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Case Report

Funiculitis causing sepsis-associated laminitis in a Mangalarga Marchador gelding

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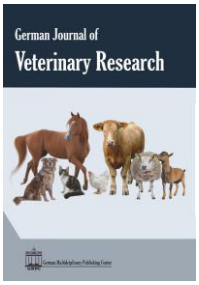

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Abstract
Castration is one of the most common surgical procedures performed in equine practice, and potential complications may range from mild to life-threatening conditions. This paper aims to report clinical and laboratory features, treatment, and long-term follow-up information in a case of funiculitis causing sepsis-associated laminitis and acute renal failure (ARF) in a Mangalarga Marchador gelding. A 5-years-old Mangalarga Marchador gelding was referred for hospital care after seven days of an open orchiectomy approach on farm-setting. Physical examination revealed hyperemic mucous membranes, dehydration, tachycardia, scrotal swelling with a foul-smelling serosanguinous discharge, increased hoof temperature and digital pulse amplitude, and lameness. Laboratory findings included leukocytosis by neutrophilia, hypoalbuminemia, high creatinine, and urea levels, and an increased number of bacteria, leukocytes, and hyaline cylinders on urine analysis. After three days of intensive care, the horse underwent general anesthesia for scrotal ablation and resection of the infected spermatic cord stumps. Microbiological assays revealed *Streptococcus* spp. and a multi-resistant *Escherichia coli*. This report highlights uncommon post-castration complications in a Mangalarga Marchador gelding as a consequence of septic funiculitis. Furthermore, the microbiological isolation of a multi-resistant *E. coli* strain raises concerns about the indiscriminate use of antibiotics in equine practice.
Keywords: Castration, Orchiectomy, Scirrhous cord, Septic funiculitis

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Introduction

Castration is one of the most common surgical procedures performed in equine practice (Kilcoyne and Spier, 2021). Although a relatively routine procedure, the reported complication rates may vary from 10.2% to 60% (Kilcoyne et al., 2013; Rosanowski et al., 2018). Potential complications are numerous and may range from mild (e.g., scrotal edema, incisional infection, and penile trauma) to life-threatening conditions (e.g., severe hemorrhage, evisceration, septic funiculitis, abdominal abscessation, and peritonitis) (Kilcoyne et al., 2013; Caniglia et al., 2014; Claffey et al., 2018; Rosanowski et al., 2018; Duggan et al., 2021; Kilcoyne and Spier, 2021). Funiculitis is the inflammation of the spermatic cord stump and may be accompanied initially by scrotal and/or preputial edema, pyrexia, and lameness occasionally, whilst scirrhous cord is considered a chronic form of funiculitis, where the surgical incisions attempt to heal with persistent infection of the spermatic cord stump (Claffey et al., 2018; Duggan et al., 2021). Laminitis is a severely debilitating, life-threatening disorder affecting the dermal and epidermal tissues of the equine digit (Van Eps, 2010). This condition develops as a sequel to many clinical conditions in the horse, including various gastrointestinal disorders, infectious causes (e.g., pneumonia, metritis, hepatitis), and grain overload. Many of these disorders may elicit a severe inflammatory response known as systemic inflammatory response syndrome (SIRS). Although SIRS can occur in both infectious and noninfectious diseases, it is often a sequela to sepsis owing to the liberation of bacteria and pathogen-associated molecular patterns (PAMPs) released into the circulation during the septic state. Dysregulated inflammatory response and coagulation, increased cellular death, and energy loss

through mitochondrial dysfunction all play roles in SIRS. The presence of a pathogen, PAMPs, or damage-associated molecular patterns (DAMPs) triggers the innate immune system by recruiting phagocytes to the effector site. Production of pro-inflammatory cytokines by phagocytes and other effector cells, such as endothelial and epithelial cells, results in the upregulation of adhesion molecules, chemokines, and additional inflammatory cytokines. Leukocyte migration to the lamellae and other organs occurs during SIRS in the horse. Although essential for the eradication of pathogens and injured cells, the release of reactive oxygen species (ROS) and proteases by leukocytes and other cells can injure surrounding tissue and subsequently precipitate a worsening of the inflammatory response. The profound systemic inflammatory effects of SIRS can lead to remote organ dysfunction and the development of multiorgan dysfunction syndrome (MODS). Typical organs involved in MODS include, but are not limited to, the heart, lungs, kidneys, and liver. In the horse, the primary remote "organ" to fail is the lamellae of the hoof, resulting in the development of laminitis (Eades, 2010; Leise and Fugler, 2021).

This paper aims to report clinical and laboratory features, treatment, and long-term follow-up information in a case of funiculitis causing sepsis-associated laminitis and acute renal failure (ARF) in a Mangalarga Marchador gelding.

Case Report

A 5-years-old and 363-kg Mangalarga Marchador stallion was the case subject. According to the referring veterinary practitioner, the horse was submitted to an open orchiectomy approach on farm-setting. Surgery occurred uneventfully, and both spermatic cords were transfixed with size-1 polyglactin suture material. After getting up (about 30 min from surgery), the gelding presented severe scrotal edema and blood dripping. After 8-h from the procedure, severe bleeding on the surgical sites occurred, and the practitioner had difficulty finding the origin of the hemorrhage. Thus, a sterile gauze package was inserted on each scrotal skin incision, aiming to compress the spermatic cords stumps and to stop the hemorrhage. After this complication, the practitioner recommendations included gauze package removal on the next day, injection of flunixin meglumine (1,1 mg/kg, q12h, intravenously [IV], q24h, five days), dimethyl sulfoxide (1 $g.kg^{-1}$; 10% solution diluted in saline, q24h, IV three days), ceftiofur (4.4 mg/kg, q24h, intramuscularly [IM], five days), gentamicin (6,6 mg/kg, IV, five days). The owner removed the gauze package after three days. Even after the treatment, the gelding still had scrotal swelling and began to present stiffness of gait. Therefore, the horse was referred for hospital care after seven days of the field surgical procedure.

Physical examination of the gelding revealed a restless behavior, regular body condition score (3/5 score), hyperemic mucous membranes, dehydration (assessed by skin turgor), tachycardia (58 beats per min [bpm]), a rectal temperature of 38.3°C, and intestinal hypomotility. The horse presented scrotal swelling and bilateral 5-8cm skin incisions draining a foul-smelling serosanguinous discharge (Figure 1A). Palpation of the swelling revealed enlarged spermatic cord stumps and elicited pain. Additionally, the gelding presented shifting of weight, increased hoof temperature, and digital pulse amplitude. At rest, a discrete "saw horse" stance was noted. At the walk, the gait appeared normal in a straight line, although turning on a hard surface exacerbated lameness on the inside limb. The hooves could be lifted off the ground without difficulty, characterizing Obel grade 2/5 lameness (Van Eps, 2010). A withdrawal reaction to the manual application of rotational force to the hoof was also present in all limbs, more intense on the hind limbs.

Serial blood samples were collected through jugular venipuncture for hematology (complete blood count and fibrinogen determination) and serum biochemistry (aspartate aminotransferase [AST] and gamma-glutamyl transferase [GGT] activities, as well as total protein, albumin, urea, and creatinine levels) (Table 1). On hospital admission (Day 1), laboratory alterations included leukocytosis by neutrophilia, hypoalbuminemia, and high creatinine and urea levels. Urinalysis revealed an increased number of bacteria, leukocytes, and hyaline cylinders. Therefore, laboratory findings combined with physical examination permitted the diagnosis of funiculitis causing SRIS-related laminitis and ARF. Intensive care was initiated with continuous intravenous fluids (lactated Ringer's solution: infusion rate of 0.3 mL/s), non-steroidal anti-inflammatory drugs (firocoxibe: 0.1 mg/kg, q24h per os, analgesics (dipyrone: 25 mg/kg, q12h, IV) therapies. Ceftiofur (5 mg/kg, q24h, IV) was continued since the gelding was already on this antibiotic choice. Additionally, omeprazole (0.1 mg/kg, once a day, per os, pentoxifylline (10 mg/kg, q12h, per os, and ketamine (0.5 mg/kg, q8h, IM) were prescribed. Due to the acute SRIS-related laminitis, cryotherapy was also initiated

Table 1. Serial hematological and biochemical findings in a 5-years-old Mangalarga Marchador gelding with funiculitis and sepsis-associated laminitis on admission (Day 1), on the surgical procedure (Day 4) and until hospital discharge (Day 15).

Parameter	Day 1	Day 4	Day 6	Day 8	Day 11	Day 15	Reference values*
Hematocrit (%)	34	34	28	30	31	34	24-46
Red blood cells (10^6/µL)	6.92	6.74	5.59	5.79	6.13	6.72	6.6-12.5
Hemoglobin (g/dL)	13.3	12.8	10.6	10.9	11.5	12.6	11-19
TPP (g/dL)	6.6	6.8	6.4	7.0	7.0	7.4	5.2-7.9
Albumin (g/dL)	2.15	2.1	ND	ND	1.87	2.2	3.03-3.55
Fibrinogen (mg/dL)	400	600	600	600	600	400	100-400
Platelets (10^3/µL)	175	249	266	349	209	151	100-400
Total leukocytes (10^3/µL)	14.4	12.8	15.8	14	16.7	13.6	5.0-12.5
AST (U/L)	319	361	ND	ND	272	104	226-366
GGT (U/L)	15	15	ND	ND	22	15	4.3-13.4
Creatinine (mg/dL)	7.3	2.2	1.9	1.7	1.4	1.5	1.2-1.9
Urea (mg/dL)	144	36	24	19	31	28	21.4-51.3

TPP: total plasma protein; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; ND: not determined; *Kaneko et al., 2008; Freeman et al., 2022.

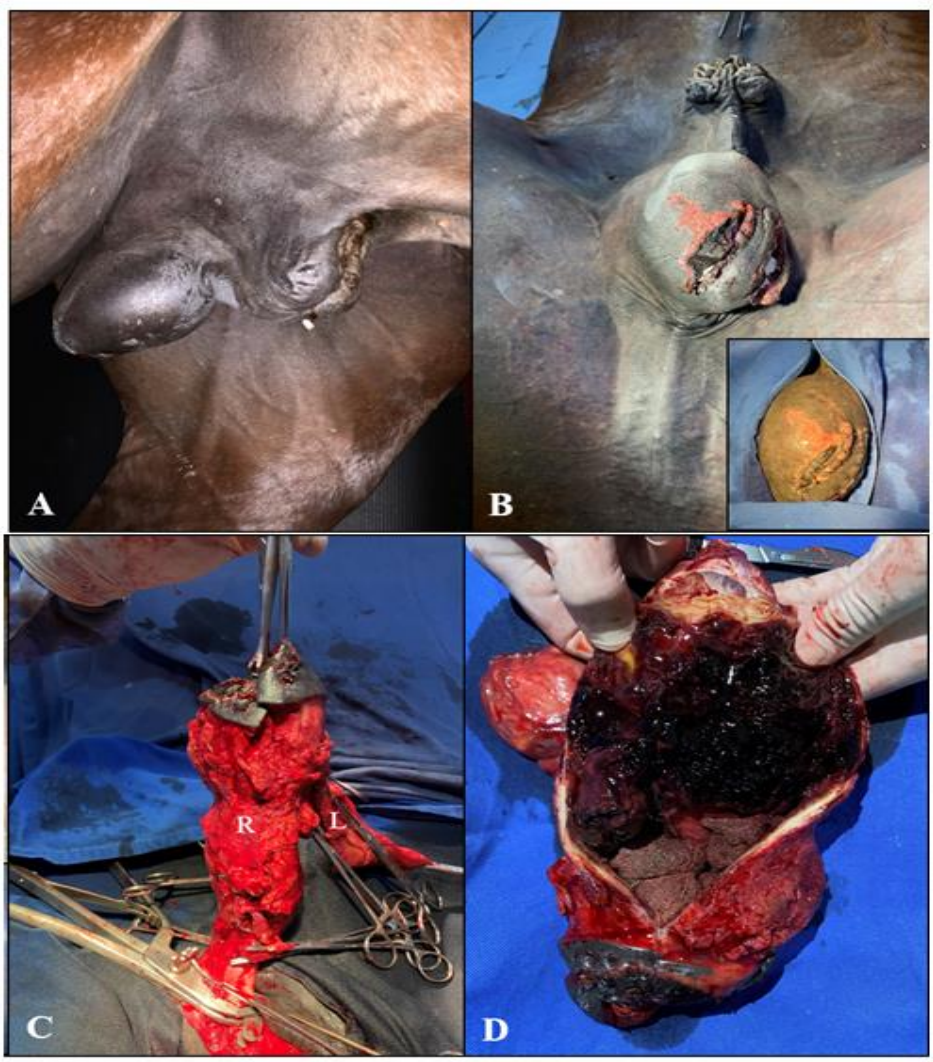

Figure 1. A 5-years-old Mangalarga Marchador gelding with septic funiculitis. (A) Scrotal swelling on hospital admission. (B) The gelding on dorsal recumbency prior to surgery. Note the severe scrotal swelling and bilateral 5-8 cm skin incisions with necrotic edges on the scrotum. Inset: Both wounds were filled with sterile gauze and sutured to avoid surgical site contamination. (C) Both (L: left and R: right) spermatic cords after blunt and manual dissection. A Reimer emasculator was used to obtain hemostasis on the healthy spermatic cord remnant. (D) Longitudinal opening of the right spermatic cord stump revealing bloody-clotted and foul-smelling content.

(Van Eps, 2010; Luethy, 2021). After 72-h of treatment, laboratory tests were repeated (Day 4), and there was a decrease in total leukocyte count, creatinine, and urea levels, whilst an increase in fibrinogen concentration and platelets count was noted. Therefore, intensive palliative treatment successfully prevented ARF, and the horse was submitted to surgery.

After pre-medication with 2% xylazine hydrochloride (1 mg/kg, IV) and morphine sulfate (0.05 mg/kg, IV), induction was obtained with ketamine hydrochloride (2.2 mg/kg, IV) and midazolam maleate (0.05 mg/kg, IV). Orotracheal intubation was performed, and general anesthesia was maintained using a 1.5 minimum alveolar concentration of isoflurane and 4.5 L/min of 100% oxygen flow in a semi-closed circuit. The gelding underwent surgery in dorsal recumbency for resection of the infected spermatic cord stumps (Figure 1B). Both draining tracts were filled with sterile gauze and sutured with size-0 nylon in a simple continuous pattern to avoid surgical site contamination (Figure 1B - inset). After surgical preparation, scrotal ablation, according to Schumacher (2019), was performed. An elliptical scrotal incision encompassing both sutured draining tracts was made, and both cords were bluntly and manually dissected. A Reimer emasculator was used to obtain spermatic cord hemostasis (Figure 1C). The subcutaneous was approximated with size-0 polyglactin in a mattress pattern and demography with size-1 nylon in a Wolf pattern. The left spermatic cord remnant evidenced mild edema. A severe enlargement was detected at the right spermatic cord stump, presenting approximately 22.8 cm long, 8.9 cm in diameter, and weighing 1.015 g. At the cut surface, a severe hemorrhage and edema and a moderate foul-smelling content surrounding a dark brown necrotic mass with indistinct contours were shown at the right spermatic cord (Figure 1D). No suture material was observed in the removed spermatic cords.

The horse improved clinically after surgery, but concerning laboratory values, there was an increase in leukocytosis by neutrophilia and hyperfibrinogenemia on the 2nd day post-surgery (6th hospitalization day) (Table 1). The gelding presented persistently elevated digital pulses, and lameness increased to Obel grade 3/5 (the horse moves reluctantly and vigorously resists attempts to lift a foot) (Van Eps, 2010). Therefore, the distal limbs were iced for more 72-h (Luethy, 2021). During this period, latero-lateral and dorso-palmar radiographs revealed a toe flaring toward, but no obvious distal phalanx displacement. Thus, the toe region was trimmed, frog support with the application of silicone material to the sole of the foot was provided, and secured with adhesive tape. This technique produces mild heel elevation, relieving the forces of breakover (Van Eps, 2010). During all hospitalization time, the gelding was placed on a high shavings-bedded stall with restricted ambulation.

On the 6th post-surgery day (11th hospitalization day), microbiological assays revealed *Streptococcus* spp. and a multi-resistant (ceftiofur, enrofloxacin, rifampicin and sulfonamides) *Escherichia coli*. Therefore, antibiotic therapy was changed to potassium penicillin (40.000 UI/kg, q8h, IV) and gentamycin (6.6 mg/kg, q24h, IV) combination. Firocoxibe, pentoxifylline, omeprazole, and ketamine administration were maintained on the aforementioned dosages. After this, there was a decrease in the leukocyte count and fibrinogen concentration (Table 1). Digital pulses and hoof temperature also diminished over the following days. Primary intention healing on the surgical site occurred uneventfully. Nonetheless, due to the owner's financial constraints, the horse was discharged on the 15th hospitalization day (11 days after surgery) and sent home with antibiotics (benzathine penicillin: 30.000 UI/kg, q48h, IM, three doses) and anti-inflammatory (firocoxibe: 0.1 mg/kg, q24h, per os, seven days) recommendations. At the time of manuscript preparation, long-term follow-up (6 months after surgery) was conducted by telephone call. The owner reported that the gelding was retired because whenever there is an attempt to ride, even light riding, lameness occurs in the left forelimb.

Discussion

Funiculitis in horses usually results from inadequate surgical site preparation, neglected perioperative antimicrobial treatment, an extension of a scrotal infection, or contamination of surgical material (Kilcoyne et al., 2013; Duggan et al., 2021; Kilcoyne and Spier, 2021). The use of ligatures has been implicated as a cause for postoperative infection, potentially acting as a nidus; however, there are conflicting reports in the literature, with no clear consensus on whether or not ligatures contribute to an increased rate of infection (Kilcoyne and Spier, 2021). Herein, the absence of suture material in the removed spermatic cords may be due to failure to perform or loosening of the transfixion ligatures, and post-surgery hemorrhage demanded a new intervention. Despite the attempt to perform compressive hemostasis with sterile gauze and the broad-spectrum systemic antibiotics, septic funiculitis

caused an unusual presentation of sepsis-related laminitis, and ARF occurred in the gelding. We hypothesized that lack of drainage and accumulation of blood clots were important risk factors for the development of funiculitis, as previously reported (Duggan et al., 2021; Kilcoyne and Spier, 2021). In addition, the involvement of a multi-resistant bacteria further complicated the clinical evolution (Caniglia et al., 2014).

Clinical signs (heart rate >52 bpm and abnormal mucous membrane coloration) presented by the gelding combined with the hematology results (total leukocytes above 12.5 x 10^3/µL) obtained at hospital admission permitted the diagnosis and classification as a SRIS 3/4 subject (Roy et al., 2017). Dehydration and the presence of septic foci (funiculitis) were alerts to the occurrence of secondary renal failure, which was confirmed laboratorially (highly increased creatinine and urea levels; presence of hyaline cylinders). Later, the isolation of a mixed bacterial growth from the spermatic cord secretion enabled the definitive diagnosis of sepsis (Leise and Fugler, 2021). Scrotal swelling, enlarged spermatic cords, and the presence of a bilateral scrotal wound with foul-smelling serosanguinous discharge are previously reported clinical signs in horses with funiculitis (Caniglia et al., 2014; Rosanowski et al., 2018; Claffey et al. 2018; Duggan et al., 2021). Additionally, in the gelding herein, more evident hind limb lameness could be wrongly associated with funiculitis, but shifting of weight, increased hoof temperature, and digital pulse amplitude in all limbs were considered hallmarks of sepsis/SRIS-related laminitis (Eades, 2010; Leise and Fugler, 2021).

Historically, laminitis affects most commonly the front limbs (Van Eps, 2010), but the condition affecting the four limbs is the second most prevalent presentation in previous studies (Hunt and Wharton, 2010; Wylie et al., 2013), whilst laminitis on both hind feet is an infrequent feature affecting 1.3% of horses in Great Britain (n=7/577) (Wylie et al., 2013).

Intensive palliative treatment successfully prevented ARF, and antibiotics and anti-inflammatory therapies helped to stabilize the SRIS/sepsis process, allowing general anesthesia and surgery to remove the infected spermatic cord stumps could be performed. Therefore, early and aggressive therapies are recommended in horses at risk for the development of sepsis/SIRS-related laminitis in order to limit inflammation and prevent lamellar injury (Eades, 2010; Leise and Fugler, 2021). Unfortunately, the delay of 7 days for referring the horse to hospital care and another 11 days for microbiological culture results of a multi-resistant bacteria played an important role in the pathophysiology of the sepsis-associated laminitis herein, and perhaps severe lamellar injury has already occurred. In addition, the horse's early discharge due to the owner's financial constraints made it impossible to monitor the evolution of laminitis, and long-term follow-up six months later revealed that the horse is still lame, probably due to laminitis sequelae. These features corroborate the evolution to chronic laminitis and reiterate that extended travel and lack of careful monitoring may be detrimental during active acute laminitis. The most common sequelae of chronic laminitis include downward displacement (sinking) and rotation of the distal phalanx (Van Eps, 2010).

Staphylococcus aureus is the most common bacteria linked to funiculitis and scirrhous cord in horses (Kilcoyne et al., 2013; Kilcoyne and Spier, 2021). Nevertheless, *Staphylococcus* spp. was not identified in any of the eight horses with microbiological results in a recent study (Duggan et al., 2021), while Rosanowski et al. (2018) reported *S. aureus* associated-funiculitis in just one horse (5.8%; 1/17). Instead, several Gram-positive and Gram-negative bacteria have been linked with this post-castration complication, including Beta-hemolytic *Streptococcus* spp., *S. equi* subspecies zooepidemicus, *S. parauberis*, *Proteus* spp., *E. coli, Acinetobacter* spp., *Enterococcus* spp., *Pasteurella* spp., and *Achromobacter* spp. (Caniglia et al., 2014; Rosanowski et al., 2018; Duggan et al., 2021). Herein, microbiological assays of the spermatic cords discharge yielded mixed bacterial growth, and we highlight the isolation of a multi-resistant *E. coli* strain.

Conclusions

Secondary ARF and laminitis as a consequence of septic funiculitis are uncommon post-castration complications in horses. This report highlights the clinical presentation, laboratory findings, treatment, and long-term follow-up of this life-threatening condition in a Mangalarga Marchador gelding. Furthermore, the microbiological isolation of a multi-resistant *E. coli* strain raises concerns about the indiscriminate use of antibiotics in equine practice.

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