Idiopathic sterile pyogranulomatous lymphadenitis in a nine-month-old springer spaniel

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<th>SUMMARY Up to 150 words summarising the case presentation and outcome (this will be freely available online)</th>
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<td>A 9-month old, intact male Springer Spaniel was presented with acute mandibular lymphadenopathy seven days following exploratory coeliotomy and biopsy of an enlarged mesenteric lymph node. Histology was consistent with sterile severe necrotizing pyogranulomatous inflammation. An underlying cause of the granulomatous lymphadenitis could not be identified. The dog responded to prednisolone, showing complete resolution of the clinical signs. This could be an unusual presentation of canine juvenile cellulitis, without a cutaneous component and without initial submandibular or prescapular lymphadenopathy.</td>
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<th>BACKGROUND Why you think this case is important – why did you write it up?</th>
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<td>Granulomatous inflammation occurs in response to chronic inflammatory stimuli such as</td>
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infection with certain intracellular pathogens or the presence of inert material. Advances in molecular diagnostic techniques have allowed identification of organisms involved in granulomatous disorders that previously were of unknown etiology (Zumla and James, 1996). In dogs, pyogranulomatous inflammation can be elicited by diverse pathogens including bacteria (*Bartonella, Staphylococcus, Mycobacterium, Nocardia* and *Actinomyces*), fungi (*Blatomyces, Histoplasma, Cryptococcus, Coccidioides, Aspergillus* and miscellaneous fungi), oomycetes (*Pythium*) and protozoa (*Toxoplasma, Neospora*) (Greene, 2012); however, an aberrant immune response with no defined etiology causing a sterile inflammatory disease has also been reported (Torres, 1999; Aikawa et al., 2008; Nishida et al., 2012).

Although the aetiology and pathogenesis of canine sterile pyogranulomatous inflammation remain unknown, absence of microbial agents and foreign material, and the fact they are controlled mainly with systemic glucocorticoid therapy, suggest an aberrant inflammatory histiocytic response (Scott et al., 2001; Aikawa et al., 2008; Nishida et al., 2012). Relatively few cases have been reported in dogs. Some of these cases were consistent with an idiopathic sterile pyogranulomatous panniculitis characterized by the localization of the major focus of inflammation to the subcutaneous fat (Torres, 1999; Dandrieux et al., 2011), although concurrent inflammation of the fat in the abdomen (German et al., 2003) epidural space (Aikawa et al, 2008; Nishida et al, 2012) and bone (Gear et al., 2006) may occur. Juvenile sterile granulomatous dermatitis and lymphadenitis (canine juvenile cellulitis, juvenile pyoderma, puppy strangles) is an uncommon, well-recognized, immune-mediated lymphocutaneous disease seen in young dogs (Reimann et al., 1989; Scott et al., 1991). This disease is a distinct clinical entity, yet it shares some clinical and histopathological features with sterile nodular panniculitis. It has been suggested that canine juvenile cellulitis is a systemic rather than a primary skin disorder, in which the pyogranulomatous sterile lymphadenitis might represent one manifestation of this disease that can occur with or without skin involvement (Reimann et al., 1989).

This case report describes a 9-month-old Springer Spaniel with marked mesenteric lymphadenopathy consistent histopathologically with sterile severe necrotizing pyogranulomatous
lymphadenitis requiring corticosteroids to adequately control the symptoms. It has been previously documented a number of Springer Spaniels with granulomatous necrotizing lymphadenitis, which could suggest a possible breed predisposition. Most dogs show generalized lymphadenopathy and pyrexia but some have concurrent pyogranulomatous dermatitis which histopathologically resembles the lesions of the sterile nodular granuloma/pyogranuloma syndrome (Hoffmann et al., 2002).

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

A 9-month-old, intact male Springer Spaniel presented to the referring veterinarian with a history of pyrexia, lethargy and inappetance. The puppy, obtained from a local breeder approximately at 8 weeks of age, had been fully vaccinated with a modified live viral vaccine and had been wormed. Treatment initially consisted of amoxicillin/clavulanic acid injection, maropitant, cimetidine and meloxicam, but, despite therapy, the dog deteriorated and developed ptyalism two days later. At this point the referring veterinarian performed an abdominal ultrasound that showed a cavitated abdominal mass which appeared to be attached to intestines. Following this, an exploratory coeliotomy was performed and an enlarged mesenteric lymph node, likely the colic lymph node, was found adjacent to the ileocaecocolic junction oozing purulent material. Biopsies of this mass were obtained and the histopathology results showed severe necrotizing pyogranulomatous inflammation.

In the following week the puppy was lethargic and weak but his appetite had improved. Three days prior to presentation at the Internal Medicine Service of the Hospital for Small Animals of The Royal (Dick) School of Veterinary Studies (University of Edinburgh), the patient developed marked mandibular lymphadenopathy, non-productive coughing and the hypersalivation recurred.

On presentation, the dog was on amoxicillin/clavulanic acid (15 mg/kg PO q12h) and metronidazole (12 mg/kg PO q12h). Initial physical examination revealed pyrexia (rectal temperature was 39.5º C), approximately 6% dehydration and a 10 cm diameter, firm mass affecting the right cranio-ventral cervical region, most consistent with a markedly enlarged mandibular lymph node. No pain was elicited on spinal palpation or neck manipulation. Moderate
resentment was elicited on abdominal palpation. The peripheral lymph nodes were all moderately
ever enlarged. No skin lesions were identified but a mild serosanguinous discharge was present from
the coeliotomy incision.

**DIFFERENTIAL DIAGNOSIS**

On the basis of the above history, physical examination and geographic location, the differential
diagnoses for the granulomatous disease included bacterial infections such as *Mycobacterium*,
*Actinomyces, Nocardia* and *Bartonella*; fungal infection such as *Aspergillus* or *Cryptococcus*; and
an autoimmune aetiology resulting in sterile pyogranulomatous lymphadenitis. The focus was,
therefore, to investigate the above mentioned organisms as potential infectious agents.

**INVESTIGATIONS**

Antibiotic therapy was discontinued on admittance to the hospital in order to obtain material for
culture and sensitivity for potential infectious agents. A complete blood cell count, serum
biochemistry profile and urinalysis were submitted. The haematology revealed a moderate
leukocytosis (WBC 30.1 x10^9/l, ref 6 - 15 x10^9/l) consisting of a mature neutrophilia (24.9 x10^9/l,
ref 3.6 – 12 x10^9/l) and moderate monocytosis (3.3 x10^9/l, ref 0 – 1.5 x10^9/l) consistent with an
inflammatory response. Serum biochemistry revealed mild hypoalbuminemia (25.1 g/l, ref 26 –
35 g/l) and moderate hyperglobulinemia (46.2 g/l, ref 18 - 37 g/l), which was also consistent with
inflammation. The remainder of the values was unremarkable. Urine culture was found to be
negative. PCR for *Bartonella* was also negative. Special staining for infectious organisms (Gram,
Grocott and Ziehl Neelson) all proved negative.

Abdominal ultrasonography revealed an enlarged colic lymph node, which was 2.8 cm thick,
rounded, hypoechoic, smoothly marginated and with mild distal acoustic enhancement (Fig 1).
Adjacent jejunal nodes were also moderately enlarged (up to 1.2 cm thick) but with normal
echogenicity. The mesentery was reactive especially adjacent to the enlarged colic node with a
hyperechoic appearance containing hypoechoic strands. This was consistent with mesenteric
oedema but no evidence of septic peritonitis was found. A scant amount of free peritoneal fluid was present but was too small to sample. Ultrasonographic examination of the right cranioventral cervical swelling revealed marked submandibular lymphadenopathy and adjacent tissue reaction. Results of subsequent ultrasonographic examinations two and four days later were unchanged. Thoracic radiographs were also obtained which revealed moderate sternal lymphadenopathy without evidence of lung pathology.

Fine-needle aspirates were taken of the mandibular lymph node. The cytology results were consistent with severe reactive lymphoid hyperplasia with granulomatous lymphadenitis. Analgesia was instituted with buprenorphine 20ug/kg IV q8 hours resulting in a positive clinical improvement and normothermia, although the dog’s demeanour remained subdued. Culture of discharge from the coeliotomy incision was positive for resistant *Pseudomonas*, sensitive only to ticarcillin and ceftazedime.

Extirpation of the right submandibular lymph node was then performed, two weeks after stopped the antibiotics, to obtain tissue for culture and sensitivity prior to reinitiating of antibiotics. Following surgery, moderate serosanguinous drainage from the site was noticed. No infectious agents were detected on haematoxylin and eosin or special stain sections. Culture of lymph node tissue revealed no aerobic or anaerobic bacterial (including *Mycobacterium*) or fungal growth. Histopathological examination of the lymph node revealed marked reactive lymphoid hyperplasia with sinus histiocytosis, erythrocytosis, neutrophilia and haemosiderosis (consistent with drainage reaction) and mild, multifocal, neutrophilic lymphadenitis. A diagnosis of neutrophilic lymphadenitis was made.
TREATMENT
Ceftazedime 25mg/kg IV q8 hours was started after the surgical extirpation of the right submandibular lymph node and continued intravenously for five days at which point the coeliotomy incision was clean and dry. Serosanguinous drainage from the right cervical incision remained. In view of the lack of response to antibiotic therapy, the negative lymph node culture and the histopathological findings, a sterile pyogranulomatous disease was suspected and prednisolone therapy was initiated 11 days after presentation (0.5 mg/kg PO q12 hours for 14 days, followed by a tapering dosage of 0.25 mg/kg PO q12 for 10 days, followed by further tapering to 0.25 mg/kg PO q24 hours for 10 days and then 0.25mg/kg PO q48h for another 10 days).

OUTCOME AND FOLLOW-UP
The dog was re-examined three weeks after he was discharged when he was receiving prednisolone every other day (0.25mg/kg PO q48h) and the owners reported that he was doing very well at home. The dog was mildly polydipsic, polyuric and polyphagic, presumably due to the glucocorticoid therapy. Physical examination was unremarkable. No pain was detected in the area of the right submandibular region, and no masses were palpable. The left submandibular lymph node was small, soft and non-painful. No abnormalities were detected on abdominal palpation. The surgical site had otherwise healed completely. The side effects of the steroid treatment were markedly reduced when tapering down the dose of prednisolone and his appetite and thirst had returned back to normal. The prednisolone was continued for another week and then stopped.

Four weeks after stopping the glucocorticoid therapy the dog was reassessed and found to be clinically normal. Abdominal ultrasonography was repeated at this time showing resolution of previous abdominal lymphadenitis. The left mandibular and the right and left medial retropharyngeal lymph nodes were moderately heterogeneous with a few irregular and ill-defined hypoechoic foci, but normal in size. At the time of writing, the dog described in this report had been normal without any sign of relapse for one year after cessation of therapy.

DISCUSSION
Granulomatous diseases have remarkably complex inflammatory foci that sequester organisms or other substances resistant to degradation. While a large number of granulomatous disorders are recognized, infections are clearly the most common underlying causes of granulomas (Zumla and James, 1996). It is apparent that granulomatous conditions of diverse aetiologies share common histologic features, although the aetiologic agent is not always identifiable. Although the histopathologic patterns in various infectious granulomas may be sufficiently different to provide an accurate diagnosis, atypical presentation may necessitate identification of the specific aetiologic agent by direct microscopic examination, culture, serology or molecular detection (Zumla and James, 1996).

In the dog reported here, the aetiology of the pyogranulomatous lesions remained unknown despite an extensive diagnostic evaluation. Cultures from lymph node biopsies did not reveal fungal or bacterial growth; however, the dog received an injection of amoxicillin/clavulanic acid two weeks before the biopsy was performed. Infectious agents were not demonstrated by special histologic staining of the affected lymph node, and specific molecular testing for specific agents such as Bartonella, which has been associated with granulomatous lymphadenitis in the dog (Pappalardo et al., 2000, 2001; Gillespie et al., 2003; Morales et al., 2007) were negative. Moreover, the lack of response to antibiotic therapy and the rapid and sustained improvement of the dog’s condition with immunosuppressive treatment, further support the diagnosis of idiopathic sterile pyogranulomatous lymphadenitis. Indeed, worsening of signs was expected to follow corticosteroid treatment if an infection had been present, as described in a dog treated for a presumptive sterile pyogranulomatous disease, which developed generalized cutaneous sporotrichosis (Bernstein et al., 2007).

It has been previously documented in a journal letter that a number of Springer Spaniels presented with generalized lymphadenopathy and pyrexia which were histopathologically diagnosed with granulomatous necrotizing lymphadenitis, resembling the lesions of sterile nodular granuloma/pyogranuloma syndrome (Hoffmann et al., 2002). Some of these dogs showed also
concurrent pyogranulomatous dermatitis. There is also a single case report where a 7 month old
English Springer Spaniel was presented with hyperthermia and generalized lymphadenomegaly
that was diagnosed with sterile neutrophilic-macrophagic lymphadenitis. This dog also developed
nodular panniculitis one day after presentation (Dandrieux et al., 2011). These common findings
could suggest that Springer Spaniels might be predisposed for the sterile granulomatous
lymphadenitis syndrome; however, further studies are warranted.

Other differential diagnoses for sterile pyogranulomatous inflammation include idiopathic sterile
nodular panniculitis and canine juvenile cellulitis. Idiopathic sterile nodular panniculitis is a
dermatologic disease occasionally seen in dogs characterized by localization of the major focus of
inflammation to the subcutaneous fat (Scott et al., 2001; Gross, 2005). Typical skin lesions are
manifested clinically as deep-seated cutaneous nodules that may occur singly or in groups, and
vary from a few millimeters to several centimeters in diameter. Nodules may be firm and well
circumscribed or soft and ill defined (Scott et al., 2001). A breed predilection for Dachshunds has
been reported; however, neither age nor sex predilections have been noted (Gross, 2005).
Predilection sites are trunk neck and proximal extremities, lymphadenopathy is uncommon, and
there are usually systemic signs such as pyrexia, anorexia, lethargy and depression (Torres, 1999;
Scott et al., 2001). Panniculitis associated with pancreatitis with intra-abdominal fat involvement
have also been reported (Scott et al., 2001; Mellanby et al., 2003; Gross, 2005). In the dog
described herein, no cutaneous lesions and no evidence of pancreatitis were found, therefore
sterile nodular panniculitis as the cause of the clinical signs of this dog was unlikely.

Canine juvenile cellulitis is an idiopathic sterile pyogranulomatous or granulomatous dermatitis
and lymphadenitis (Scott et al., 2001; Scott et al., 2007). The condition presents acutely in
puppies three weeks to nine months of age, with most puppies being less than four months old
(Mason and Jones, 1989; White et al., 1989; Malik et al., 1995; Scott et al., 2001; Bassett et al.,
2005; Scott et al., 2007) but has occasionally been reported in older dogs (Jeffers et al., 1995;
Neuber et al., 2004). It should be considered as a differential diagnosis in puppies younger than 4
months that present with lymphadenopathy, oedema, papules, pustules, or crusts affecting the
head and ears (White et al., 1989). The prescapular and mandibular lymph nodes are more frequently affected, but the inguinal and popliteal lymph nodes may also be involved (Reimann et al., 1989). Generalised lymphadenopathy has been reported by others but usually in association with widespread skin lesions (White et al., 1989; Malik et al., 1995; Scott et al., 2001). However, other reports support that the lymphadenopathy can precede the development of clinical dermatitis or be present in the absence of any skin involvement, showing that the pyogranulomatous lymphadenitis might represent one manifestation of this disease that can occur with or without skin involvement (Reimann et al., 1989). A striking feature of our case was the systemic extension of the disease. Not only was mesenteric pyogranulomatous lymphadenitis found, but also granulomatous lymphadenitis was found in the right mandibular lymph node, which is considered a hallmark for canine juvenile cellulitis. The presentation of this case is atypical for canine juvenile cellulitis, however the lymph node involvement, apparent lack of response to antibiotic therapy, the cytological and histopathological findings and response to prednisolone support the possibility of atypical canine juvenile cellulitis.

The prognosis for juvenile cellulitis is good and relapses are rare. At the time of writing, the dog described in this report had been normal without any sign of relapse for one year after cessation of therapy.

**LEARNING POINTS/TAKE HOME MESSAGES**

- Springer Spaniels might be predisposed for the sterile granulomatous lymphadenitis syndrome; however, further studies are warranted.

- Lymphadenopathy can precede the development of clinical dermatitis or be present in the absence of any skin involvement, showing that the pyogranulomatous lymphadenitis might represent one manifestation of this disease that can occur with or without skin involvement.

- Granulomatous lymphadenitis can have an atypical presentation with systemic extension. In this case report not only the mandibular lymph nodes were involved, but also there was mesenteric pyogranulomatous lymphadenitis.
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Dachshunds. *Journal of Veterinary Medical Science* 74, 1071-1074.


**FIGURE**

Figure 1. Ultrasonographic image of the right colic lymph node (RCL) of the dog taken at the time of initial presentation at the RDSVS. The node is thickened (2.8 cm width), rounded, hypoechoic, smoothly marginated without a visible echogenic hilus, with mild distal acoustic enhancement and is surrounded by hyperechoic omentum (arrows). The adjacent ileocaecocolic
juncture (arrowheads) appears normal.

**OWNER’S PERSPECTIVE Optional**

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