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TITLE OF CASE ***Do not include "a case report"***

Immune-mediated haemolytic anaemia secondary to haemotrophic mycoplasma infection in a pet ewe

SUMMARY ***Up to 150 words summarising the case presentation and outcome (this will be freely available online)***

A three-year-old pet ewe was assessed after collapsing, following a four-day history of lethargy, anorexia and discoloured urine. Haematological assessment revealed a regenerative anaemia, with spherocyte-like cells and basophilic structures on the surface of erythrocytes. A haemotrophic mycoplasma was detected in blood using polymerase chain reaction amplification of the 16S rRNA gene followed by denaturing gradient gel electrophoresis. Treatment with enrofloxacin or oxytetracycline achieved short-lived relief of symptoms, whereas tulathromycin was associated in longer lasting control of clinical signs. Haemotrophic *Mycoplasma* species are an uncommon cause of anaemia in sheep, which until recently had been difficult to diagnose. This report describes a case of immune-mediated haemolytic anaemia associated with infection with an ovine haemotrophic mycoplasma.

BACKGROUND ***Why you think this case is important – why did you write it up?***

Haemotrophic *Mycosplasma* species (haemoplasmas) are adapted to adhere to erythrocyte cell membranes of hosts,[1] resulting in a range of clinical presentations. Clinical signs of *Mycoplasma ovis* (previously known as *Eperythrozoon ovis* [1]) in sheep range from unapparent infection to poor weight gain in lambs, and mild to severe haemolytic anaemia.[2,3] Mortality is rare, but sometimes seen in lambs.[4] Transmission occurs by the translocation of infected erythrocytes from one animal to another,[5] through reused needles, tagging equipment, shearing and arthropod vectors.

Most haemoplasmas were thought to be host specific. However, since the development of polymerase chain reaction (PCR) DNA amplification of mycoplasma 16S ribosomal RNA genes and denaturing gradient gel electrophoresis (DGGE) for the identification of *Mycoplasma* species[6,7], *M. ovis* has been reported in deer [8], horses [9] and humans.[10] Also two sheep specific strains, *M. ovis* and '*Candidatus* M. haemovis', have been differentiated.[11] '*Candidatus* M. haemovis' was first found during the investigation of severe anaemia with

fatalities in sheep in Hungary,[11] in which *M. ovis* and *Anaplasma ovis* were also present. 'Candidatus M. haemovis' has also been reported since, for example in Japan [12] and China.[13] However, the distinction between these two ovine haemoplasmas has been questioned, after full genome sequencing suggested that they may be the same species with two variants of the 16S rRNA gene.[14] As these species cannot currently be cultured, it is difficult to definitely differentiate between them.

Reports of anaemia due to *M. ovis* are not common, but immune-mediated haemolytic anaemia (IMHA), as either a primary or secondary condition, is rarely reported in sheep. IMHA, however, is well recognised in humans and dogs [15] and, therefore, knowledge of this condition primarily comes from these species. Furthermore, cases of IMHA thought to have been secondary to haemotrophic *Mycoplasma* species infections have been reported in cats [16] and cattle.[17] This report details a case of suspected IMHA secondary to infection with an ovine haemoplasma in a pet ewe.

CASE PRESENTATION ***Presenting features, clinical and environmental history***

In July 2016, a three-year-old, 55kg cross-bred ewe presented to the Royal (Dick) School of Veterinary Studies (R(D)SVS) with a four-day history of lethargy, anorexia and discoloured urine. The ewe was one of three pet ewes, kept at grass, in woodland and fed a handful of lamb concentrates once a day. A multivalent *Clostridium* spp. and *Pasteurella* spp. vaccine (Heptavac P Plus, MSD Animal Health) had been administered seven days prior to admission. This ewe had a history of tick infestation as a lamb and a chronic cough for the first four months of life, which then resolved. Ticks were known to be present in the woodland used for grazing, therefore pharmaceutical control of ticks consisted of cypermethrin alpha pour-on (40ml, 12.5 g/l, Dysect, Zoetis UK Limited) or cypermethrin (40ml, 1.25%, Crovect, Elanco UK AH Limited), applied in July in 2016 and 2017. Prior to admission, a course of amoxicillin and clavulanic acid had been initiated by the referring veterinary surgeon. On the third day of treatment the ewe collapsed and was admitted to the R(D)SVS. A single dose of enrofloxacin and a single dose of meloxicam were also administered shortly before to admission.

On examination the ewe had a body condition score of three out of five, was pyrexic (temperature 40.3°C), tachycardic (96 beats per minute), was hyperventilating and had pale mucous membranes. The patient was quiet alert and responsive with good mentation and menace response, rumen fill was reduced, otherwise the abdominal examination was unremarkable. Lymph nodes, head, jaw, limbs, umbilicus and udder were all within normal limits and no ticks were found.

INVESTIGATIONS ***If relevant***

Initial complete blood count revealed a regenerative anaemia, with a packed cell volume (PCV) of 14% (26-38), and marked neutrophilia, 14.3 x10^9/l (0.4-5). On blood smear there was marked anisocytosis and polychromasia with frequent basophilic stippling, indicative of erythrocyte regeneration. A few Heinz bodies were present suggesting mild oxidative damage and spherocyte-like cells that are often associated with an immune-mediated component to anaemia. In addition, there were rare small (1-2 μm) basophilic structures on the surface of erythrocytes, which could have been stain precipitate, but haemotrophic *Mycoplasma* species could not be ruled out. Autoagglutination was assessed using the Slide Agglutination Test: a single drop of ethylenediaminetetraacetic acid (EDTA) anti-coagulated blood was placed on a microscope slide and mixed with two to three drops of saline and rocked back and forth. Macroagglutination was noted, therefore a coverslip was added, and microscopic assessment was made, which revealed autoagglutination. No Coomb's reagent is commercially available in the UK for sheep, so this result could not be verified. These observations suggestive of IMHA were only made during the ewe's first episode of haemolytic anaemia and autoagglutination testing was not repeated.

A biochemistry panel showed multiple abnormalities (Table 1). These changes were considered to be secondary to intravascular haemolysis (e.g. increased glutamate dehydrogenase), inflammatory response (e.g. increased copper) or hypoxic damage to organs (e.g. increased urea).

Table 1: Biochemistry results from the patient. Testing was carried out by the Royal (Dick)

School of Veterinary Studies Easter Bush Pathology Department. (parameters outside of the expected reference range are in bold)				
Blood parameter	Result	Range	Unit	Comment
Total Protein (serum)	**65.8**	73-89	g/l	Albumin and Globulin were within normal limits
Gamma-Glutamyl Transpeptidase (GGT)	**162**	34-100	iu/l	Mild [18]
Glutamate dehydrogenase (GLDH)	**297**	1-12	iu/l	Present in RBC, therefore value can increase with intravascular haemolysis [19]
Aspartate Aminotransferase (AST)	**2670**	45-134	iu/l	Present in RBC, therefore value can increase with intravascular haemolysis [19]
Creatinine Kinase	**4439**	34-190	iu/l	Raised in haemolysis, due to false readings when chromatic measurement techniques are used [19]
Urea	**16.2**	2.6-6.6	mmol/l	Suggestive of kidney hypoxia
Creatinine	97	40-150	µmol/l	
Copper	**26.7**	9.4-18.8	umol/l	Seen in inflammatory conditions, due to elevation in acute phase proteins
Glutathione peroxidase (GSH-Px)	49.5	>40	U/ml cells	Normal
RBC = Red blood cell				

Urine collected by urinary catheterisation was analysed via dipstick and was strongly positive (++++) for the presence of both blood and protein. Centrifugation did not produce an erythrocyte sediment, indicating haemoglobinuria rather than haematuria. Abdominal ultrasound and radiography were unremarkable and did not reveal a metallic foreign body. ELISA serology (performed by SAC Consulting, Edinburgh) for *Mycobacterium avium* subspecies *paratuberculosis* (MAP) was negative.

PCR-DGGE of whole blood (collected via jugular venepuncture into 10ml vacutainers containing EDTA) from this ewe was carried out by the Animal and Plant Health Agency (APHA), Weybridge, at the time of initial presentation and again eight months later (March 2017). Both samples were positive for *Mycoplasma* species, showing a match for *M. ovis*. In March 2017, short sequencing revealed a 99% match for *M. ovis*, however the segment retrieved was shorter than the actual product, therefore this could not be distinguished from *M. wenyonii*. Consequently, the sample underwent full 16S rRNA gene sequencing. However, the full length of the 16S rRNA gene could not be sequenced. The closest match for the truncated sequence was '*Candidatus* M. haemovis',[12] but only by 99%, therefore this could not be definitively differentiated from *M. ovis.* It was concluded that the ewe had an ovine haemoplasma of undetermined species. (Dr A. Ridley, APHA, personal communication)

DIFFERENTIAL DIAGNOSIS *If relevant*

Red discolouration of urine can either be due to haematuria caused by blood loss into the urinary tract, for example due to pyelonephritis or bladder neoplasia, or haemoglobinuria due to intravascular haemolysis. Alongside this, anaemia is caused by haemorrhage, haemolysis or reduced production of erythrocytes. Haemoglobinuria with a regenerative anaemia was found in this case, therefore intravascular haemolysis was suspected. Differential diagnoses of intravascular haemolysis in sheep include:

- Toxicities

- Copper [20]
- Allium species, such as onions [21]
- Brassica species [22]

- Bacterial infections
  - Leptospirosis [23]
  - *Clostridial* species [21]
  - Haemoplasmas [2,3]
- Parasitic infections
  - Babesiosis [24]
- Miscellaneous
  - Water intoxication [21]
  - Immune-mediated haemolytic anaemia (IMHA)
    - Primary [15]
    - Secondary – infection (including haemoplasmas), post vaccination,[25] hormone imbalance [15]

Based on the laboratory findings of a regenerative anaemia with spherocytosis and autoagglutination and the finding of an ovine haemoplasma, haemoplasma induced IMHA was considered the most likely diagnosis for this case.

TREATMENT ***If relevant***

The treatment of haemoplasma induced IHMA can be controversial. The standard treatment for IMHA is immunosuppressive therapy,[15] however corticosteroid treatment can cause patients with *M. ovis* infection to deteriorate.[2] Therefore corticosteroid was considered to be a high risk treatment option and would have only been used if the patient had deteriorated or not responded to antibiotic therapy. Cats with haemoplasma associated IMHA normally show good response to antibiotic therapy, without the use of immunosuppression.[16]

The antibiotic treatment history for this case was complicated, as decision making involved multiple vets from the referring practice, often called out in an emergency situation without prior knowledge of the case, as well as vets from R(D)SVS. Also, the client had knowledge of human medicine and contributed significantly to the treatment decision making. Potentiated amoxicillin was used initially, before a diagnosis had been made. This would not have been effective against *Mycoplasma* species due to their lack of cell wall. Tetracyclines, fluoroquinolones and macrolides have been shown to be effective against *Mycoplasma* species.[26] In this case, clinical recovery appeared to be achieved in late 2016, after a short course of a fluoroquinolone (Table 2), followed by a long acting injection of a tetracycline. However, in spring 2017, clinical signs returned. At this time, a 21-day course of enrofloxacin produced only a short-lived clinical response, followed by clinical deterioration. Subsequently, no clinical response was seen within three days of long acting oxytetracycline. Consequently, a longer course of oxytetracycline was not attempted and the ewe was given a macrolide, after which there appeared to be prolonged clinical improvement. Tulathromycin was the chosen macrolide due to the reported efficacy against *Mycoplasma* species,[26] its prolonged duration of action and its license for use in sheep for another condition, to adhere to the production animal prescribing cascade.

Tulathromycin was given by intramuscular injection on three occasions. Two injections were given nine days apart, as a course of treatment in response to clinical signs. Subsequently, one injection of tulathromycin was given prophylactically at a time of stress (shearing). Currently available data from sheep plasma concentration curves for tulathromycin suggest that levels should remain above the minimum inhibitory concentration (MIC) for most bacterial respiratory agents for nine days (Zoetis Internal Study 1542N-60-12-231). Also, Moyaert et al demonstrated a protective effect for nine days of tulathromycin against *Mycoplasma bovis* in a challenge trial in cattle [27]. Therefore, although these data are not specific for haemoplasmas in sheep, it was expected that the two injections of tulathromycin, nine days apart, would provide the ewe with 18 consecutive days of treatment.

Table 2: Antibiotic treatments given to the patient from initial presentation until the time of death

Start date	Antibiotic	Dose	Route of administration	Duration of treatment (days)
06/07/2016	Amoxicillin and clavulanic acid~	8.75mg/kg daily	Intramuscular	3
09/07/2016	Enrofloxacin*	7.5mg/kg	Intramuscular	1
16/07/2016	Enrofloxacin*	7.5mg/kg daily	Intramuscular	3
27/07/2016	Oxytetracycline^	20mg/kg	Intramuscular	3
13/03/2017	Enrofloxacin*	7.5mg/kg daily	Intramuscular	21
19/04/2017	Oxytetracycline^	20mg/kg	Intramuscular	3
22/04/2017	Tulathromycin$	2.5mg/kg	Intramuscular	9
01/05/2017	Tulathromycin$	2.5mg/kg	Intramuscular	9

30/06/2017	Tulathromycin[$]	2.5mg/kg	Intramuscular	9

~ Noroclav, 140/35mg/ml, Norbrook Laboratories Ltd
* Baytril, 100mg/ml, Bayer PLC
^ Alamycin LA, 200mg/ml, Norbrook Laboratories Ltd
[$] Draxxin, 100 mg/ml, Zoetis UK Ltd

Blood transfusion was considered in this case, and cross-matching of blood was carried out between the patient and the other two sheep in the flock. However, the patient was stable and, due to the high risk of complications, the blood transfusion was not performed.

OUTCOME AND FOLLOW-UP

The ewe was discharged six days after admission to R(D)SVS. Over the following year, she presented with intermittent episodes of lethargy, anorexia, pyrexia and haemoglobinuria. These signs improved within 24 hours of effective antibiotic therapy. The level of anaemia fluctuated (Table 3). Urine colour (Figure 1), blood and protein content were monitored regularly by the owner and varied throughout the year. These clinical signs were consistent with the initial presentation, however, it was not clear whether these relapses were due to lack of clearance of the same haemoplasma infection or re-infection due to inadequate control of arthropod exposure.

Approximately 12 months from the initial episode, the ewe suffered a four-day period of melaena, severe lethargy, anorexia and anaemia, she then died. The client took the decision to provide supportive care from home during this episode. The body was not available for postmortem examination, therefore the cause of death was not known.

Table 3: Packed Cell Volumes results of the patient.

Date	Packed Cell Volume, % (27 – 45)
08/07/2016	14
09/072016	14
10/07/2016	15
11/07/2016	16
12/07/2016	16
13/07/2016	20
14/07/2016	22
15/07/2016	23
16/07/2016	24
13/03/2017	12
15/03/2017	16
21/03/2017	19
28/03/2017	23
04/04/2017	29
17/04/2017	22
08/09/2017	25
22/09/2017	15

DISCUSSION ***Include a very brief review of similar published cases***

This case enabled a level of diagnostic testing and intervention for ovine medicine which would be unusual in commercial farms, as it involved a pet ewe. It also allowed for a final diagnosis to be reached and for an adequate therapeutic protocol to be put in place, with valuable follow up. There are many reports of anaemia due to haemoplasma infection in sheep,[1,2,3,11] but not enough data is available from the literature to determine whether IMHA was involved in any of these cases. The suspicion of IMHA in this case was due to the presence of haemoglobinuria, regenerative anaemia with spherocytosis and autoagglutination.[15] Circumstantial evidence was suggestive of possible aetiologies, including the recent history of vaccination. Vaccination was suspected to be the initiating cause of IMHA, and immune-mediated thrombocytopenia, in a

cow.[25] However, vaccination was not associated with the subsequent episodes of anaemia in this case. Whereas, an ovine haemoplasma was shown to be present in the ewe's blood during two clinical episodes, eight months apart and clinical signs were responsive to antibiotic therapy. Therefore, ovine haemoplasma was considered to be the aetiological agent in this case.

The reliability of diagnosing haemoplasmas has been improved by the advent of PCR-DGGE for the mycoplasma 16S rRNA gene.[6,7] Historically, detection of these microbes on blood smears had a low sensitivity.[3] Although basophilic structures were seen on the surface of erythrocytes in this case, there was some concern that they may have been artefacts, so confirmation was sought through molecular techniques.

Sheep that survive initial disease associated with *M. ovis* infection can have subsequent bouts of parasitaemia after stressful events or immunosuppressive therapy.[2] The ewe in this case appeared to present with recurrent clinical disease from haemoplasma, due either to recrudescence of the same infection or new infections. However, no evidence of immunosuppression was identified, as the ewe had an apparently stress-free environment, with no production requirements and was seronegative for MAP. In a haemolytic episode in spring 2017, clearance of infection was not achieved by a 21-day course of a fluoroquinolone (enrofloxacin). Nevertheless, treatment with a macrolide (tulathromycin), appeared to achieve longer term relief of clinical signs. These observations contrast with reports of therapeutic outcomes in cats with *Mycoplasma haemofelis*,[28] where clearance of infection was achieved in five out of 15 cats by up to 28 days of parenteral tetracycline (doxycycline) and in the remaining cats by 14 days of parenteral fluoroquinolone (marbofloxacin). Fluoroquinolone treatment did not appear to have the same impact in the case of the ewe described here, although rapid re-infection could not be ruled out.

Fluoroquinolones and macrolides are categorised as 'highest priority critically important antibiotics' by the World Health Organisation [29] and the use of these antibiotics should be restricted in animals. Initial treatment of ovine haemoplasma should be undertaken with a first line antibiotic, such as a tetracycline.[28] Progression to other antibiotic classes is, however, justified in the face of treatment failure. In these instances, culture and sensitivity testing techniques are recommended to guide the choice of antibiotics. However, these were not available for haemoplasmas at the time of writing, therefore antibiotic selection was made based on data from other *Mycoplasma* species and reports of successful treatment regimes.

Haemoplasma, with the possibility of induced IMHA, should be considered a possible differential diagnosis for haemolytic anaemia in sheep. Although this case does demonstrate significant difference between the approach to single animal cases in pet sheep, compared with commercial flock situations. In these situations, it can be useful to seek collaboration with small animal or medical colleagues.

LEARNING POINTS/TAKE HOME MESSAGES ***3 to 5 bullet points – this is a required field***

- Haemotrophic *Mycoplasma* species can be associated with clinically apparent anaemia in sheep, and may be associated with IMHA
- Detection of this bacteria on blood smears has low sensitivity, but molecular methods can improve detection
- Investigation of individual animal disease can require different skill sets and knowledge to flock medicine
- Antibiotic therapy for haemotrophic *Mycoplasma* species can be difficult to navigate and requires careful client communication

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FIGURE/VIDEO CAPTIONS *figures should NOT be embedded in this document*

Figure 1: Urine sample from the patient on initial presentation at the Royal (Dick) School of Veterinary Medicine. The urine is tinged red due to the presence of haemoglobin.

OWNER'S PERSPECTIVE *Optional*

The most important thing for me was feeling part of the team and taking part in all the clinical decisions regarding Bramble's (the ewe's) treatment. In such complexity, although I am a retired physician, the vets' communication skills and compassion must have been exceptional, as I truly felt part of her care. This meant that when the time came to consider how much longer we should be trying to save her, it was an obvious though terribly sad decision for me. Good communication and working together leads to trust and I was greatly comforted in my certainty that it was right to let her go. She slipped away at home with her two sheep companions at her side. If I had not been able to be part of all that was done, it would have been much more difficult. I will always be grateful and I hope this report may help other sheep in the future.

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