

Cystitis is uncommon in horses and not typically associated with obvious haematuria, although this might depend on the underlying cause and severity of disease. The significance of the proteinuria detected on initial dipstick urine analysis is questionable in this case, as there were no other indicators of renal disease and quantification was not performed. Alkalotic urine or increased haemoglobin concentrations will both result in a positive protein reaction on dipstick analysis; the latter being the most likely explanation in the current case (Wilson 2007). Urinalysis was not consistent with an ascending bacterial infection of the bladder and predisposing factors (e.g. urolithiasis or neurological bladder dysfunction) for cystitis were not identified in this case. Further, no signs of abnormal urination or systemic illness were reported to suggest a pre-existing cystitis that could have led to formation of the polypoid lesions. The clinical improvement following antibiotic treatment provides circumstantial evidence of bacterial involvement; urinary culture might have helped to delineate that relationship but, unfortunately, was not performed in this case. Interestingly, numerous bacterial species have been cultured from dogs with polypoid cystitis perhaps suggesting that opportunistic bacteria are harboured within the polypoid tissue rather than causing the lesions (Martinez *et al.* 2003). In addition to urine culture, culture of biopsy samples is recommended as urine culture is often negative even when bacteria are present (Kiliç *et al.* 2002; Martinez *et al.* 2003).

Where relevant, the removal of potential irritants is advocated for the resolution of polypoid cystitis. Removal of permanent indwelling urinary catheters resulted in disappearance of the polypoid lesions in one case series in human patients (Ekelund 1983). If this fails, surgical excision or partial cystectomy is recommended and is considered the more effective treatment strategy for polypoid cystitis in humans and dogs (Kiliç *et al.* 2002; Martinez *et al.* 2003). Antibiotics such as amoxicillin, enrofloxacin and potentiated sulphonamides have been used with initial resolution of clinical signs in dogs, but cessation of treatment was generally followed by recurrence of haematuria (Martinez *et al.* 2003). The decision to use a potentiated sulfonamide in this case was based on the availability of an oral formulation to facilitate long-term administration by the horse's owners, its broad spectrum of activity and the ability to reach high concentrations in the urinary tract (Duijkeren *et al.* 1994).

As with many clinical cases, financial constraints limited some aspects of the investigation of this case. As mentioned, culture of urine and biopsy samples might have helped determine the role of bacteria in this condition and allowed more targeted antimicrobial therapy. The high erythrocyte count and leukocytes present in the ureteral samples was considered most likely due to trauma during sample collection or secondary to vesicoureteral reflux rather than of renal origin, but this could not be confirmed with concurrent or follow-up analysis from ureteral and bladder urinary samples. Additionally, inconsistency in the way that erythrocyte counts were reported prevented useful comparison between urine samples collected from different sites (ureter versus bladder) and at different time-points. This last point highlights the importance of consistent testing methodology, particularly in chronic cases. A final cystoscopy to confirm complete resolution of the polypoid formation would have been ideal, but was not performed.

The aetiology of polypoid cystitis in humans and domestic animals appears complex and remains poorly understood. Whilst the condition is commonly associated with irritation or trauma to the bladder mucosa, this is not always the case. Further, the role of bacteria in polypoid cystitis remains to be elucidated. Surgical removal is currently advocated for treatment of polypoid cystitis in dogs and humans because, although initially responsive, the condition tends to recur with even very prolonged courses of antibiotics. However, in the equine case described here, remission or resolution of the condition appeared to be associated with the prolonged administration of broad-spectrum antibiotics, suggesting that some cases of polypoid cystitis might not require surgical intervention.

Authors' declaration of interests

No conflicts of interest have been declared.

Ethical animal research

Institutional animal ethics approval was not required for this case report.

Authorship

All authors contributed to clinical case management. The manuscript was drafted by C. Rosales and revised by the other authors. All authors approved the final version of the manuscript.

Manufacturers' addresses

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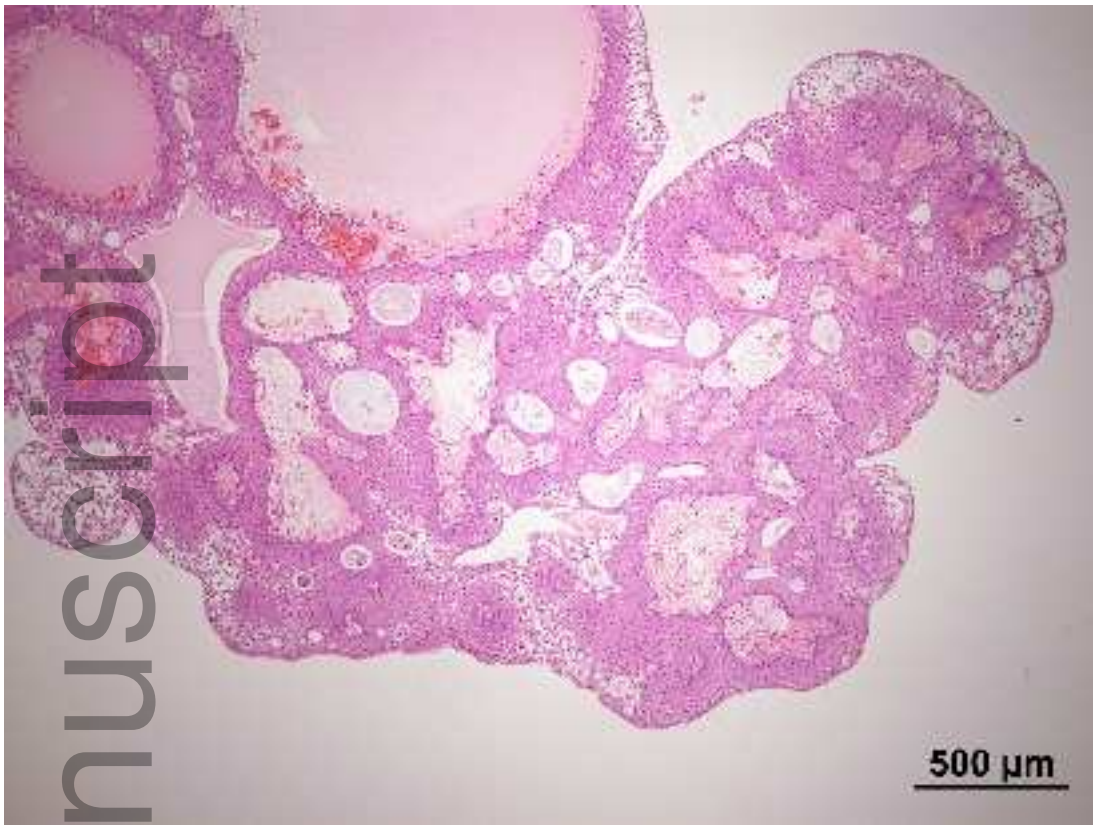
Figure legends

Fig 1: Cystoscopic view of one of the polyps emerging from the bladder mucosa at the initial visit.

Fig 2A: Biopsy of urinary bladder displaying markedly hyerplastic urothelium with neutrophilic infiltrate and intraepithelial microabscess formation, supported by loose oedematous submucosa. HE stain.

Fig 2B: Biopsy of urinary bladder (at higher magnification) showing projections of hyperplastic urothelium with multifocal neutrophil infiltration, supported by oedematous stroma containing marked dilated vessels. HE stain.



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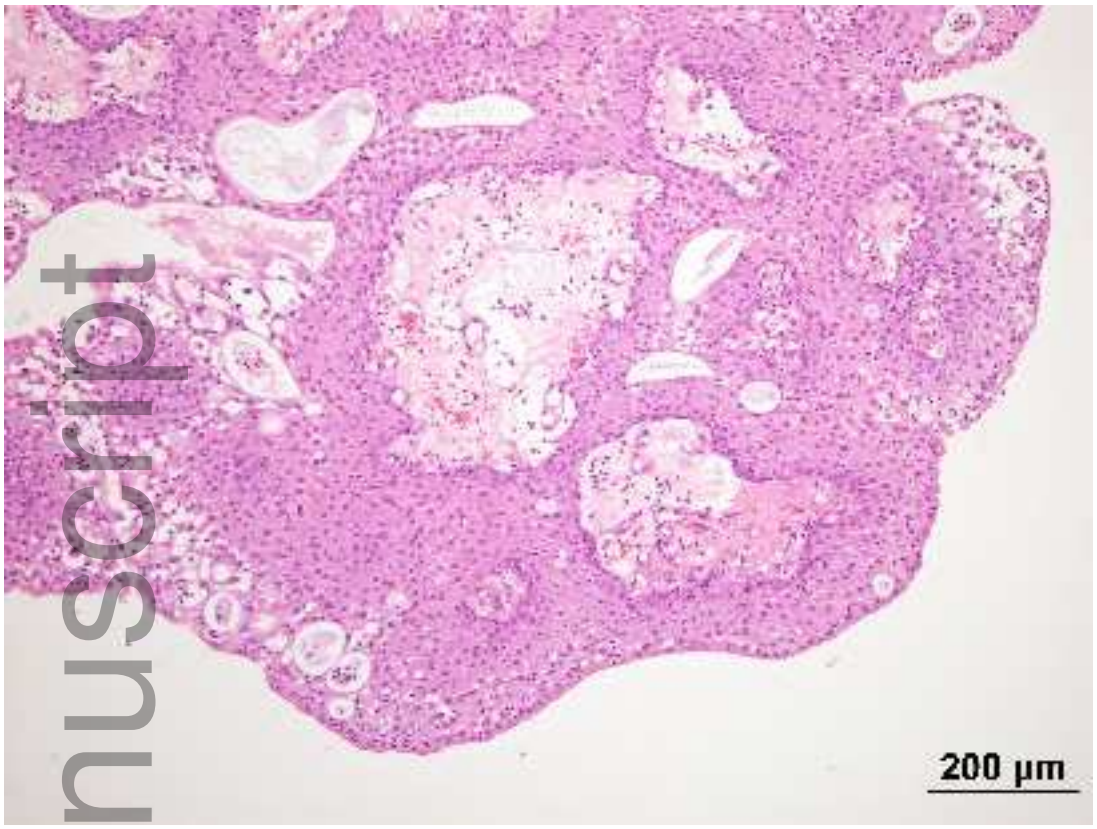

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