Extra-pulmonary *Rhodococcus Equi* in the Foal

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Introduction

Rhodococcus equi is a commonly diagnosed cause of bronchopneumonia and subsequent morbidity or death in young foals. Although less commonly reported, extrapulmonary manifestations of *R. equi* can occur as well.[11] Extrapulmonary disorders (EPDs) can be a result of direct *R. equi* infection, a hematological spread of infection, or an immune-mediated response to it.[10] Although gastrointestinal and musculoskeletal systems are the most commonly reported systems to be affected by EPDs, there are many potential manifestations. In the abdomen, manifestations include mesenteric lymphadenopathy, ulcerative enterotyphlocolitis, peritonitis, and large intra-abdominal abscesses. Lameness is often a presenting complaint in foals with joint-related manifestations, which include nonseptic polysynovitis, septic arthritis and osteomyelitis. Furthermore, there have been reports of EPDs presenting as mediastinal lymphadenopathy, uveitis, pyogranulomatous hepatitis, intracranial abscesses, cellulitis, subcutaneous abscesses and more.[11] EPDs are often subclinical and can easily go undetected until necropsy. They can occur with or without concurrent pneumonia that is typically associated with *R. equi*. Due to the associated poorer prognosis, recognition of EPDs is important. Survival is much higher in foals without EPDs (82%) compared to foals with EPDs (43%). Certain EPDs may be associated with a better prognosis than others, but additional studies are needed for verification.[10] Varied treatment protocols have been used for *R. equi* and EPDs, and there is no single best option. Therefore, it is important to thoroughly examine foals presenting with potential *R. equi* infections and report case outcomes. The following report outlines the presentation, treatment, and outcome of a 3-month old quarter horse foal with EPD.

History and Presentation

A 3-month old quarter horse filly presented to MSU-CVM for worsening lameness of the left forelimb. Symptoms of lameness and a mild fever started approximately 10 days prior to presentation. The farm veterinarian reported that *Rhodococcus equi* was endemic on the farm. When lameness began, the foal was put on stall rest, a restricted diet, and was administered minocycline for approximately one week. After this, the left carpus still appeared swollen and radiographs were performed. These revealed lucency in the distal radius. Radiocarpal and middle carpal joints were lavaged with amikacin. The Saturday prior to presentation, the foal was laying down, non-weight bearing lame, and the carpus appeared very large. No diarrhea had been seen, and failure of passive transfer was unlikely due to the farm's protocol of administering plasma, as well as the foal's adequate nursing.

Upon presentation, vital parameters were within normal limits (Temperature=99.4 F, Pulse=88 bpm, Respiration=48 brpm) with a weight of 368 lbs (167 kgs) and body condition score of 5/9. GI motility was heard in all 4 quadrants. Mucous membranes were pink, with a CRT<2 seconds. No digital pulses were felt in the unaffected limbs. The left distal radius and carpus was very enlarged and warm. The foal had a lameness score of 4/5 on the basis of the American Association of Equine Practitioners lameness scale. She was mildly depressed but was nursing adequately.

Diagnostic Approach/Considerations

Serial Complete Blood Count and Serum Chemistries were taken to assist in decisions about treatment and assess further development of infection. The initial CBC and Serum Chemistry

performed upon presentation revealed leukocytosis (35.5 K/ul, reference range 5.0-11.9 K/ul), segmented neutrophilia (30,175/ul, rr 2500-6000/ul), hypoalbuminemia (2.1 g/dl, rr 2.8-3.9 g/dl), and monocytosis (2,485/ul, rr 0-800/ul).

Radiographs were performed of the left carpus and the thorax. Radiographic findings of the left carpus included a large (65 mm in height and 28 mm in width), ovoid, irregularly marginated heterogenous lucent and sclerotic structure on the medial aspect of the distal radial metaphysis, extending to the physis and epiphysis. A thin, lucent rim was seen surrounding the structure, which was also surrounded by a rim of sclerosis. There was also severe intra- and extracapsular soft tissue swelling surrounding the carpus. At this time, the heterogenous lucency was interpreted as an abscess or sequestrum with suspected infectious etiology.

Thoracic radiographs showed overall haziness and increased opacity diffusely, suggesting unstructured interstitial pulmonary pattern diffusely, most severely in the dorsocaudal lung lobes. Air bronchograms can be seen ventrally, consistent with an alveolar pattern in this area. No abscesses were seen, which is atypical for *R. equi* lung infections. These radiographic findings indicated bronchopneumonia, with consideration given to bacterial, parasitic, or viral etiologies. Ultrasound was used to assess lungs and gastrointestinal tract as well. No abnormalities were noticed in the lungs, but at least 5 irregularly marginated mixed echogenicity structures varying in size presumed to be within the colonic wall, or possibly within lymph nodes were found adhered to the GI mesentary. These were most likely abscesses, which is consistent with extrapulmonary *R. equi*.

Pathophysiology (Include Anatomical Considerations)

Rhodococcus equi is a facultative intracellular pathogen in soil that establishes an infection by inhalation or ingestion. The incubation period ranges from 9 days to 4 weeks depending on the amount of bacteria and host factors.[7] At-risk foals include those 1-4 months, with horses older than 1 year being rarely affected. This may be due to decreased expression of interferon-gamma in foals compared to adults, however the evidence for this is conflicting. There has been some evidence suggesting a genetic basis for susceptibility to *R equi* infection. Polymorphisms in the LC11A1 gene in Arabians, and the transferrin gene in Thoroughbreds have been associated with *R. equi* infections. Additionally, the interleukin-7 receptor gene has been associated with significantly higher burdens of virulent *R. equi* recovered from tracheobronchial aspirate (TBA) fluid when compared to foals without the gene.[8]

R. equi is usually inhaled, and then phagocytized by alveolar macrophages. Typically, bacteria are engulfed by a macrophage, a phagosome is formed, which then fuses with a lysosome and destroys the captured bacteria. However, *R. equi* is able to modify the phagocytic vacuole to prevent acidification and phagosome-lyosome fusion, thus prolonging survival.[8] This is one of the reasons it is very difficult to treat. Once a foal inhales the bacteria, it can establish an infection in the lungs. The foal may cough up and swallow mucus containing *R. equi*, which then replicates in their gastrointestinal tract. If the bacteria gets into the vasculature, the foal can become bacteremic and spread to various locations in the body, which can be described as an extrapulmonary disorder (EPD). One of the potential locations the bacteria can spread is the metaphyseal plate.[13] The vascular anatomy of a foal's metaphysis predisposes it to infection. The physes contains 'hairpin loops' that allow blood flow to slow and bacteria to 'sludge' and proliferate.[1] Therefore, hematogenous osteomyelitis can occur as a result of the bacteremia which was the case for the foal in this report.

Treatment & Management

Treatment was initiated with a regional limb perfusion of 500 mg Meropenem above the carpus utilizing the cephalic vein in the left forelimb. Topical Nitrofurazone and a sweat bandage were applied to reduce edema in the affected area. Azithromycin (10 mg/kg PO q24h) was given orally. This caused intermittent severe diarrhea and frequency of administration was decreased accordingly. It was necessary to discontinue administration for approximately one week due to dehydration. IV fluids were administered due to the antibiotic-induced dehydration (34 L of LRS over 3 days, 2 L bolus of Plasma *R. equi*). Probiotics (Probios 1 scoop PO q12h, Platinum Balance 1 scoop PO q12h, Biosponge 3 tablespoons in 30 cc of water PO q6h) and gastroprotectants (Ranitidine 7 mg/kg PO q8h, Misoprostol 3 ug/kg PO q8h) were given orally to alleviate diarrhea associated with antibiotic treatment. Anti-inflammatories (Flunixin meglumine) were administered orally with the frequency varying based on clinical signs and other ongoing treatments. The foal was monitored and a physical exam was performed every 8 hours. She was allowed short walks once a day.

Two days after presentation, the foal was placed under general anesthesia and synovial fluid of the left radiocarpal and middle joints were taken to be submitted for cytology and culture. Results of the culture confirmed *Rhodococcus equi*. The joints were then lavaged with 5 L of Hartman's fluid, and medicated with 500 mg of Meropenem in each joint. An incision was made on the medial aspect of the left distal radius. Upon incision of the skin a large amount of purulent debris drained from the tissue. The area was debrided with a curette and a periosteal elevator was used to remove a soft focal lesion of about 0.5 cm in the cortex of the distal radius. Immediately proximal to the lesion, the bone appeared gray in color, but was not soft and

therefore remained intact. A drill bit was then used to drill a hole into the bone to allow access for intraosseous administration of antibiotics. A circuit catheter was positioned and sutured in place to allow further antibiotic delivery on subsequent days. A bandage and cast were applied to the entire forelimb. Recovery of anesthesia was uneventful. Daily intraosseous injections of meropenem were administered for 7 treatments. On the last intraosseous injection, a poloxamer gel mixed with Clindamycin was administered through the catheter, and the catheter was subsequently removed. The use of a poloxamer gel allows for antibiotics to be held at the site of injection and released slowly.

Repeat carpal radiographs were performed 6 days after placement of the intraosseous catheter. These revealed a relatively unchanged physitis along with progressive widening of the lucent zone surrounding the previously described heterogenous structure. This increased area of lucency could be due to curetting during surgery. Extracapsular swelling had improved. Repeat thoracic radiographs were performed 10 days after presentation, and were found to be unchanged.

Discussion and Case Outcome

Treatments for EPDs are varied, and little research has been done to determine the best possible protocol. In this case, once ultrasound revealed multiple gastrointestinal abscesses, importance of oral antibiotics as well as gastroprotectants, was reinforced. Azithromycin was chosen due the macrolide's intracellular concentration in phagocytes, extensive volume of distribution, high oral bioavailability, and long half-life.[3,6] Although previous literature recommends the use of Rifampin with a macrolide when treating *R.equi*, recent studies have

found that Rifampin decreases the bioavailability of Clarithromycin by 90%, which is below the minimum inhibitory concentration (MIC) of *R. equi*. One reason for this may be that Rifampin blocks the transport mechanism of macrolides into GI epithelial cells.[9] While coadministration of Rifampin with Azithromycin hasn't specifically been studied in foals, it is likely to respond similarly.[5]

Although bloodwork intermittently improved, it was not within normal limits by time of discharge. The last bloodwork, performed on the 10 day, revealed leukocytosis (32.2 K/ul, rr 5.0-11.9 K/ul), segmented neutrophilia (27,768/ul, rr 2500-6000) and hypoalbuminemia (2.3 g/dl, rr 2.8- 3.9 g/dl). While lab values did not reflect improvement, the carpus decreased in swelling significantly while in hospital, and lameness and mentation improved. Approximately one month following presentation, the foal was ambulating well, diarrhea had resolved, and she was discharged with instructions to continue monitoring. She made a full recovery with no persistent lameness.

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