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Case Report

Medical management of a large intra-abdominal mass caused by *Rhodococcus equi* in a foal

***S. D. Shaw*[†], *L. G. Arroyo*[†]*, *A. zur Linden*[†], *C. Allen*[‡], *A. Giraldo*[†] and *N. D. Cohen*[§]**

[†]*Department of Clinical Studies, Ontario Veterinary College, University of Guelph, Guelph, Ontario;* [‡]*Allen Equine Services, Etobicoke, Ontario,Canada; and* [§]*Department of Large Animal Clinical Sciences, College of Veterinary Medicine, Texas A&M University, College Station, Texas, USA*
**Corresponding author email: larroyo@uoguelph.ca*

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Summary

A 4-month-old Thoroughbred filly presented with pyrexia, inappetence and diarrhoea. Abdominal ultrasonography revealed a multilobulated abdominal mass that was determined to be associated with the caecum using computed tomography. Computed tomography also identified mesenteric lymphadenopathy and a pulmonary mass in the left caudal lung lobe. Percutaneous aspiration of the abdominal mass yielded pure growth of *Rhodococcus equi*. The filly responded in a positive fashion to the administration of clarithromycin, rifampin and gallium maltolate. Follow-up computed tomography revealed complete resolution of the abdominal mass and lymphadenopathy. Extrapulmonary disorders associated with *R. equi* should be considered even when thoracic ultrasonography reveals no evidence of pulmonary pathology. Although intra-abdominal abscesses have a grave prognosis, successful treatment is possible. Gallium maltolate can be safely administered to foals and may improve patient outcomes.

Introduction

Rhodococcus equi has both economic and animal welfare implications for the horse industry. It typically causes pulmonary consolidation or abscesses in foals 3 weeks to 6 months of age. Sonographic screening programmes are often employed at farms with endemic *R. equi* infections in order to identify subclinical pulmonary lesions, although recent evidence has demonstrated that a large proportion of foals with pulmonary lesions will remain subclinical and lesions can resolve without antimicrobial treatment (Venner *et al*. 2012, 2013).

At least 39 different extrapulmonary disorders (EPDs) have been associated with *R. equi* infection. In two post-mortem studies, between 54% and 59% of foals had an EPD associated with *R. equi* infection (Zink *et al*. 1986; Takai *et al*. 2000). A retrospective study identified EPDs in 74% (111/150) of foals with *R. equi* infection admitted to a teaching hospital (Reuss *et al*. 2009). Intra-abdominal abscesses were one of the more common EPDs (17%; 25/111) and carried a grave prognosis. The most commonly identified EPDs included diarrhoea, ulcerative enterotyphlocolitis, abdominal lymphadenitis, intra-abdominal abscessation, immune-mediated polysynovitis, septic synovitis, uveitis, peritonitis and pyogranulomatous hepatitis (Reuss *et al*. 2009).

The current recommended treatment of lesions causing clinical signs (either bronchopneumonia or an extrapulmonary manifestation) is a combination of a macrolide and rifampin. The emergence of macrolide resistance in *R. equi* that has been associated with higher mortality in affected foals (Giguère *et al*. 2010; Huber *et al.* 2019) underscores the need for adjunctive treatments to improve efficacy and reduce the development of bacterial resistance to the standard antimicrobial regimen. Gallium maltolate (GaM) is a semi-metallic compound that has no known physiological role but has been demonstrated to have therapeutic biological activities. Gallium is chemically similar to ferric iron (Fe^{3+}) but cannot be reduced to the divalent state under physiological conditions (Bernstein 1998). It has been shown to have antimicrobial activity against *R. equi* with the ability to kill *R. equi* within macrophages in vitro (Coleman *et al*. 2010). Gallium maltolate has been demonstrated to be safe when administered to foals at a dose of 25–30 mg/kg per os q. 24 h. Treatment of subclinical *R. equi* pneumonia with GaM has yielded similar outcomes to treatment with macrolides (Cohen *et al*. 2015). In this case report, we describe the diagnosis and successful management of multiple large intra-abdominal masses caused by *R. equi* using a combination of a macrolide, rifampin and gallium maltolate.

Case history

A 4-month-old, 150 kg Thoroughbred filly developed pyrexia, inappetence and diarrhoea following an 800-km trailer ride (approximate distance between the farm in Southern Ontario and Lexington, Kentucky). There was no history of prior illness, and the filly had undergone routine thoracic ultrasonographic screening at 4, 6 and 8 weeks of age for *R. equi* pneumonia with no evidence of pulmonary pathology. Treatment was initiated with ceftiofur (2.2 mg/kg bwt i.m. q. 12 h), sucralfate (30 mg/kg bwt per os q. 8 h), ranitidine (6.6 mg/kg bwt per os q. 8 h) and 150 mg flunixin (i.v. or per os) as needed to control pyrexia. Complete blood count (CBC) and serum biochemistry profile revealed an elevated white blood cell count ($16{,}800 \times 10^9$/L; reference range $5.1–12.5 \times 10^9$/L) characterised by a mature neutrophilia (11.93×10^9/L), a monocytosis (0.84×10^9/L), mild hypoglobulinaemia (21 g/L; reference range 22–39 g/L) and a mildly elevated alkaline phosphatase (776 U/L; reference range 50–325 U/L). A faecal PCR panel tested

positive for virulent *R. equi*. Referral was elected for further diagnostic imaging.

Clinical findings

On presentation, the filly was quiet, alert and responsive. Physical examination revealed pyrexia (39.0°C), mild tachycardia (66 beats/min) and a normal respiratory rate (20 breaths/min). Eyes and nostrils were free of discharge, and no abnormal sounds were heard in the trachea and lungs. Abdominal ultrasonography (SonoSite Edge II, 5–2 MHz curved probe)[1] revealed a mass of mixed echogenicity extending from the right ventral flank across midline to the left (**Fig 1**). The lesion measured 10 cm deep from ventral to dorsal and 17 cm from cranial to caudal. A second, homogenous and well-vascularised mass, measuring approximately 5 cm deep × 6 cm in length, was appreciated in the left ventral flank region. Thoracic ultrasonography revealed no abnormal findings of the pleural surface of either hemithorax.

The filly was anaesthetised and underwent computed tomography (16 slice detector, GE Lightspeed[2] – 0.625 mm slice thickness, 50 cm field of view, helical mode, 1 s rotation time, 0.562:1 pitch, 120 kV and 220 mAs) pre- and post-contrast medium administration (iopamidol 300 mgI/mL, Isovue)[3] to better characterise the lesion size and organ involvement. An ill-defined, multilobulated, soft-tissue mass with central gas and fluid dense regions was identified in the right ventral abdomen, consistent with marked caecal wall thickening (up to 4 cm) of both the body and the base of the caecum (**Fig 2**). The mass extended from the level of the 17th thoracic to 4th lumbar vertebra and crossed midline to the left, and measured 18.1 × 12.9 × 22.2 cm. Marked mesenteric lymphadenopathy was also present. In the left mid-abdomen, adjacent to the mesenteric vasculature, one enlarged mesenteric lymph node was identified, measuring 6.2 × 7.5 × 5.5 cm. Incidentally, within the dorsal aspect of the left caudal lung, adjacent to the aorta, an amorphous multilobulated soft-tissue dense mass that was 6.3 × 5 × 5.7 cm was identified, consistent with a pulmonary abscess (**Fig 3a**).

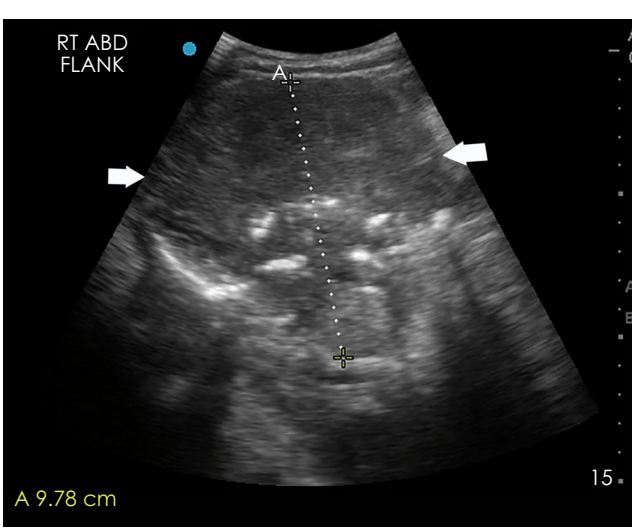

Fig 1: Transabdominal ultrasound image captured on the right ventral flank showing a large mass (between white arrows) of mixed echogenicity extending deep into the abdomen (9.78 cm from the abdominal wall).

Immediately following CT imaging and while the foal was under general anaesthesia in dorsal recumbency, percutaneous aspiration of the abdominal mass was performed under ultrasound guidance (5–8 MHz curvilinear probe, Philips IU22)[4] using a 16 gauge × 2-inch needle. Aspiration yielded a thick purulent material, cytologically characterised by severe suppurative inflammation with large numbers of markedly lytic neutrophils, and intracytoplasmic bacteria with coccoid to rod-shaped morphology (pleomorphic rods). Aerobic culture yielded pure heavy growth of *R. equi* susceptible to several common antibiotics use for the treatment for *R. equi* infections (i.e. MIC for Rifampin < 1 ug/mL and Clarithromycin < 1 ug/mL). A tracheal wash was not performed as the foal had no clinical sings of pneumonia (i.e. cough, nasal discharge, abnormal lung sounds), and the sample obtained from the abdominal mass was considered superior and most relevant to the clinical disease presentation.

Clinical course and treatment

Following imaging, the filly returned to the home farm. Treatment of the filly commenced with clarithromycin 7.5 mg/kg bwt per os q. 12 h and rifampin 5 mg/kg bwt per os q. 12 h. The administration of sucralfate and ranitidine was continued as previously directed by the farm veterinarian. Gallium maltolate suspension[5] became available 3 days after the filly's CT scan and was added to her treatment plan at 30 mg/kg per os q. 24 h. No further episodes of pyrexia were identified after the second dose of clarithromycin and rifampin so flunixin administration was discontinued.

On recheck examination on Day 13, the filly was bright, alert and responsive. The filly's diarrhoea had resolved. Temperature, pulse and respiration were all within normal limits. Recheck ultrasonography revealed a slight decrease in the size of the abdominal mass. Serial CBCs, serum biochemistry profiles and ultrasonography were then repeated at approximately 2-week intervals. Markers of inflammation (SAA and/or fibrinogen) were not serially measured prior or during the course of the antimicrobial treatment.

Six weeks following the initial diagnosis, the remnants of the abdominal mass measured 5.4 × 5.2 cm. Eight weeks following the initial CT scan, thickened caecal wall measuring up to 1.2 cm was noted sonographically but a discreet mass could not be identified. Computed tomography of the abdomen was repeated on Day 65, and caecal wall thickening and lymphadenopathy were no longer evident. Treatment with clarithromycin and rifampin was discontinued. Gallium maltolate administration was then ceased approximately 12 weeks after the initial identification of the abdominal mass. Follow-up examination at 18 weeks revealed no abnormal findings on either thoracic or abdominal ultrasonography.

Discussion

This foal presented with an atypical *R. equi* infection characterised by a large intra-abdominal mass, mesenteric

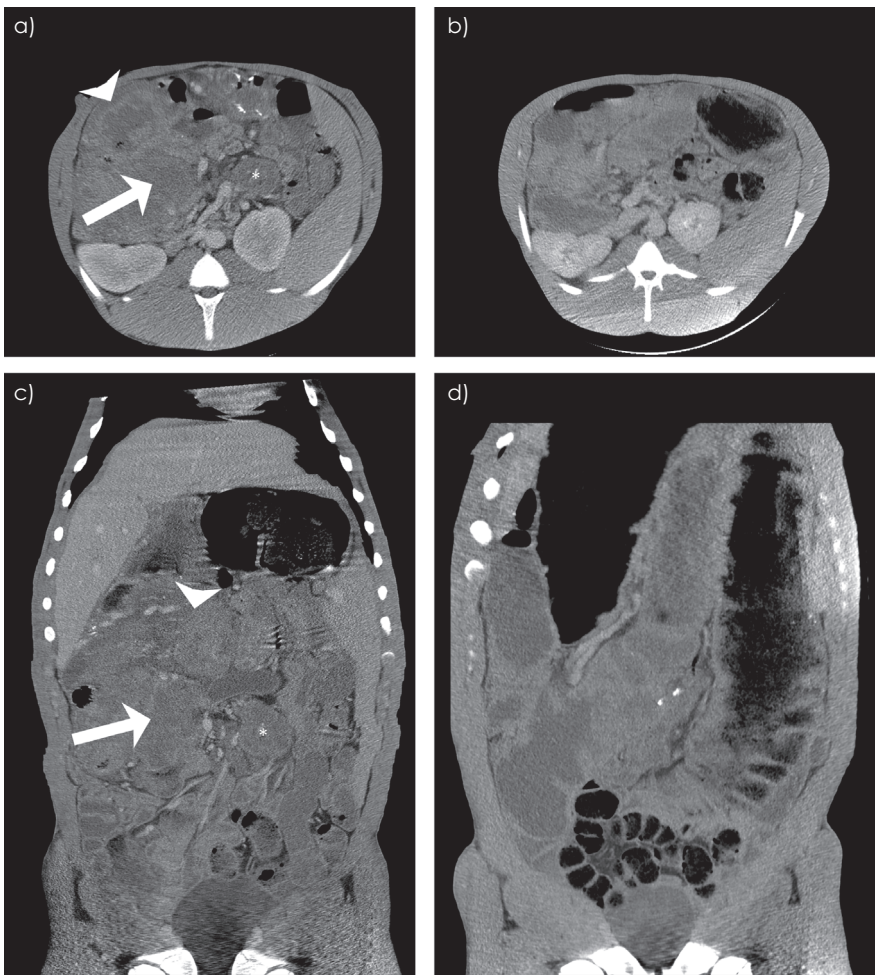

Fig 2: Computed tomography images from the filly performed on presentation (a and c), and 2 months later following treatment, (b and d). All images shown are following contrast medium administration and reformatted to 5 mm slice thickness. a and b) are transverse images at the same location, and similarly (c and d) are dorsal plane reformatted images at approximately the same location. The caudal lung was not imaged 2 months later as the foal had grown. a and c) There is marked thickening of the caecal body (white arrowhead) and the base of the caecum (white arrow), as well as marked mesenteric lymphadenopathy (*). b and d) The caecal wall thickening and the lymphadenopathy have resolved.

lymphadenopathy and a pulmonary abscess, in the absence of clinical signs of bronchopneumonia. The filly initially presented with persistent pyrexia and diarrhoea. These clinical signs are important manifestations of *R. equi* infection and potential EPDs. Differential diagnoses for diarrhoea in a 4-month-old foal are numerous and include salmonellosis, infections with rotavirus, coronavirus, *R. equi*, *Lawsonia intracellularis*, or clostridial agents, endoparasitism or diet changes. Faecal polymerase chain reaction (PCR) panels can be helpful in determining the presence of various pathogens. However, faecal PCR can yield both false-positive and false-negative results due to intermittent shedding of pathogens, sample handing and the presence of faecal enzymes that may interfere with DNA recovery. Further, clinically healthy foals from farms with endemic *R. equi* have been shown to shed *R. equi* in their faeces (Shaw *et al*. 2015; Madrigal *et al*. 2016). Although evidence exists that quantitative PCR may be of diagnostic value for foals with *R. equi* pneumonia (Shaw et al. 2015) , this technique has not been developed for commercial use. Thus, positive results of PCR for *R. equi* should be interpreted cautiously in foals and in conjunction with clinical data.

Up to 74% of clinical *R. equi* cases at a referral hospital have been found to have at least 1 EPD (Reuss *et al*. 2009). This is likely an underestimate, as some diagnoses are only made histologically at post-mortem examination (ulcerative typhlocolitis, pyogranulomatous hepatitis and pyogranulomatous nephritis), whereas others require more intensive diagnostics that are not routinely performed. Intra-abdominal abscesses are associated with nonsurvival (Reuss *et al.* 2009). The association between intra-abdominal abscesses and nonsurvival may be due to the late recognition of this EPD or difficulty in achieving adequate antimicrobial penetration in large abscesses. Reuss *et al.* (2009) found that only 40% of foals with an intra-abdominal abscess had diarrhoea, which was similar to the 38% of foals with intra-abdominal EPDs that demonstrated antemortem signs referable to the gastrointestinal tract in the study by Zink *et al.* (1986). Overlooking EPDs in *R. equi* infection carries potentially lethal consequences. In cases

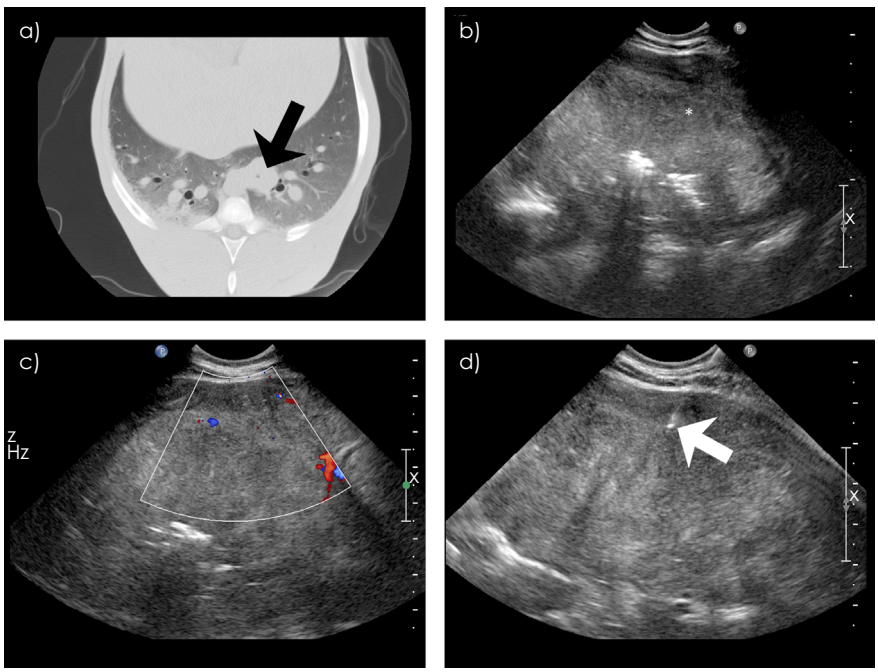

Fig 3: a) CT scan of the caudal lungs revealed a small soft-tissue dense mass in the left caudal lung lobe (black arrow) just to the left of the aorta that contained a few small central gas densities. b) Ultrasound examination revealed marked thickening of the caecal wall (*), while colour Doppler revealed blood flow throughout the wall (c). d) Ultrasound-guided fine-needle aspirates were performed of the caecal thickening for cytological evaluation. Ultrasound of the mass following the CT scan revealed marked thickening of the caecal wall and allowed percutaneous fine-needle aspirates of the caecal wall mass to be performed (5–8 MHz curvilinear probe, Philips IU22, Philips, Bothell, USA) while the filly remained anaesthetised (Fig 2b–d). *Aspiration yielded thick purulent material that was submitted for cytology and aerobic culture. Cytology revealed severe suppurative inflammation characterised by large numbers of markedly lytic neutrophils. Intracytoplasmic bacteria with coccoid to rod-shaped morphology (pleomorphic rods) were observed. Aerobic culture yielded pure heavy growth of* R. equi.

that present atypically or fail to respond to empirical treatment, repeated physical examinations, CBCs, serum biochemistry profiles, and thoracic and abdominal ultrasonography are warranted (Valdes and Johnson 2005).

Antimicrobial resistance in *R. equi* infections in foals has been documented (Giguère *et al*. 2010; Burton *et al*. 2013; Huber *et al*. 2019). This resistance combined with a lack of effective alternatives to macrolides creates a necessity for therapeutic options beyond standard antimicrobials. Gallium maltolate has been demonstrated to have antimicrobial activity against various pathogens, including *R. equi* and methicillin-resistant *Staphylococcus aureus* (Coleman *et al*. 2010; Arnold *et al*. 2012). Further, no negative side effects have been reported in association with the administration of GaM in foals, compared to hyperthermia and diarrhoea that can result from macrolide therapy. This trivalent semi-metal exploits the iron dependency of bacteria to inhibit their growth (Bernstein 1998; Hijazi *et al*. 2018). Gallium is taken up and concentrated in macrophages, which ultimately results in failure of *R. equi* to replicate intracellularly. The rationale for including GaM in the treatment of this filly was to enhance antimicrobial concentration at the site of inflammation and to apply a multi-modal treatment approach to potentially reduce the mutant prevention concentration of the macrolides and rifampin. Unfortunately, follow-up bacterial samples were not available to determine antimicrobial susceptibility testing after the initiation of antimicrobial therapy.

The filly's clinical appearance improved within days of the initiation of therapy. Improvement in the CBC, serum biochemistry parameters and abdominal ultrasonography, however, did not correlate with the clinical findings. The filly's WBC did not return to values within the reference range 4 months after initial presentation; however, the improvement in WBC did not correlate with the improvement of other parameters, particularly the size of the lesion.

While serial ultrasonography revealed improvement in the size of the abdominal mass, parts of the abdomen were persistently obscured by the gas-filled large colon. In this case, the availability of computed tomography aided in determining the presence and extent of any organ involvement and the decision to discontinue antimicrobial therapy. Without access to advanced imaging (i.e. CT) for EPD cases, serial monitoring of WBC, fibrinogen and ultrasonographic findings may be helpful in monitoring treatment response. SAA concentrations vary greatly amongst foals with *R. equi* pneumonia however, and this inflammatory marker should be interpreted with caution in these cases (Cohen *et al.* 2005).

The long-term effects of prolonged antimicrobial therapy in young horses have yet to be determined, but the impact on the gastrointestinal flora and risk of colitis must be considered against the prolongation of treatment.

This case of an *R. equi* abdominal mass, lymphadenopathy and pulmonary abscess demonstrated successful treatment with clarithromycin, rifampin and gallium

maltolate, and demonstrated the value of computed tomography for characterising and monitoring the extent and regression of these findings. Further investigation into the use of GaM and other standard antimicrobial sparing treatments in cases of *R. equi* infection is warranted.

Authors' declaration of interests

No conflicts of interest have been declared.

Ethical animal research

Not applicable.

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Authorship

S. Shaw and C. Allen involved in clinical and ultrasound imaging diagnosis, and medical treatment management and patient follow-up. A. Giraldo, L. Arroyo and A. zur Linden involved in ultrasound and CT imaging diagnosis work-up.

Manufacturers' addresses

[1]Fujifilm Sonosite Inc., Bothell, Washington, USA.
[2]GE Healthcare, Milwaukee, Wisconsin, USA.
[3]Bracco USA Ltd., Princeton, New Jersey, USA.
[4]Phillips Ultrasound, Bothell, Washington, USA.
[5]Hagyard Pharmacy, Lexington, Kentucky, USA.

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