

Case Report

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## Case Report

# Presumed Immune- Mediated Hemolytic Anemia in Foal with *Rhodococcus equi* Infection- Case Report

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**Simple Summary:** A 4-month-old Holstein foal presented with depression, anorexia, diarrhea, icterus and hemoglobinuria at the Lithuanian University of Health Sciences, Large Animal Clinic. After clinical examination, blood tests results, thoracic ultrasound and X-ray examination and transtracheal wash culture *R.Equi* pneumonia was diagnosed. Severe anemia and hemolysis were detected, with decreased PCV, RBC, HB, elevated serum iron levels. The blood smear indicated severe anaemia, characterised by a notable presence of schistocytes, a limited number of prominent elliptocytes and spherocytes, isolated echinocytes and a reticulocyte count significantly below the average. Poikilocytosis and microcytosis were detected. Toxic nuclear granulation of segmented neutrophils was also observed in the blood smear. Hemolytic anemia concurrently *R.Equi* infection were diagnosed. Along with antimicrobial treatment, to prevent further hemolysis dexamethasone therapy and whole blood transfusion was applied. Due to severe sepsis, worsening clinical condition and lack of response to treatment the foal was euthanized ,necropsy was performed.

**Abstract:** In foals, *Rhodococcus equi* infections are typically linked to a range of non-pulmonary conditions, with hemolytic anemia being an uncommon complication. The authors are aware of only one case report involving immune-mediated hemolytic anemia in foals infected with *Rhodococcus equi*, highlighting the need for further research. This report aims to describe the clinical presentation, progression, outcome, and pathological findings of 4-month-old Holstein foal with *Rhodococcus equi* infection concurrently with presumed immune-mediated hemolytic anemia. Due to severe sepsis and worsening clinical condition, the foal was euthanized and necropsy was performed.

**Keywords:** rhodococcus equi; foal; hemolysis; hemolytic anemia; blood transfusion

## 1. Introduction

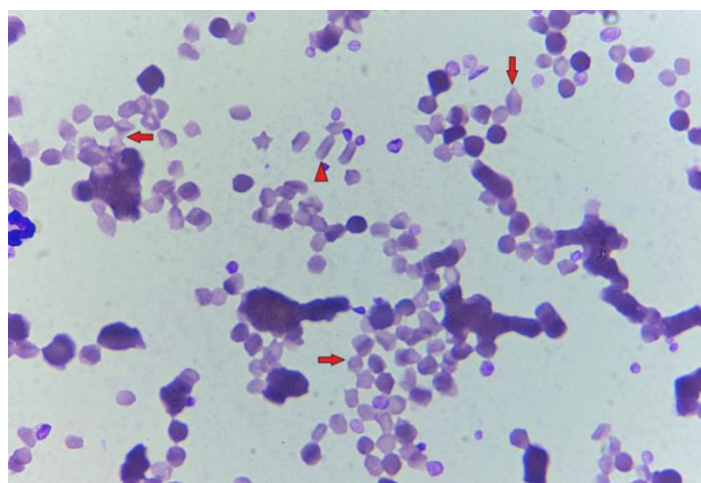
Non-pulmonary *Rhodococcus equi* infections are typically seen as intestinal and mesenteric abscesses, septic phytitis and osteomyelitis, endophthalmitis, guttural pouch empyema, sinusitis, pericarditis, nephritis, non-septic uveitis, and hepatic and renal abscessation [11]. Hemolytic anemia in these cases is rare and, to the authors' knowledge, there has been only one reported case of presumed immune-mediated hemolytic anemia linked to *Rhodococcus equi* infection in foals [15]. This case report aims to explore the clinical presentation, progression, and outcomes of a foal infected with *Rhodococcus equi*, which was also suspected of suffering from severe immune-mediated hemolytic anemia. Dexamethasone is often used to treat immune-mediated hemolytic anemia, although its use can be contraindicated in foals with severe bacterial infections [15]. Despite antimicrobial treatment and supportive therapy in this case, a lower dose of dexamethasone was administered, also whole blood transfusion performed. Regardless of treatment, the foal's condition deteriorated, and it was euthanized on day 56.

## 2. Case History

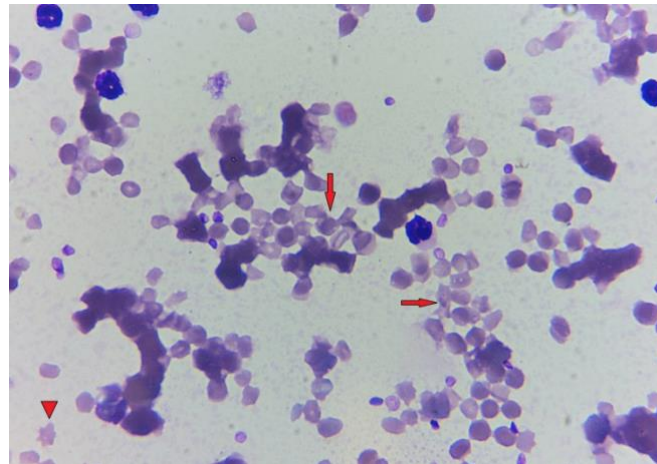
A 4-month-old Holstein foal (weighing 130kg) presented with depression, anorexia, diarrhoea, and epiphora at the Lithuanian University of Health Sciences, Large Animal Clinic. The foal was born on a farm where *Rhodococcus equi* pneumonia had been previously reported, and its dam had been vaccinated for *Rhodococcus equi*. Upon examination, the foal had tachycardia (80 bpm), a respiratory rate of 20/min, capillary refill time (CRT) of 1 second, a temperature of 38.3°C. Icterus and haemoglobinuria were observed. During auscultation crackles were heard in the trachea, bronchovesicular sounds were increased in the cranial lung parts, no dyspnea or abdominal breathing pattern was noted. Bilateral, non-painful effusion was observed in the hocks and stifles.

Morphological blood test was performed using the Abaxis HM5 VETSCAN Haematology analyser. Visually, after taking a blood sample, significant blood hemolysis was observed in vacutainer (Figure 7) Blood analysis showed WBC at  $39.41 \times 10^9/l$  (norm  $5.4\text{--}14.3 \times 10^9/l$ ), neutrophils at  $25.49 \times 10^9/l$  (normal range  $2.3\text{--}9.5 \times 10^9/l$ ), and RBC at  $5.76 \times 10^{12}/l$  (normal range  $6.8\text{--}12.9 \times 10^{12}/l$ ), with haemoglobin at 54 g/l (normal range 110–190 g/l), packed cell volume (PCV) at 18.41% (normal range 32–53%), PLT ( $69 \times 10^9/l$ , normal range  $100\text{--}400 \times 10^9/l$ ), and MCV was 32 fL (normal range 37–59 fL), with MCHC was 293 g/dL (normal range 12.3–19.7 g/dL). Blood morphology hemodynamics of the whole treatment course was present at (Figure 8).

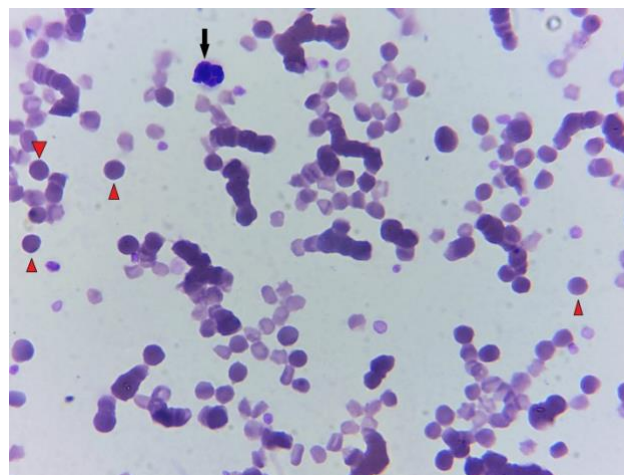
The biochemical blood test was conducted by the DiaSys respens®910VET analyzer. Serum parameters revealed hypoalbuminemia (18.5 g/l, normal range 25–42 g/l), elevated ALP (419.3 U/l, normal range 109–315 U/l), hypocalcemia (2.66 mmol/l, normal range 2.7–3.4 mmol/l), and elevated iron level (38,9  $\mu\text{mol/l}$ , normal range 13–25  $\mu\text{mol/l}$ ). Blood gases showed hyperlactatemia (5.15 mmol/l, normal range  $>2$  mmol/l) and hyponatremia (120 mmol/l, normal range 128–142 mmol/l). Serum amyloid A was elevated at 326 mg/l (normal range 0–20 mg/l). During blood smear analysis, poikilocytosis and microcytosis were noted. The blood smear indicated severe anemia, characterized by a notable presence of schistocytes (Figure 1–2), a limited number of prominent elliptocytes (Figure 1 and 4) and spherocytes (Figure 3), isolated echinocytes (Figure 2), and a reticulocyte count significantly below the average. Toxic nuclear granulation of segmented neutrophils was also observed in the blood smear (Figure 3–4).



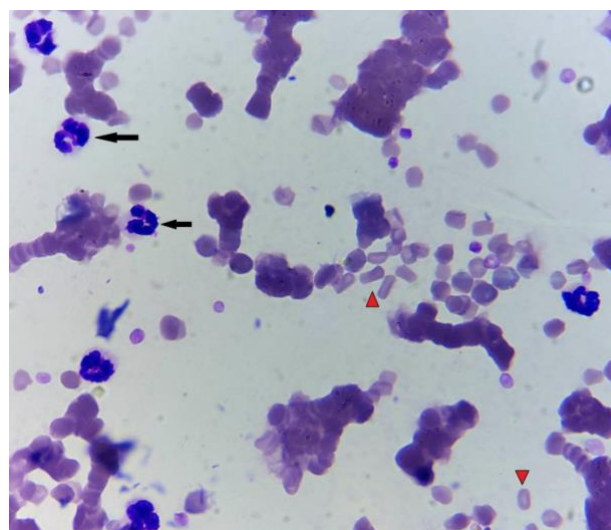
**Figure 1.** Large number of schistocytes (arrows) and several elliptocytes (arrowhead). Hemacolor, x1000.



**Figure 2.** A significant quantity of schistocytes (arrows) and one echinocyte visible (arrowhead). Hemacolor, x1000.



**Figure 3.** Single spherocytes (red arrowheads) and segmented neutrophil with toxic nuclear granulation (black arrow). Hemacolor, x1000.



**Figure 4.** Several segmented neutrophils with toxic nuclear granulation (black arrows) and elliptocytes (red arrowheads). Hemacolor, x1000.

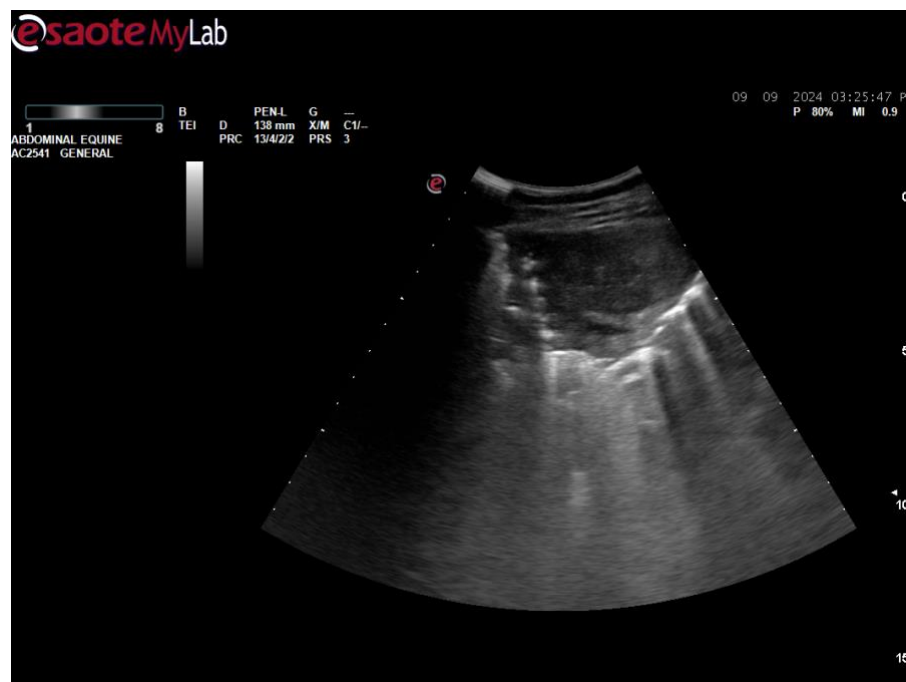
Faecal examination using the modified McMaster method did not detect helminth eggs. A bronchoscopy revealed a hyperemic trachea with yellowish discharge all over trachea and bronchi (grade 2) and bifurcation edema 2/4 (according to B. Wysocka, W. Klucinski 2014). The cytological



analysis of a transtracheal wash (TTW) revealed 94.5% neutrophils, 2.75% macrophages, 2.25% lymphocytes, 0.5% mast cells, and a limited quantity of bacteria was detected individually.

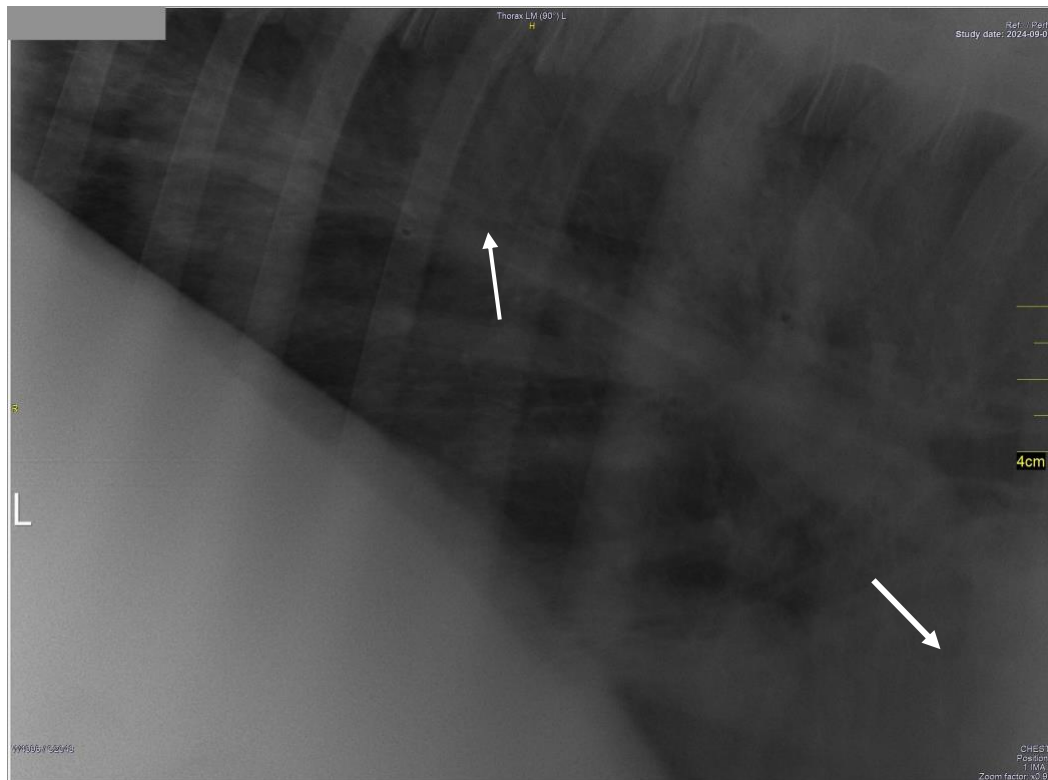
Thoracic ultrasound (EsaoteMyLab, depth 138mm, P 80%, MI 0.9) revealed a 45mm x 50mm anechoic, airless derivative in the left lung cranioventral part (Figure 5), lesion grade 5 from 10 according to Nathan M. Slovis et al. 2005 grading system). On both sides, prominent B- lines were visible almost everywhere throughout the pleura. During treatment period derivatives did not change its size and echogenicity ultrasonographically.

Using percutaneous ultrasound, mixed echogenicity mas (approximately 7 cm in diameter) was observed in lower abdomen with significant vascularization (video S1). Mesentery lymphadenopathy or abscesses were presumed. During treatment it was observed that mas was changing its location in the abdomen, sometimes it was not seen at all. During hospitalization, the mass tended to grow and permanently stay in the lower abdomen and increased in size (approximately 12 cm in diameter).



**Figure 5.** Anechoic, airless derivative in the left lung cranioventral part.

Thoracic radiographs revealed a severe patchy alveolar pattern with rounds of soft tissue opacities with areas of gas lucency (**Figure 6**).

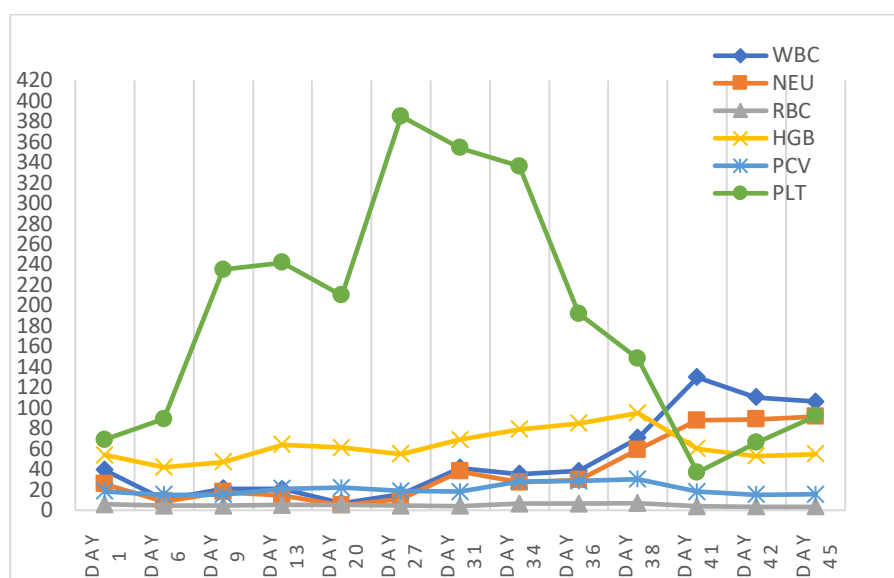


**Figure 6.** A severe patchy alveolar pattern with rounds of soft tissue opacities with areas of gas lucency (arrows).

A diagnosis of bronchopneumonia due to *Rhodococcus equi* was made. The foal was treated with rifampin (5 mg/kg bw, PO, q12h) and clarithromycin (7.5 mg/kg bw, PO, q12h), along with supportive therapy (vitamin C, B, and IV fluids) to correct electrolyte imbalances.

Flunixin meglumine (Vetaflumex 50mg/ml, VetAgro, Poland, dose 1.1mg/kg bw q12h) and later metamizole sodium monohydrate (Pyralgine 500mg, Biowet Pulawy, Poland, 20-50mg/kg bw q4h) were used for fever, and 2 liters of hyperimmunised plasma was administered for colloidal support. Gentamicin was added after TTW's culture revealed *Pasteurella multocida* infection. Despite treatment, the foal's condition deteriorated, and it was re-admitted to the clinic because of persistent pyrexia, anorexia, depression.



**Figure 7.** Blood hemolysis after taking a blood sample for blood morphology.**Figure 8.** Hemodynamics of white blood cells (WBC), neutrophils (NEU), red blood cells (RBC), hemoglobin (HGB), packed cell volume (PCV), and platelets (PLT) during hospitalization.

After re-admission, a blood test indicated a further decrease in PCV to 15%, a reduction in RBC to  $3.36 \times 10^{12}/l$  (normal range  $6.8\text{--}12.9 \times 10^{12}/l$ ), stable haemoglobin at 53 g/l (normal range 110–190 g/l), and an increase in WBC to  $110.19 \times 10^9/l$  (normal range  $5.4\text{--}14.3 \times 10^9/l$ ), with neutrophils at  $88.79 \times 10^9/l$  (normal range  $2.3\text{--}9.5 \times 10^9/l$ ). Additionally, iron levels remained elevated for a long time ( $37.5 \mu\text{mol}/l$ , normal  $13\text{--}25 \mu\text{mol}/l$ ). Antimicrobial treatment was changed to azithromycin (Summamed 500 mg, Teva, dose 10 mg/kg bw, PO, q24h) and doxycycline (DOXYFORT 500, Centrowet Sp. Zo.o., dose 10 mg/kg bw PO q12h) for 14 days. Treatment with dexamethasone i.v. was continued for 14 days (dose 0.04 mg/kg bw every two days). On consecutive days foal's clinical condition was deteriorating frequently; anorexia, depression and small amount of anechoic-free fluid on the ride side of thorax were detected. Due to worsened clinical condition bronchoscopy was performed a second time, and TTW bacteriology sample was taken. In the pharynx, the dorsal recess, and trachea were hyperemic. Thick yellowish discharge was seen up to bifurcation. Bifurcation edema was 2/4. Foal started to show colic signs periodically. On 32nd day of hospitalization foal's blood morphology worsened (WBC  $41.15 \times 10^9/l$  (normal range  $7.29\text{--}11.68 \times 10^9/l$ ), NEU  $38.11 \times 10^9/l$  (normal range  $4.8\text{--}8.20 \times 10^9/l$ ), RBC  $4.23 \times 10^{12}/l$  (normal range  $8.20\text{--}9.80 \times 10^{12}/l$ ), HGB 69 g/l (normal range 106–130 g/l), PCV 18.12 %, normal range 30.34–40.18%). TTW bacteriology revealed *Pseudomonas Aeruginosa* (sensitive to enrofloxacin), *Pseudomonas spp.* (sensitive to enrofloxacin, doxycycline, ceftiofur), *Staphylococcus Aureus* (sensitive to ceftiofur, amikacin) and *Rhodococcus spp.* (sensitive to enrofloxacin, ceftiofur and amikacin) growth. High bacterial resistance was observed. Antimicrobials were changed to ceftiofur (Eficur 50mg/ml, LABORATORIOS HIPRA, S.A., Spain, dose 10mg/kg bw IM q12h).

On day 38 WBC increased to  $70.68 \times 10^9/l$  (normal range  $7.29\text{--}11.68 \times 10^9/l$ ), and PCV dropped to 12% (normal range 30.34–40.18%). Foal's clinical condition worsened, no response for antimicrobial treatment was observed, and consistent pyrexia was seen. Due to dramatically dropped PCV, severe anemia, and septicemia blood transfusion was performed from a donor identified as compatible via cross-matching (21ml/kg bw). A slight improvement of RBC, HB, PCV was observed after the transfusion, which deteriorated after a couple of days. On day 45 of hospitalization due to worsened clinical condition (anorexia, apathy, pyrexia, shortness of breath, colic) and septicemia foal was euthanized.

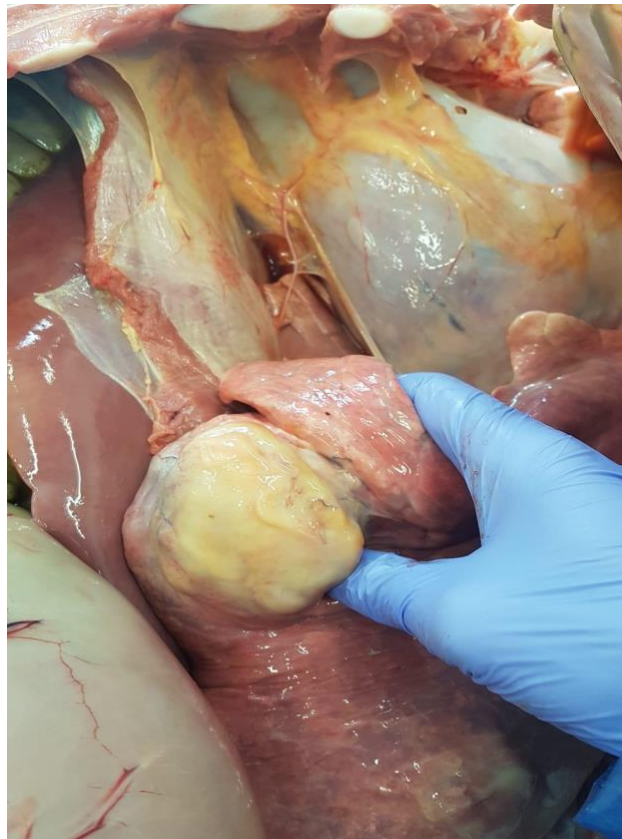
### 3. Post-Mortem Examination

The foal's body condition score was 3.5 (Henneke Horse Body Condition Scoring System). At necropsy, pale and jaundiced mucous membranes were noted. The inguinal lymph nodes were enlarged, and cross-sections of the hock joints revealed marked jaundice and significant synovial fluid. Subcutaneous tissues appeared pale, yellowish, and dry, and all abdominal organs were similarly pale. A small amount of exudate was found in the abdominal cavity. The mesenteric lymph nodes were enlarged and purulent (**Figure 9**). The spleen and kidneys were also enlarged and pale. The heart and liver contained chicken fat blood clots. The lungs had multiple small nodules, some up to 5 cm in size, with pus-like exudate present inside (**Figure 10**). Flootation tests showed emphysema in the lungs.



**Figure 9.** Nodules in mesentery.





**Figure 10.** Nodule in the lung.

#### 4. Discussion

*Rhodococcus equi* pneumonia primarily affects foals aged 1–6 months and causes significant economic losses in the equine breeding industry [8]. Immune complex deposition can cause polysynovitis which contribute to the development of uveitis, anemia or thrombocytopenia in infected foals [14]. While pneumonia is the most common manifestation, *R. equi* in horses ,infections can also present with other extra-pulmonary conditions distant to the respiratory tract such as polysynovitis, abdominal abscesses and uveitis. Extrapulmonary findings are often associated with more severe cases and worse prognosis [29]. Anemia, fever of unknown origin is reported in human medicine with *Rhodococcus equi* infection in an immunocompetent patient [33]. Immune-mediated hemolytic anemia (IMHA) associated with *R. equi* is rare, with only one previous case reported in foals [15]. *Rhodococcus equi* is generally thought to be non-haemolytic although some earlier investigations reported minor haemolytic activity. A case of a haemolytic *R. equi* isolate from a swine lymph node with granulomatous lesions is reported [23].

Immune-mediated hemolytic anemia (IMHA) is a rare condition in horses. In adult horses IMHA is mostly associated with chronic bacterial (for example *clostridium* induced) or viral infection, lymphoma or drug administration [18], idiopathic immune- mediated hemolysis [6]. Secondary IMHA is often triggered by infections or medications that provoke antibody production against red blood cell (RBC) antigens. In cases of secondary IMHA, antibodies are formed against substances, that abnormally coat the red cells [32]. The predominant antibody intent in equine IMHA is IgG. Blood hemolysis for the equids can be intravascular or extravascular. Intravascular hemolysis is less common and characterised by hemoglobinemia and hemoglobinuria. Generally, hemolysis occurs extravascularly, while monocyctic-phagocytic system removes immunoglobulin- coated RBC's by spleen [32,40]. At present case, weakness, tachycardia, depression, icterus and hemoglobinuria suggested intravascular hemolysis [7]. Unique feature of *R.Equi* is synergistic hemolysis, which occurs when *R. equi* are cultured on sheep blood agar are cross-streaked with other bacteria, including *Staphylococcus aureus*, *Listeria monocytogenes*, and *Corynebacterium pseudotuberculosis* [26].

Preliminary IMHA diagnosis begins with reduced PCV with normal (or increased) total protein (TPP) concentration [4]. In the current case, reduced PCV and decreased TPP concentration occurred. Icterus, hemoglobinemia, hemoglobinuria is supportive of diagnosis of intravascular IMHA, as seen at present case. Further evidence that this case may be haemolytic anaemia comes from the continued detection of low haemoglobin levels and low MCT. In this case the increased number of inflammatory cells suggests that the haemolytic anaemia could have been initiated by an infection, during which inflammatory cells mistakenly target and eliminate their own erythrocytes. The analysis of the smear indicates a diagnosis of haemolytic anaemia, as it reveals significant alterations in the shape and structure of erythrocytes, including schistocytes, elliptocytes, spherocytes, and other abnormally shaped erythrocytes present in the blood. In chronic disease-related anaemia, erythrocytes typically remain unchanged in shape and size, resulting in normocytic - normochromic anaemia, with haemoglobin levels generally unaffected [17]. This type of anaemia typically results from inhibited erythropoiesis, leading to a decreased number of erythrocytes. In hemolytic anemia, the iron concentration in the serum is elevated due to the destruction of red blood cells, as iron from the red blood cells enters the plasma, as it was observed at present case. Justification of IMHA may be supported by direct agglutination or Coomb's test [32]. However, false negative results can occur, as in previous case report [15], Coomb's test was also false negative. Test sensitivity reported in dogs are 37-89% [22,38].

Reported IMHA causes are the use of beta-lactam and potentiated sulphonamide antimicrobials [37]. In horses, commonly implicated with IMHA antimicrobials are penicillin and trimethoprim [32]. In human medicine, rifampin and erythromycin (which were used in the current case) were also reported as possible drugs caused by IMHA in humans. Furthermore, the occurrence is extremely rare [21,25]. Drugs related to IMHA were considered unlikely in this case, because foal already arrived in the clinic highly anemic, before using any of IMHA-related drugs.

Blood loss anemia was ruled out in this case. In blood smear, a limited quantity of reticulocytes was observed, suggesting that the anemia was challenging to regenerate. Horses release reticulocytes from bone marrow very rarely. Typically, hemolytic anemias induce a greater reticulocyte response than blood-loss anemias. Previous studies have documented that horses do not have reticulocytes in peripheral blood in blood-loss anemia [34]. Typically, anemia caused of chronic disease is mild to moderate, slowly progressive and clinically insignificant. Thus, in this case anemia was severe and considered most likely hemolytic.

Corticosteroids are a golden standard in IMHA treatment. They inhibit sequestration and phagocytosis of RBC and decrease antibody production against RBC [18,20]. However, corticosteroid use for IMHA treatment is still debatable among equine practitioners. For horses with severe bacterial infection, corticosteroid use can interfere with the immune response to clearing the infection. Corticosteroids decrease oxygen radicals and lysosomal enzyme release from PMNs also disturbs intracellular bacteria phagocytosis [18,30]. It's doubtful improvement in hemogram. Permanent or worsening anemia and poor response to antimicrobial treatment will force equine practitioners to strongly consideration of corticosteroid use. Usually, 0.04-0.06 mg/kg bw q24h dexamethasone dosage is used [16,18]. However, there are no clear guidelines in equine medicine for dexamethasone use to prevent further cell destruction. In the present case imminently anemia using corticosteroids was deemed to take precedence over the long-term goal of bacterial cure, bearing in mind the lack of response to antimicrobial treatment, persistent pyrexia, anorexia, and hemolysis. In the current case, the initial dose of 0.1mg/kg bw [24] of dexamethasone was used, with the following dose of 0.04 mg/kg bw q24h, later q48h. A relatively low corticosteroid dose was used.

In order to reduce endotoxemia and septicemia and provide colloidal support plasma was applied in the current case [36]. On day 38 when PCV dropped to 13%, a whole blood transfusion was performed. A slight improvement of RBC, HB, PCV (**Figure 8**) was observed after the transfusion, which deteriorated after a couple of days. The purpose of whole blood transfusion is to restore oxygen delivery to the tissues [13]. According to [12] PCV as low as 10-12% is considered too low and blood transfusion is recommended, because adequate oxygen delivery to tissues is not

provided. Usually, horses become tachycardic, tachypneic, and depressive while adequate oxygen delivery is not provided. Transfused blood cells have a relatively short half-life and antibody production against transfused cells occurs rapidly [16,34]. In the current case, only one blood transfusion was performed. Despite a slight clinical and hematological increase, the foal condition deteriorated, and septicemia occurred later, so it was decided to perform euthanasia.

Post-mortem examination revealed spleen and kidney enlargement, jaundice in mucus membranes. All internal organs were anemic. Generalized icterus, splenomegaly, enlarged kidneys is characteristic feature of hemolytic anemia [7]. Severely enlarged and purulent mesenteric lymph nodes of foals with *R. Equi* infection are limitedly described in literature [10,28]. As in [15] case report, a large masses of mixed echogenicity, presumed to be enlarged lymph nodes or abscesses were seen in mesentery, performing percutaneous ultrasound of foal's abdomen. Mesenteric lymphadenopathy is commonly found on postmortem examination in horses with infectious, inflammatory, or neoplastic disease but has been rarely reported as an ultrasound finding. Autoimmune hemolytic anemia (AIHA) has been associated with lymphoproliferative disorders in human medicine [5]. Mesenteric lymph nodes are not often visualized by ultrasound because of their location deep within the abdomen [3]. Ultrasonographically, lymph nodes are hypoechoic to the perinodal tissue, ovoid with smooth well-delineated margins and show an homogeneous echotexture [1,19,27,31]. It is reported, that lymph nodes can have characteristic blood perfusion, which is seen using Color Doppler ultrasound imaging [2,35]. It helps to distinguish mesenteric lymphadenopathy from abscessation. Our case report provides valuable information about ultrasonography imaging of mesenteric lymphadenopathy in foal (**video S1**).

During the past decade, *Rhodococcus equi* treatment has become more and more challenging because of multidrug resistance (MDR) which results as lack of positive response to antimicrobial treatment in vivo [9]. Many equine breeding facilities use thoracic ultrasonographic screening and antimicrobial treatment of subclinically affected foals [11]. Vaccination is a promising approach to prevent disease, but most *R. equi* vaccine candidates tested to date have not been sufficiently effective. In the present case, foals dam was vaccinated against *R. Equi*, however *R. Equi* infection affects foal significantly. Doxycycline use in place of macrolides and rifampicin suggests potential for reduction of resistance in some in vitro studies [8,39,40]. At present case MDR was observed not only for *R. Equi* but also to secondary bacterial infections detected during culture: *P. Aeruginosa*, *Pseudomonas spp.*, *Staphylococcus aureus*.

Diagnosis of hemolytic anemia in this case was made based on strong clinical evidence, changes in blood morphology and biochemistry, blood smear analysis, positive response to dexamethasone therapy and post-mortem changes but could have been supported by further diagnostic testing.

This article provides valuable information about clinical course, progression and outcome of presumed immune-mediated hemolytic anemia in foal with *Rhodococcus equi* infection, especially about postmortem examination, which is not reported in Imogen C. John et. Al article, because both foals survived.

## 5. Conclusion

Although immune-mediated hemolytic anemia is a rare complication of *Rhodococcus equi* infections in foals, it is important to consider this diagnosis in cases of severe anemia. The case described highlights the need for further investigation into the clinical progression, treatment strategies, and prognosis of foals affected by *R. equi* infection and concurrent immune-mediated hemolytic anemia. Further studies will help develop optimal treatment plans and improve the outcomes for foals diagnosed with these rare, but significant extra-pulmonary disorders, associated with *R. Equi* infection.

**Supplementary Materials:** The following supporting information can be downloaded at: [www.mdpi.com/xxx/s1](http://www.mdpi.com/xxx/s1), Video S1: mixed echogenicity mas in lower abdomen, using percutaneus ultrasound.

**Author Contributions:** R.T-S.: writing original draft; I.M.- Writing - review & editing ,R.G.- Writing - review & editing, B.P.- Writing - review & editing, J.H.- Writing - review & editing and data curation, M.U.D.- Writing - review & editing and data curation, A.U.- Writing - review & editing and data curation

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**Institutional Review Board Statement:** Given that blood and other biological samples were collected for routine diagnostic purposes and solely for the animal's benefit, and the owner had signed a consent form that authorized the use of their data and excess specimens for research purposes, formal approval from the University's Ethical Committee was not required.

**Informed Consent Statement:** Not applicable

**Data Availability Statement:** The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding authors.

**Conflicts of Interest:** The authors declare no conflicts of interest.

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