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CASE REPORT

Treatment of *Francisella philomiragia* bacteremia in a dog

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Abstract

To describe the diagnosis and successful treatment of systemic francisellosis in a dog. An 11-year-old female spayed Labrador retriever presented for progressive lethargy, hyporexia, and cough. The dog was febrile with a neutrophilia, nonregenerative anemia, thrombocytopenia, and had increased activity in serum of liver-derived enzymes. *Francisella philomiragia* was isolated from aerobic blood culture. The dog was treated for 6 weeks with enrofloxacin orally. Repeated aerobic blood cultures after 2 and 6 weeks of antibiotic therapy were negative. The dog was clinically normal 7 months after diagnosis with no evidence of relapse.

KEYWORDS
canine, fever, hepatopathy, infection, sepsis

1 | INTRODUCTION

Francisella philomiragia is an aerobic gram-negative coccobacillus that uncommonly leads to opportunistic diseases in humans.[1] Most infections occur in immunocompromised people with near-drowning events in salt water.[1] Infection is reported in 1 dog that did not survive.[2] This case report describes *F. philomiragia* infection in a dog without known salt water exposure.

1.1 | Case

An 11-year-old female spayed Labrador retriever was presented to a tertiary university emergency service for tachypnea and several days of hyporexia, lethargy, and a progressive hacking cough. The tachypnea had been progressive over 1 month and the hacking cough occurred intermittently. Previous medical conditions included a several year history of pruritus managed with 5.4 mg oclacitinib (Apoquel) PO Q24h and 5 days of cephalexin (250 mg PO Q12h) the week before presentation for a suspected urinary tract infection. The dog was also administered monthly fipronil (Frontline) and ivermectin/pyrantel (Heartgard). The dog's environment was rural with access to tall grassy fields, wooded areas, and multiple freshwater sources within Wisconsin with no known access to salt water. On physical examination, the dog was estimated to be 5% dehydrated and it had an abnormal rectal temperature of 105.1 °F as well as cranial abdominal pain and bilateral hock effusion.

Given the fever, blood cultures were obtained sequentially from the left lateral saphenous and right cephalic veins as 3 mL samples using paired aerobic and anaerobic bottles (BACTEC, Becton-Dickenson) after clipping of the fur, aseptic skin preparation, and with the use of sterile gloves. Both aerobic blood culture bottles were positive at ~48 h on an automated instrument (BACTEC FX40, Becton-Dickenson). Gram staining indicated the presence of gram-negative coccobacilli, and subsequent subculture and identification via MALDI-TOF (Biotyper, Bruker, Billerica, MA), identified the isolate as *F. philomiragia* with a score of 2.11. While a score on this instrument >2.0 is consistent with a valid species-level identification, additional molecular characterization was performed. Speciation of the organism isolated upon hemoculture was pending throughout hospitalization but

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; CGD, chronic granulomatous disease; CSF, cerebrospinal fluid; GGT, gamma-glutamyl transferase; IV, intravenous; PCR, polymerase chain reaction; PO, by mouth; SRMA, steroid responsive meningitis-arteritis.

was eventually definitively identified as *F. philomiragia*. Because the MALDI-TOF identification of the blood culture isolate indicated the genus *Francisella*, the isolate was sent for *F. tularensis* PCR at a CDC Laboratory Response Network laboratory (Colorado State University Veterinary Diagnostic Laboratory) and was negative. For species-level identification, the bacterial isolate was recultivated for DNA extraction and subsequent whole genome Illumina sequencing. Illumina reads were de novo assembled with SPAdes 3.13.0 and scaffolds were uploaded for analysis to PATRIC (http://www.bv-brc.org).[3,4] The isolate was identified as *F. philomiragia* using the PATRIC phylogenetics pipeline with high confidence (maximum likelihood method, most similar to *F. philomiragia* ATCC strain 25017, bootstrap value = 100). The GenBank accession number for this isolate is JAPEBX00000000. Antimicrobial susceptibility testing was not performed.

A mixed hepatopathy (ALT 197 U/L reference interval [RI], 14-87 U/L, and ALP 236 U/L, RI, 20-157 U/L) as well as a higher than reference triglycerides at 370 mg/dL (RI, 32-190 mg/dL) were seen at presentation. Mild biliary sludge and a 5 cm × 4 cm heterogeneous hyperechoic liver mass were identified in the cranial left liver lobe by abdominal ultrasonographic examination. Given the ultrasonographic appearance of the liver mass, an abscess was considered unlikely. A fine needle aspirate was not performed because of the risk of bleeding with concurrent thrombocytopenia. While evidence of pancreatitis was not noted on abdominal ultrasonographic examination, a quantitative spec cPLI was increased (2000 µg/L; RI, 0-200 µg/L) consistent with pancreatitis. The dog's cholestatic liver enzymes progressed during hospitalization to an ALP of 314 U/L (RI, 20-157 U/L) and a newly identified increased total bilirubin at 1.1 mg/dL (RI, 0.1-0.8 mg/dL) which resolved by discharge.

Complete blood cell (CBC) count initially revealed a non-regenerative normocytic normochromic anemia with a hematocrit of 38% (RI, 39%-57%), a thrombocytopenia confirmed via manual platelet count of 114 × 10^3/µL (RI, 175-500 × 10^3/µL), and a neutrophilia at 10.4 × 10^3/µL (RI, 2.6-10.0 × 10^3/µL). The thrombocytopenia progressed throughout hospitalization, decreasing to 60 × 10^3/µL and remained static by discharge. There was also evidence of further inflammation with 200/µL band neutrophils with 2+ toxic change that resolved during hospitalization.

Because of the fever and mild bilateral hock effusion, arthrocentesis was performed with left carpus joint fluid showing no cytologic abnormalities. Diagnostically useful joint fluid samples from the tarsi were difficult to obtain and radiographs of the right tarsus showed moderate degenerative joint disease and soft tissue swelling increasing suspicion that the effusion was secondary to chronic arthritis. No pathogens were observed cytologically in the joint fluid and aerobic cultures were not submitted.

A *Blastomyces* urine antigen test (Miravista) was negative. A SNAP 4dx (IDEXX SNAP) test did not detect heartworm antigen or antibodies directed against *Ehrlichia canis/ewingii*, *B. burgdorferi*, or *Anaplasma phagocytophilum/platys*. Microscopic agglutination titers for *Leptospira* spp. were all <1:100. Urine obtained via free catch had a specific gravity of 1.042 and 2+ proteinuria. Urine culture showed no relevant growth on aerobic culture.

Abdominal and thoracic radiographs performed at the time of presentation showed a tapered caudal vena cava consistent with hypovolemia and a mild bronchial pattern in the caudal lung lobes, more severe on the left which were interpreted as age related changes.

Treatment initiated on day 1 included fluids administered intravenously (Plasmalyte A at a maintenance rate plus 5% dehydration over 24 h), ondansetron (0.5 mg/kg IV Q8h), maropitant (1 mg/kg IV Q24h), pantoprazole (1 mg/kg IV Q12h), and a ketamine constant rate infusion (3 µg/kg/min). Antibiotic therapy was initiated on day 2 of hospitalization with enrofloxacin (10 mg/kg IV Q24h) and doxycycline (5.4 mg/kg PO Q12h). Throughout hospitalization the dogs hydration status improved and fever resolved within 24 h of antibiotic therapy. The dog experienced large bowel diarrhea suspected to be secondary to pancreatitis that also improved throughout hospitalization. The dog was discharged home after 5 days with the following medications: doxycycline 150 mg every 12 hours (5.4 mg/kg PO Q12h), enrofloxacin 272 mg every 24 h (10 mg/kg PO Q24h), gabapentin (7.2 mg/kg PO Q8-12h) as needed for discomfort, omeprazole (1 mg/kg PO Q12h) 30 min before feeding, ondansetron (0.5 mg/kg PO Q8-12h) as needed for nausea, and capromorelin (1.5 mg/kg PO q24h) as needed to stimulate appetite.

Ten days after discharge, the dog was doing well at home. Repeated blood cultures from the right and left lateral saphenous veins showed no growth after 5 days. CBC was within the normal range as were the blood chemistry values with the exception of her elevated liver enzymes (ALT 107 U/L RI, 14-87 U/L, ALP 169 U/L RI, 20-157 U/L) that showed moderate improvement. At this time her antibiotics were de-escalated with discontinuation of doxycycline because of small bowel diarrhea. The dog remained on enrofloxacin.

A second recheck examination was performed 2 days after completing treatment with enrofloxacin for 6 weeks. The dog was clinically normal at home, and blood cultures were negative. A repeat abdominal ultrasonographic examination showed progression of the liver mass, now measuring at 8 cm × 5.2 cm and mild biliary sludge. The liver enzyme elevations also progressed (ALT 670 U/L RI, 14-87 U/L, ALP 168 U/L RI, 20-157 U/L, GGT 18 U/L RI, 5-16 U/L) which was suspected to be because of her progressive liver mass given that the dog was clinically well. Owners elected to not proceed with additional diagnostics for the liver mass. After this visit, the dog followed up with their primary veterinarian 7 months later and was reported to be doing well with no recurrence of clinical signs. Liver values and ultrasound were not re-evaluated.

2 | DISCUSSION

This report documents bacteremia with *F. philomiragia* in a dog, with successful resolution of bacteremia and clinical signs after 2 weeks of treatment with doxycycline (5 mg/kg PO Q12h) and enrofloxacin

(10 mg/kg PO Q24h); an additional 4 weeks of enrofloxacin alone was completed and 7 months later the dog remained clinically well. It is possible that a shorter treatment course could have been successful. In the other documented case of *F. philomiragia* septicemia in a dog, the dog was euthanized because of progressive disease.[2] Factors that potentially contributed to successful treatment include prompt identification of bacteremia on blood cultures, appropriate antibiotic therapy, and discontinuation of all immunomodulatory medications.

Francisella philomiragia shares phenotypic features with *Francisella tularensis*. *F. tularensis* is primarily transmitted via tick or contact with infected animals and can cause disease in healthy, immunocompetent hosts because it is a more virulent intracellular pathogen.[5] Because of the zoonotic concern of *F. tularensis* following identification of the genus *Francisella* on blood cultures, PCR and sequencing was performed to ensure *F. tularensis* was not present.

In humans *F. philomiragia* infections rarely occur and are often associated with either drowning events in salt water or immunocompromised patients. There are case reports of people with chronic granulomatous disease (CGD, an inherited disease of phagocyte dysfunction) developing infections from *F. philomiragia*.[1] Most *F. philomiragia* infections in humans have had direct exposure to salt water or live along the coast; however there are reports of *Francisella* species being isolated from other sources. *F. philomiragia* has been isolated from multiple warm springs in Utah, brackish-water ponds in Massachusetts, and air conditioning systems in China.[6-8] *F. philomiragia* infection in humans can manifest clinically as signs of pneumonia or sepsis.[9] In this case report the dog did have a hacking cough and tachypnea at presentation, but there was no evidence of pneumonia and her most relevant clinical signs were lethargy, hyporexia, and fever. A thoracic CT or bronchoscopy and bronchoalveolar lavage was considered to document infection within the lungs but was not performed because of clinical improvement.

While successful treatment of *F. philomiragia* is not reported in the veterinary literature, there are reports of successful treatment in human medicine. A case report in a 19-year-old man with CGD describes bacteremia with *F. philomiragia* that was successfully treated with gentamicin for 2 weeks and ciprofloxacin for 6 weeks. Clinical signs included fever and chills and he did have exposure to brackish water in Maryland ~2 months before.[1] There was a report of a human renal transplant patient receiving immunosuppressive medications that was found to be bacteremic with *F. philomiragia* and successfully treated with 2 weeks of doxycycline. The patient presented for shortness of breath, nonproductive cough, and peripheral edema without any known exposure to saltwater or drowning.[10] Another case report in an immunocompromised patient with *F. philomiragia* isolated from blood showed the strain to be susceptible to both doxycycline and ciprofloxacin which is similar to other reports showing most isolates are susceptible to fluoroquinolones, chloramphenicol, carbapenems and potentially cephalosporins, aminoglycosides, and tetracyclines.[9,11] While *F. philomiragia* is susceptible to tetracyclines, it is proposed that treatment with bacteriostatic antibiotics could lead to treatment failure or relapse as compared to bactericidal antibiotics, although this requires more research.[1,12] Originally this dog was administered doxycycline to empirically treat vector borne diseases as well as enrofloxacin to provide treatment for potential bacterial cholangiohepatitis. After blood culture results were available, these antibiotics were both continued given the reported susceptibility of *F. philomiragia*. Susceptibility testing was not performed because the isolate could not be propagated in susceptibility test media. After 2 weeks, doxycycline was discontinued because of signs of gastrointestinal disease that were presumed to be side-effects.

Other abnormalities noted during hospitalization like the nonregenerative anemia and moderate thrombocytopenia were suspected to be secondary to inflammation from bacteremia. The originally noted proteinuria was not further quantified and therefore the significance is unknown. The large bowel diarrhea was suspected to be secondary to pancreatitis diagnosed based off of cranial abdominal discomfort and an elevated spec cPLI.

This dog had no known drowning events or exposure to salt water. The dog had chronically been on oclacitinib (Apoquel) which could have made her more susceptible to opportunistic infection. Oclacitinib is a selective JAK inhibitor used for allergic pruritus and could potentially increase susceptibility to secondary infections through effects of JAK inhibition on T-cell signaling.[13] An in vitro study of oclacitinib in healthy dogs showed significant immunosuppressive activity through reduction of secretion of clonal activator cytokines and proinflammatory cytokines, however this was at higher doses of oclacitinib than normally utilized.[13] There is a report of a dog receiving oclacitinib that developed a skin infection with *Burkholderia cepacia* complex which could have been secondary to the immunomodulatory effects from the oclacitinib.[14] One prospective study assessed the risk of urinary tract infection in dogs on oclacitinib and found no increased risk in any of the 55 dogs.[15] Another recent retrospective paper looked at risk of infection following orthopedic stifle surgery in dogs on oclacitinib and did not find a significant increased risk.[16] It is therefore unclear if treatment with oclacitinib played a role in increasing susceptibility to infection.

This is similar to the only other case report of *F. philomiragia* in a dog that had immune modulation secondary to prednisone.[1] Originally, that dog presented for neck pain and lethargy and had been treated with doxycycline and clindamycin for potential tick borne disease and toxoplasmosis. Because of lack of improvement, further diagnostics were performed and a cerebrospinal fluid (CSF) analysis was consistent with a diagnosis of steroid responsive meningitis-arteritis (SRMA) and therefore immunosuppressive prednisone was started. A CSF culture was not performed. Several weeks later, the dog re-presented because of clinical decline and was hospitalized on IV ampicillin/sulbactam and treated for disseminated intravascular coagulation. Ultimately the dog was euthanized and *F. philomiragia* was isolated via aerobic culture from CSF and whole blood.[1] That dog was suspected to potentially contract *F. philomiragia* from nearby salt water and was predisposed to infection secondary to immunosuppression.

Although rare in dogs and humans, the identification of *F. philomiragia* in this case highlights the critical diagnostic role that blood cultures play in febrile animals that are immunosuppressed. A retrospective study showed that blood cultures are most commonly performed in dogs with pyrexia and yielded a positive result in 20% of

cases.[17] Exactly 63% of dogs with positive blood cultures and 19% of dogs with negative blood cultures had de-escalation of antimicrobial therapy showing how culture results can help guide antimicrobial therapy and stewardship.[17] This further supports why veterinary medicine should strive to follow the recommendation in human medicine that in patients suspected to be septic, blood cultures should be obtained promptly and before antimicrobial therapy.[18] In these patients, prompt identification and treatment of bacteremia with targeted antibiotic therapy can be life-saving.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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