Canine Bartonellosis: Diagnosis, Treatment, and Public Health Implications

Charlie
- 8.5 year old, male, neutered Bichon Frise
- Presentation to Referring DVM
  - 8 day history of “seeming depressed”
  - Temp. of 104.7°F

Initial Blood Work and Clinical Findings
- WBC 1.99 x 10^3
- Absolute neutrophil count (?)
- Repeated blood (#?) - consistent marked neutropenia despite antimicrobial therapy
- Currently on enrofloxacin (5 mg/kg divided BID); doxycycline (5 mg/kg BID)
- Persistent FUO
- Refer to UF-VMC for evaluation

Physical Exam Findings
- Temp. 102.9°F
- Membrane color – pink
- Capillary refill time - < 2 sec.
- H.R. 96 BPM; Resp. 24
- Pulse 96; character strong and synchronous
- Enlarged, left prescapular LN
- Grade 1/4 bilateral patellar luxation
Medical History

- “Contact” allergy dermatitis and pyoderma
- Skin condition currently under control
  - Recently stood was soft with mucus
- No history of myelosuppressive medications
- Neutered: both testicles descended

CBC Results

- WBC 1.91 (6.0 – 17.0) x 10^3
- Neuts 0.13 (3.0 – 11.5) x 10^3
- Bands 0.02 (0.0 - 0.3) x 10^3
- Lym. 0.7 (1.0 – 4.8) x 10^3
- Mon. 0.99 (0.15 – 1.35) x 10^3
- MCHC 34.3 (34.0 – 36.0) g/dL
- Fibrinogen 700 (150-300) mg/dL

- Blood film evaluation
  - 4 NRBCs / 100 WBC
  - RBC morphology otherwise normal
  - No polychromasia
  - Platelets adequate
  - Leukocyte morphology (we will evaluate, but first)?

Biochemical Profile (significant results)

- ALP 757 (16 – 111) U/L
- ALT 207 (16 – 77) U/L
- AST 37 (10 – 46) U/L
- T. Bili 0.2 (0.0 – 0.4) mg/dL
- Glucose 80 (87 – 126) mg/dL
- Proteins (normal)
- BUN/Creat. (normal)
- TCO2 14 (17 – 27) mEq/L
- Electrolytes (normal)
Urinalysis

- NSF

Problem List

- FUO
- Severe neutropenia with toxicity
- NRBCs without anemia or polychromasia
- Elevated ALP, ALT
- Hypoglycemia
- ?

Problem List

- FUO
- Severe neutropenia with toxicity
- NRBCs without anemia or polychromasia
- Elevated ALP, ALT
- Hypoglycemia
- Suggests \( \rightarrow \) septicemia
- Enlarged left, prescapular LN

$64,000 \text{ Question}$

- Which came first?
- Neutropenia \( \rightarrow \) septicemia
  (immune-mediate / bone marrow disease)
**$64,000 Question**
- Which came first?
- Neutropenia → septicemia
  (immune-mediated / bone marrow disease)
- Infection → neutropenia

**Diagnostic Plan**
- Normally would evaluate response to antimicrobials
  - Response to Abs → rising neutrophil count = septicemia induced neutropenia
  - Response to Abs → clinical improvement but remains neutropenic = BM disease or IMN
- Charlie already on antimicrobials . . . to no affect
- Find source of problem

**Diagnostic Plan**
- Blood culture (on antimicrobials)
- SNAP 4Dx (rickettsial diseases)
- Thoracic and Abdominal radiographs
- Abdominal ultrasound
- Bone marrow aspirate
- FNA left prescapular LN

**Results**
- Radiographs: NSF
- Ultrasound: Liver, diffusely and moderately hyperechoic with prominent portal vessels
  - FNA
    - Moderate vacuolar hepatopathy
    - Mild to moderate lymphocytic infiltration
- Interpretation: mild to moderate chronic inflammatory disease
Bone Marrow Aspirate
- Hypercellular marrow, predominantly myeloid
- Left-shifted, but complete maturation
- Toxic
- Infectious Ds. / Immune-mediated neutropenia?
- No bone marrow damage / disease – but peripheral consumption or destruction (better prognosis)

Lymph Node Aspirate
- Primarily small lymphocytes
- Increased numbers of plasma cells
- Histiocytic infiltrate
- Neutrophilic infiltrate
- Interpretation: reactive lymphoid hyperplasia with pyogranulomatous lymphadenitis

Assessment of Charlie
- Septicemic
- No bone marrow disease
- Pyogranulomatous lymphadenitis
- Suspected: Canine Bartonellosis
  - B. henselae
  - B. vinsonii
  - Other Bartonella spp.
Assessment of Charlie

- Septicemic
- No bone marrow disease
- Pyogranulomatous lymphadenitis
- Suspected: Canine Bartonellosis
  - B. henselae
  - B. vinsonii
  - Important cause of septicemia and/or FUO and/or pyogranulomatous inflammation
  - Lymph nodes, spleen, liver other tissues

Treatment

- The antibiotic of choice and duration of therapy not clearly established
- Drugs most commonly used
  - Azithromycin
  - Enrofloxacin
  - Doxycycline
- Prolonged therapy is required

Plan for Charlie

- Await further test results
- Start on Azithromycin at 10 mg/kg SID
- Keep on enrofloxacin
  - Increase dose to 5 mg/kg BID

Bartonella species

- Gram negative, short, pleomorphic rods
- Class: Alpha Proteobacteria
- Fastidious: Division time 22-24 hrs
- Cellular Targets:
  - Erythrocytes
  - Endothelial Cells
  - Microglia Cells
  - Macrophages
  - CD34 Progenitor Cells

Kordick DL, Breitschwerdt EB: JCM 1999
**About the Bug**

- Gram-negative hemotropic bacteria
- Invades erythrocytes and endothelium of a variety of mammalian hosts
- Causes persistent infection and long-lasting bacteremia
- Rare to find organisms on peripheral blood films
- Vector-transmitted
  - Suspected multiple tick species, possibly fleas and other insects

**Bartonella spp.**

*B. henselae* = cat flea

- Bartonella spp. – multiple insect vectors
- Cats can act as reservoir and source of infection
- Veterinarians and other animal care workers are an at-risk group for exposure
- Common clinical signs include – recurrent fever, fatigue, insomnia, recurrent headaches, muscle and/or joint pain, photophobia and neurological disease
- Can establish chronic, persistent infections in animals and people

---

**Bartonella: Other Reservoir Hosts**

- Rodents
- Dogs
- Wildlife
- Ruminants
- Human beings
- Others

---

**Known Vector Transmitted Bartonella spp.**

*B. bacilliformis* - sandfly, *Lutzomia verrucarum*

*B. quintana* - human body louse, *Pediculus humanus humanus*

*B. henselae* - cat flea, *Ctenocephalides felis*

*B. grahamii* - rodent flea, *Ctenocephalides nubilis*

*B. bovis* – horn fly, *Haematobia spp*
Cat Scratch Disease: Russell Regnery, 1992

Historical perspective: Generally considered a self-limiting illness characterized by fever and lymphadenopathy

Now known to cause persistent intravascular infection

Inoculation Papule  Lymphadenopathy

Occupational Risk: Veterinarians and Animal Health Workers

- Exposure to various arthropod vectors: fleas, ticks, lice, keds
- Exposure to reservoir hosts, cats, dogs, cattle, various rodent and wildlife species
- Needle stick transmission


Occupational Risk: Veterinarians and Animal Health Workers

- Up to 11 species responsible for human illnesses
- B. henselae and B. vinsonii subsp. Berkhoffii, B. claridgeiae, B. koehlerae
- Persistent intravascular infection
- Signs may include fatigue, arthritis, myalgia, insomnia, headaches, photophobia, seizures, incoordination, memory loss and other neurocognitive abnormalities

Factors Associated with Clinical Disease in Animals

- Chronic infections well-tolerated for months to years (Asymptomatic carriers)
- Appearance of clinical signs
  - Stress factors, parturition, and co-infection
- Role of Bartonella in manifestation of other tick-borne diseases
    - Immune-suppression
    - Impaired phagocytic function of monocytes
    - Reduction in circulating CD8+ lymphocytes
    - Increase in CD4+ lymphocytes
Spectrum of Clinical Signs Associated with Seropositivity

- Extremely variable: asymptomatic infection to sudden death
- Dogs can have multiple clinical signs/laboratory abnormalities
- Endocarditis (joint pain, thromboembolic ds)
- Granulomatous disease
  - Lymphadenopathy
  - Splenomegaly (granulomatous)
  - Granulomatous rhinitis (nasal discharge)
  - Granulomatous meningoencephalitis
- Cutaneous vasculitis
- Uveitis
- Epistaxis
- Hepatitis (lymphocytic hepatitis, peliosis hepatitis)
- IMHA/IMT: Coombs’ positive

Laboratory Abnormalities

- Thrombocytopenia (50%)
- Anemia (33%)
  - 40% of anemias nonregenerative
  - Hemolytic anemia [5 of 24 (21%)]
  - 3 of 4 tested Coombs’ +
- Neutrophilia (50%) +/- left-shift
- Monocytosis (33%)
- Eosinophilia (30%)
- Liver enzyme elevations (hepatitis)

Diagnosis

- Serology, PCR analysis and blood or tissue culture
- Visualization of organisms very uncommon
  - During Acute phase of granulomatous lesions prior to antimicrobial therapy (Warthin-Starry stain)
Serological Diagnosis

- IFA most common serological method of diagnosis
- Positive titer > 1:64
- No cross-reactivity between two species affecting dogs
- False negative results due to inability of host to mount immune response
  - Not accessible to host immune system
  - Bacteria immunosuppressive

Detecting Organisms

- PCR analysis
  - Can be done on blood or affected tissue
  - More sensitive than microscopic identification
  - Galaxy Diagnostics (Galaxydx.com)
    - Enrichment PCR (ePCR) – gold standard in Bartonella diagnosis
      - Bartonella alpha Proteobacteria growth media (BAPGM)
        - PCR on whole blood and blood culture for 6 weeks
        - DNA sequencing for species identification

Treatment

- The antibiotic of choice and duration of therapy not clearly established
- Drugs most commonly used
  - Azithromycin
  - Enrofloxacin
  - Doxycycline
  - Rifampin
- Prolonged therapy is required

Doxycycline?

- Not effective in clearing infection
- Case reports in literature and personal experience where doxy was initially used without lasting effect
- Clinical significance
  - Many animals with suspicion of tick-borne disease are empirically administered doxy
  - Non-responders or relapse of clinical disease when doxy is removed
  - Test for Bartonella spp.
Azithromycin

- Current treatment of choice
- Effective in treatment of canine, feline and human Bartonellosis
- Dose du jour
  - 5-10 mg/kg PO Q24 for 5 to 7 days
  - same dose every other day for 5 more weeks
- May be used in combination with Rifampin
  - 5 mg/kg Q 24 hours for 6 weeks

Next Day: Friday

- Temperature 102.3°F
- Clinically improved
- Sent Charlie home for the weekend with instructions to return to Ref. Vet. Monday AM for evaluation
- SNAP 4Dx: Negative for D. immitis, E. canis, B. burgdorferi and A. phagocytophilum


- Charlie doing great!
- Temperature normal
- WBC 5,200 / μL
- Neutrophils 2,400 / μL

Before


- Charlie doing great!
- Temperature normal
- WBC 5,200 / μL
- Neutrophils 2,400 / μL

After
**Recommendations**

- Continue Azithromycin daily for one week
- EOD for 5 weeks
- Continue Enrofloxacin for 2 weeks

**Follow-up**

- Charlie No Neuts had uneventful recovery
- Blood culture: Negative
  - Typical of *Bartonella* septicemia
- Serology:
  - *B. henselae* titer: <1:16 (Negative)
  - *B. vinsonii* titer: <1:16 (Negative)
  - Not uncommon (25% or more may be seronegative
    - Organism immunosuppressive
    - Different species
    - Wrong diagnosis

---

**Follow-up**

- Charlie No Neuts had uneventful recovery
- Blood culture: Negative
  - Typical of *Bartonella* septicemia
- Serology:
  - *B. henselae* titer: <1:16 (Negative)
  - *B. vinsonii* titer: <1:16 (Negative)
- Final Diagnosis: A. D. D.

**Follow-up**

- Charlie No Neuts had uneventful recovery
- Blood culture: Negative
  - Typical of *Bartonella* septicemia
- Serology:
  - *B. henselae* titer: <1:16 (Negative)
  - *B. vinsonii* titer: <1:16 (Negative)
- Final Diagnosis: A. D. D.

*A*zithromycin *D*eficient *D*og