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Canine Sterile Steroid-Responsive Lymphadenitis in 49 dogs

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Structured Summary

Objectives: To report clinical and laboratory features, treatment responses and outcome in dogs diagnosed with canine sterile steroid-responsive lymphadenitis in the United Kingdom.

Methods: Medical records of dogs diagnosed with canine sterile steroid-responsive lymphadenitis from 2009 to 2016 at six specialist referral centres were evaluated retrospectively.

Results: The study included 49 dogs. springer spaniels appeared to be over-represented (16/49 dogs). Young dogs (median age 3 years and 9 months) and females (31/49) were frequently affected. Clinical presentation was variable, with pyrexia (39/49), lethargy (35/49) and anorexia (21/49) being the most commonly reported clinical signs. Lymph node cytology and/or histopathology demonstrated neutrophilic, pyogranulomatous, granulomatous or necrotizing lymphadenitis without a detectable underlying cause in all cases.

As a sterile immune-mediated aetiology was suspected, all dogs received prednisolone with a subsequent rapid resolution of clinical signs and the lymphadenopathy in most of the cases.

Clinical significance: Canine sterile steroid-responsive lymphadenitis should be considered in dogs with pyrexia of unknown origin with inflammatory lymphadenopathy when no underlying cause can be found and often responds well to therapy with immunosuppressive corticosteroids.

Keywords: Pyrexia, Lymphadenopathy, Fever of unknown origin, Corticosteroids

Introduction

Lymph node enlargement or lymphadenopathy is often encountered during physical examination in canine patients (Thangapandiyan *et al*, 2010). Lymph node enlargement is categorised into solitary (single lymph node), regional (chains of lymphatic nodes draining a specific anatomic region) or generalised (multicentric lymph node enlargement affecting multiple anatomic regions) lymphadenopathy. The causes of lymph node enlargement include oedema, reactive hyperplasia, inflammation, infection and neoplasia (Sapierzynski *et al*, 2009). Fine needle aspiration cytology (FNAC) is a valuable diagnostic test to investigate the cause of lymph node enlargement due to its low cost, simplicity and rapid results (Cowell *et al*, 2003).

The normal cell distribution on cytological evaluation of the lymph node is reported to be 85-90% of small lymphocytes, <10% of medium-sized and large lymphocytes, <3% of plasma cells, and rare neutrophils, eosinophils and macrophages (MacNeill, 2011).

Lymphadenitis is defined as an infiltration of one or more non-lymphoid inflammatory cells in a lymph node (Teske, 2014). Neutrophilic lymphadenitis, also called purulent or suppurative lymphadenitis, is characterised by a neutrophil population exceeding 5% of the cellular population within a lymph node (Raskin *et al*, 2016). It may be associated with bacterial, neoplastic or immune-mediated diseases. Granulomatous lymphadenitis is diagnosed when the percentage of histiocytic cells is greater than 2% of the total cell population in a lymph node. Pyogranulomatous lymphadenitis is considered when lymph nodes contain mixed inflammation comprised of increased numbers of neutrophils and macrophages (McNeill, 2011). Pyogranulomatous lymphadenitis can be associated with fungal, mycobacterial and neorickettsial infections, leishmaniasis, bartonellosis, prothotecosis, juvenile cellulitis, vasculitis and idiopathic lymphadenitis (Ishida, 2017; Raskin *et al*, 2016). There is a small number of cases reported with sterile lymphadenitis but

this disease is currently poorly understood (Day, 1996; Hoffmann *et al*, 2002). These cases can often present with pyrexia.

Pyrexia, or fever, is defined as increased body temperature due to an elevation of the thermal set point in the anterior hypothalamus secondary to pyrogen release (Ramsey *et al*, 2017). Fever of unknown origin (FUO) is a major diagnostic challenge in both human and veterinary medicine (Chervier *et al*, 2012). Although the human literature is relatively complete regarding FUO, there are few studies in the veterinary literature to explore the more common causes of canine FUO (Battersby *et al*, 2006; Chervier *et al*, 2012; Dunn *et al*, 1998).

The aim of this study was to report the clinical presentation, diagnostic testing, treatment response and outcome of canine sterile steroid-responsive lymphadenitis (CSSRL), which is not well described in the veterinary literature.

Materials and Methods

The medical records of dogs diagnosed with canine sterile steroid-responsive lymphadenitis from 2009 to 2016 at six specialist referral centres in the United Kingdom (UK) were retrospectively evaluated. The data from each institution was retrieved via searches of practice management systems with computerised and paper-based records. Collaboration between institutions was achieved by completing a standardised spreadsheet. Data collected included signalment, history (including time to referral and pre-referral treatment), physical examination findings (including lymph node size and distribution), clinical pathology data (including results of lymph node cytology and/or histopathology and infectious disease screening), diagnostic imaging results, treatment and outcome (including time to relapse, repeat treatment). Pyrexia was defined as a temperature >39.2°C. Dogs with incomplete medical records were excluded. The study was approved by the ethics committee of the School of Veterinary Medicine and Science, University of Nottingham.

Case inclusion criteria required a diagnosis of lymphadenitis either with cytology, histopathology or both in which no underlying cause was identified and a positive response to treatment with glucocorticoids . Dogs that clinically improved on treatment with antimicrobial agents were excluded. When cytology was performed, neutrophilic lymphadenitis was diagnosed when the neutrophil population in the lymph node was >5%; granulomatous lymphadenitis was diagnosed when histiocytic cells comprised >2% of the lymph node population and pyogranulomatous lymphadenitis was diagnosed when there was a mixed inflammatory infiltrate with increased numbers of neutrophils and macrophages within the lymph node; necrotizing lymphadenitis was diagnosed when there was neutrophilic or histiocytic inflammation accompanied by necrosis within the lymph node; reactive hyperplasia was diagnosed when there were increased numbers (15-30%) of medium

and large lymphocytes with increased numbers of plasma cells (Raskin, 2016). When histopathology was performed, the type of lymphadenitis was established based on the predominant cell present, its distribution within the lymph node and the quality and character of the neutrophil nuclei and the presence of granulomas/pyogranulomas (Valli, 2016). Diagnostic investigations in each case excluded other potential causes of lymphadenopathy such as infectious, other inflammatory and neoplastic causes. In all cases, haematology, biochemistry, urinalysis, urine culture, thoracic radiographs and abdominal ultrasound were performed. When appropriate, echocardiography, abdominal radiographs, arthrocentesis with synovial fluid analysis and culture, cerebrospinal fluid analysis, tests for arthropod borne diseases including *Ehrlichia canis*, *Anaplasma phagocytophilum*, *Anaplasma* platys, Borrelia *burgdorferi*, *Leishmania infantum* and *Bartonella henselae*, lymph node culture, Ziehl Neelsen and Periodic acid-Schiff (PAS) staining of lymph node FNAC aspirates, bronchoscopy and bronchoalveolar lavage cytological analysis and culture, computed tomography (CT), magnetic resonance imaging (MRI), C-reactive protein (CRP), pleural or peritoneal fluid cytological analysis, FNAC of liver or spleen, skin biopsies, faecal analysis, exploratory laparotomy and haemoculture were also performed.

All the cases were treated with glucocorticoids, with gradual dose decreases over the following weeks to months depending on response. Clinical reassessment was performed regularly and response to treatment assessed on the basis of owner's perception of clinical signs and physical examination (resolution of the pyrexia if present, resolution or improvement of the lymphadenopathy by more than a 50% reduction of the lymph node size if assessable or improvement of the dog's demeanour). In some cases diagnostic imaging was repeated to assess for resolution of lymphadenopathy (if not externally assessable) or measurement of C-reactive protein if it was measured initially and was elevated. Follow-up

was considered when the animal died or based on clinical impression in the cases that progressed adequately.

Results

Canine sterile steroid-responsive lymphadenitis was diagnosed in the forty-nine dogs enrolled in this study. These included nineteen different breeds as well as 7 mixed-breed dogs. English Springer spaniels (16/49) were the most common breed followed by cocker spaniels (4/49), Border collies (3/49), German shepherds (2/49) and beagles (2/49). (Table 1)

The median age at presentation was 3 years and 9 months (range 6 months to 10 years). Thirty-one of the dogs were female (62%; 40% neutered) and 18 were male (36%; 18% neutered). There were no significant differences between English springer spaniels and other breeds with regard to age (median 44 months *versus* 44.7 months) and sex (female 58.8%, 60% neutered *versus* 68.7%; 72.7% neutered).

Previous history included idiopathic epilepsy in 2 dogs, intervertebral disc disease in one dog, previous septic peritonitis in one dog, hamartoma in the right hip and otitis in one dog and protein losing nephropathy and spontaneous (resolved) haemothorax in another dog.

Prior to referral, 45 dogs received antimicrobial and/or anti-inflammatory therapy without a significant clinical response. Forty-one dogs were treated with antimicrobials which included co-amoxiclav (31/41) metronidazole (7/41), enrofloxacin (6/41), doxycycline (6/41), marbofloxacin (5/41), cephalexin (4/41), clindamycin (1/41) and pradofloxacin (1/41). Twenty-eight dogs received non-steroidal anti-inflammatories (NSAIDs) which included meloxicam (20/28), carprofen (7/28) and firocoxib (1/28). Five dogs were treated with an anti-inflammatory dose of glucocorticoids (0.5-1mg/kg/once a day) including 4 dogs treated with prednisolone, and 1 dog treated with methylprednisolone. Nine of the 45 dogs that received treatment prior to referral presentation had a partial clinical response, this included 3 dogs treated with antimicrobials and NSAIDs, 3 dogs receiving antimicrobials and glucocorticoids, 2 dogs only receiving antimicrobials and 1 dog receiving glucocorticoids.

Five of the forty-nine dogs did not receive any medication prior to referral. Median time to referral (TTR) was 30 days (range 2 to 90 days).

Clinical presentation varied widely between animals but the most common clinical signs were pyrexia (39/49), lethargy (30/49) and anorexia (21/49). Other clinical signs are summarised in table 2. Thirty-three animals were pyrexic at presentation, with a median rectal temperature of 39.9°C (range 39.1°C-40.9°C).

Although lymphadenopathy was grossly palpable in most cases, eleven animals presented without any external sign of lymphadenopathy, but thoracic and intraabdominal lymphadenopathy was later diagnosed through further investigation. In four cases there was only one lymph node affected (inguinal in one case, retropharyngeal in two cases and mandibular in one case) and in the remaining forty-five cases there were multiple lymph nodes affected. The mandibular (31/49), superficial cervical (22/49 and popliteal (20/49) lymph nodes were most commonly affected. Objective measurements of the lymph nodes were not available in many cases; however, subjectively lymphadenopathy ranged from mild to marked. Intra-thoracic and intra-abdominal lymphadenopathy was documented with diagnostic imaging (thoracic radiographs, abdominal radiographs, abdominal ultrasound, CT or MRI) performed or interpreted by boarded radiologists. Intrathoracic lymphadenopathy was noted in 4 of the 49 cases affecting the sternal (2/49) and tracheobronchial (2/49) lymph nodes. Other changes on thoracic imaging included the presence of a mild to moderate bronchointerstitial pattern in 3 dogs, focal alveolar infiltrate in 2 dogs and nodular pattern in one dog. Bronchoalveolar lavage cytological analysis included mixed inflammation with a negative culture in all dogs that presented with radiographic changes on thoracic imaging. Intraabdominal lymphadenopathy was documented in 25 of the 49 dogs affecting the

mesenteric (15/25), medial iliac (9/25) and sublumbar (1/25) lymph nodes. Other changes on abdominal imaging included the presence of minimal volume abdominal effusion in 5 dogs, mild splenomegaly in 4 dogs and hepatomegaly in 3 dogs. In 2 dogs analysis of the peritoneal fluid revealed the presence of a neutrophilic transudate with negative culture. Splenic FNAC revealed reactive hyperplasia in 3 of the 4 dogs with splenomegaly and hepatic FNAC documented mild vacuolar change and mild neutrophilic inflammation in one dog.

Main clinicopathological findings included mild, non-regenerative anaemia (haematocrit 0.31-0.35L/L; RI: 0.37-0.55) in 5 cases (10%), mild to moderate neutrophilic leucocytosis (neutrophil count 20-35x10^9/L; RI: 3-11.5x10^9/L) in 11 cases (22%), monocytic leucocytosis (monocyte count 1.7-6.7x10^9/L; RI: 0.2-1.4) in 4 cases (8%), neutrophilic and monocytic leucocytosis in 4 cases (8%) and moderate regenerative anaemia (HCT: 0.17L/L; RI: 0.37-0.55) and severe thrombocytopenia in one case (2%). Main biochemical abnormalities included mild to moderate elevation in alkaline phosphatase activity (ALP: 154-600IU/L; RI: 14-105) in 8 cases (16%), mild to moderate hypoalbuminaemia (albumin values 16-21g/l; RI: 25-40) in 4 cases (8%) and mild hyperglobulinaemia (globulin values 47-52g/l; RI: 23-45) in 2 cases (4%).

Arthropod-borne disease testing was performed in 37 of the cases (74%) and of these, 100% of the cases were tested for *Borrelia burgdorferi* with serology, 34 cases (91.9%) were tested for *Bartonella henselae* with PCR from blood, 9 cases (24.3%) were tested for *Anaplasma phagocytophilum* with PCR from blood, 4 cases (10.8%) were tested for *Ehrlichia canis* with PCR of blood and 1 case (2.7%) was tested for *Leishmania infantum* with serology. All the results were negative.

Arthrocentesis and subsequent synovial fluid cytological analysis and culture was performed in 9 out of 49 cases (18%) as part of a FUO work-up; from which 4 (44.4%) were considered

normal, 4 (44.4%) showed marked neutrophilic inflammation and 1 (11.1%) showed mild neutrophilic inflammation. All the cultures were negative.

Cerebrospinal fluid analysis was performed in 7 out of 49 cases (14%). This was performed in 2 dogs because of lumbosacral pain, in 2 dogs as part of FUO work-up, in 1 dog because of neck pain, in 1 dog because of ataxia and in 1 dog because of stiff gait. Cerebrospinal fluid was cytologically normal in 6 dogs (85.7%) and revealed neutrophilic and lymphocytic inflammation in one dog (14.3%).

CRP was assessed in 6 out of 49 cases and was elevated in all (range 84.1-689mg/L; reference interval <10mg/L).

In all dogs, a diagnosis of lymphadenitis was reached with cytology and/or histopathology (Tables 3 and 4). Cytological assessment was performed in 44 of the 49 dogs, histological assessment in 27 of the 49 dogs and both in 21 dogs. The predominant type of lymphadenitis diagnosed on cytology was neutrophilic (28/44), followed by pyogranulomatous (6/44), granulomatous (5/44) and reactive hyperplasia (5/44). Conversely, the predominant type of lymphadenitis diagnosed on histology was pyogranulomatous (13/27) followed by neutrophilic (8/27), necrotizing (4/27) and granulomatous (2/27). In the cases in which both cytology and histopathology was performed, good agreement was found in seven of the 21 cases, whereas in the remaining 14 cases cytological diagnosis differed from histological diagnosis. In eight cases with a cytological classification of neutrophilic lymphadenitis, five were classified as pyogranulomatous lymphadenitis and three as necrotizing lymphadenitis on histology. In the five dogs classified as reactive hyperplasia based on cytology, two were classified as neutrophilic lymphadenitis, one as pyogranulomatous lymphadenitis, one as granulomatous lymphadenitis and one as necrotizing lymphadenitis on histology. In one case classified as having pyogranulomatous lymphadenitis on cytology, neutrophilic

lymphadenitis was identified on histology and one dog with granulomatous lymphadenitis on cytology was classified as having pyogranulomatous lymphadenitis on histology. Culture of lymph node tissue or aspirates was performed in 28 dogs and was negative in all instances.

Four of the 49 cases were diagnosed with other concurrent immune mediated diseases. One dog had concurrent immune mediated anaemia (IMHA) and immune mediated thrombocytopenia (ITP) one dog had concurrent immune mediated polyarthritis (IMPA), one dog was diagnosed with concurrent IMPA and meningitis and one dog was diagnosed with concurrent IMPA and pyogranulomatous skin nodules.

All the animals were treated with corticosteroids. Prednisolone was the first line treatment chosen in 47 of the 49 dogs, of which 34 dogs were started on 1mg/kg per day (dose range 0.5-3mg/kg per day). One of the 49 dogs was started with dexamethasone (dose 0.2mg/kg per day) and later was transitioned to prednisolone. Only one of the 49 dogs initially responded to antimicrobial therapy (co-amoxiclav), but it relapsed four weeks after stopping therapy, and was subsequently started on prednisolone, with rapid improvement in clinical signs.
Forty-seven of the forty-nine animals (96%) showed marked improvement in clinical condition, decrease in pyrexia and decrease in lymphadenopathy within 12-48 hours of initiation of corticosteroid administration. The subsequent treatment protocol followed in each case was different due to the multicentre retrospective nature of this study, but overall, a decrease of 25-50% of the prednisolone dose was scheduled every 2-4 weeks, continuing treatment for at least 3-6 months.

In nine of the 49 dogs, additional immunosuppressive treatments were used in combination with prednisolone. Of these nine cases, four received azathioprine (2mg/kg/SID in three cases

and 2mg/kg/EOD in one case), two ciclosporin (5mg/kg/SID), one cyclophosphamide (250mg/m^2 once), one mycophenolate (30mg/kg/EOD) and one chlorambucil (2mg total dose SID). In five of the cases, additional immunosuppressives were used at the time of recurrence of clinical signs, whereas in four of the cases they were used initially to decrease the side effects related to the corticosteroids. The most common adverse effects of corticosteroids reported were those commonly attributed to this medication, including polyuria, polydipsia, polyphagia and lethargy. Other less common adverse effects included alopecia, muscle atrophy, gastrointestinal clinical signs and wound infections.

In terms of outcome, median follow up was 168 days (range 8 days to 108 months); 22 of 49 dogs were not receiving medication and had no clinical signs after stopping medication. Eight of 49 dogs were still receiving tapering doses of prednisolone without a relapse detected three months after diagnosis. One of 49 dogs remained on 0.35mg/kg of prednisolone every other day. Due to the multi centre nature of the study, and the fact that many dogs continued their care at their primary veterinary clinic, 13 dogs were lost to follow-up whilst receiving decreasing doses of prednisolone. Five of 49 dogs had an initial good response to treatment; however they died or were euthanized during or after treatment. The cause of death was unknown in these dogs and no post-mortem examination information was available..

Eighteen dogs had a recurrence of their clinical signs during the study period of which 13 were springer spaniels. The average time to return of clinical signs was 19 weeks after diagnosis. In 12 of the 18 cases, prednisolone had been withdrawn before the time of recurrence of clinical signs whereas the rest were still on tapering doses of corticosteroids. Two dogs were monitored without adding further treatment and they did not show further progression of signs. Fourteen dogs recommenced increased doses of prednisolone, which

resulted in resolution of the clinical signs and the lymphadenopathy. Two other dogs had two episodes of return of clinical signs of which one responded well to re-treatment with prednisolone on each occasion while the other responded well on the first occasion but not the second. In one of the 18 cases with recurrence of clinical signs there was a rapid decrease in prednisolone dose over 3-4 weeks the rest had a reduction over 3-6 months.

Relating outcome with cytological/histological diagnosis, of the 22 dogs that were clinically well without treatment, 10 had neutrophilic lymphadenitis, 10 had pyogranulomatous lymphadenitis, one had granulomatous lymphadenitis and one had necrotizing lymphadenitis. Of the five cases that were euthanized or died, two had neutrophilic lymphadenitis and three (50%) had pyogranulomatous lymphadenitis.

Twelve of the 22 dogs that were well after discontinuing treatment presented initially with external lymphadenopathy, six dogs with internal lymphadenopathy and four had both internal and external lymphadenopathy. Of the five dogs that were euthanized or died, four had external lymphadenopathy and 1 had documented internal and external lymphadenopathy.

Discussion

This study describes sterile steroid-responsive lymphadenitis (CSSRL) as a cause of lymphadenopathy and FUO in dogs, its medical management and treatment outcomes. To the authors' knowledge, primary sterile lymphadenitis without evidence of other diseases has not been well described in the veterinary literature.

Dogs in this study were mainly presented for pyrexia, lethargy and inappetence; varying degrees of peripheral or internal lymphadenopathy were subsequently documented.

Lymphadenopathy is encountered in many disease processes and determining the cause of lymphadenopathy can require time-consuming and expensive investigations. Thorough diagnostic investigations were performed in all the patients that were recruited for this study; however, several diagnostic evaluations performed were different between cases due to the different clinical presentations and clinicians involved. Investigations in all the cases failed to find an underlying infectious (bacterial [Bartonella, Mycobacteria, Rickettsia, Ehrlichia, other Gram positives or negatives], protozoal [Leishmaniasis] or fungal), neoplastic or another inflammatory condition. All the animals that had tissue samples submitted for culture (lymph node, blood, urine, bronchoalveolar lavage fluid, synovial fluid or cerebrospinal fluid) showed no bacterial growth; however, this particular point is difficult to fully characterise, as many animals were pre-treated with antimicrobials, which could preclude the growth or bacterial organisms. On the other hand, the fact that many of these animals were treated with antimicrobials and showed no clinical improvement and responded well to steroid therapy would suggest that an infectious aetiology was unlikely.

In this UK population of dogs with CSSRL it appears that females were more affected compared to males (31 females and 18 males). This finding is similar to findings in other immune mediated diseases such as IMHA or ITP being also overrepresented in female dogs in some studies (Carr *et al*, 2002; O'Marra *et al*, 2011; Putsche & Kohn, 2008; Weinkle *et al*, 2005).

Median age at initial presentation was 3 years and 9 months, with ages ranging from 6 months to 10 years. This is similar to the age incidence of other primary immune mediated diseases, for example IMPA, being more prevalent in young adult dogs (Johnson & Mackin, 2012)

The most frequent clinical signs documented were lethargy, pyrexia and inappetence. In addition, a small number of dogs presented with neck pain and abdominal pain, both of which could account for anorexia. Respiratory signs were present in several cases: 7 animals presented with cough and 2 animals were dyspnoeic. One dog developed severe respiratory complications (acute onset dyspnoea) soon after initiating treatment with corticosteroids but in most of them the thoracic abnormalities resolved after starting treatment. This cause of the respiratory decompensation in this dog remains uncertain, but some of the changes noted could be vasculitis-related or potentially a secondary sequelae of the underlying primary immune-mediated disease process or a pulmonary thromboembolism. Therefore, even if pyrexia, inappetence and lethargy are the most common clinical signs according to the cases studied here, a variety of other clinical signs can be present with this condition. Additionally, concurrent immune mediated conditions such as IMHA, ITP, IMPA and meningitis were detected in 4 individual cases. Lymphadenopathy in these four dogs may be part of a reactive process secondary to these individual primary immune-mediated lymphadenitis or part of a multi-systemic immune mediated condition. This would be further supported by the fact that these dogs had generalized external and even internal lymphadenopathy rather than local lymphadenopathy from the affected areas. These cases did not appear to require higher doses of glucocorticoids in this study population compared with the cases that did not had concurrent diseases.

Regarding the lymphadenopathy, it was not restricted to peripheral lymph nodes, and in certain cases there were no signs of peripheral lymphadenopathy. From the results we obtained, mandibular, superficial cervical and popliteal lymph nodes were the lymph nodes that were most frequently affected. Also, these are the lymph nodes more readily palpated on

general physical examination. Regarding outcome, there was no relationship noted between the number of nodes affected or their location as to outcome or response to treatment.

In all dogs, a diagnosis of lymphadenitis was reached with lymph node cytology and/or histopathology. Based on cytology, the predominant type of lymphadenitis was neutrophilic, whereas the predominant type of lymphadenitis that was documented from the histopathology samples was pyogranulomatous. The discrepancy between cytology and histopathology may be attributable to the fact that sections obtained for histopathology may have been more representative samples, particularly as they would have preserved the architecture of the lymph node. However, the type of inflammation present did not appear to alter overall outcome for dogs in this study.

Prednisolone was the first line immunosuppressive treatment chosen for most dogs, of which 34 dogs commenced with 1mg/kg dose per day (dose range 0.5-3mg/kg per day). Due to the inherent difficulties with a retrospective study from a multi-centre database, the reasoning for the starting doses and protocol of continuation of treatment was difficult to establish. Forty-seven dogs showed marked improvement in clinical condition, decrease in pyrexia and decrease in lymphadenopathy within 12-48 hours of initiation of corticosteroid administration. In six of the cases, CRP concentration was used for monitoring response to the treatment and the values normalised when there was clinical improvement. Animals had previously received intravenous fluid therapy, non-steroidal anti-inflammatories, and antimicrobials of varying classes, all of which had showed minimal improvement and when started on corticosteroids their clinical signs improved dramatically within 12-48 hours. One case initially responded to antimicrobial therapy, but it relapsed four weeks after stopping the therapy, and was subsequently commenced prednisolone therapy, which immediately

improved its clinical signs. It is uncertain if there was non-detected infectious aetiology or if its apparent response was a consequence of the waxing and waning nature of immune-mediated disease.

Eighteen dogs (36%) had recurrence of clinical signs during the study period, of which 13 were English springer spaniels. Only one dog that relapsed had a shorter treatment period before relapse (3-4 weeks) compared to the other cases (3-6 months), making a short duration of treatment an unlikely reason for relapse in the majority cases. This could suggest that particularly in English springer spaniels with over 70% of this breed relapsing within the time period of this study, a longer tapering period of corticosteroids could be necessary and owners should be warned that a relapse may be more likely in the breed.

A minority of animals (9/49; 18%) required a second line immunosuppressive medication in order to either control the lymphadenitis (5/9) when they relapsed or reduce the adverse effects of corticosteroids (4/9).

Sixteen of the forty-nine cases in this study were English springer spaniels, which could suggest a breed predisposition. A case of sterile neutrophilic-macrophagic lymphadenitis associated with nodular panniculitis in a springer spaniel has been previously reported (Dandrieux *et al*, 2011). Indeed, a journal letter published in 2002 also reported a number of springer spaniels presenting with generalised lymphadenopathy consistent with granulomatous necrotising lymphadenitis and pyrexia with or without pyogranulomatous dermatitis (Hoffman *et al*, 2002). Moreover, English springer spaniels (among other breeds) have also been reported to be affected by a rare form of mineral-associated lymphadenopathy (Day, 1996). Nineteen breeds were represented in this study, three of which were spaniel breeds (English springer spaniel, cocker spaniel and Cavalier King Charles spaniel). It has

been well documented that there is a breed predilection for IMHA in Springer Spaniels and cocker spaniels (Weinkle *et al*, 2005; Reimer *et al*, 1999), whether any links to susceptibility to immune-mediated disease could be extrapolated from this study remain to be evaluated and could provide an area for future work.

This study was limited by issues inherent to most retrospective studies, including mainly a lack of uniformity of the diagnostic investigations and the treatment plans. The diagnostic work-up was not always the same because the cases were seen during different periods of time and by different clinicians from different referral centres. Also, the varied presentations of the cases initially guided investigations based on the clinical signs presented. For the same reason, some of the cases were lost in follow-up, which makes difficult to interpret the long-term response or outcome of the dogs with this condition.

To the authors' knowledge, primary sterile lymphadenitis without evidence of other diseases has not been well characterised in dogs. Diagnosis of canine sterile steroid-responsive lymphadenopathy involves extensive investigations to rule out any detectable underlying infectious, inflammatory or neoplastic causes. Most cases responded to prednisolone therapy and the rapid resolution of clinical signs was associated with normalisation of the lymphadenopathy. In addition, some of the cases relapsed after discontinuation of the treatment or while decreasing the dosage of the medication, being also suggestive of a primary immune-mediated disease process.

In conclusion, idiopathic or primary sterile steroid-responsive lymphadenitis should be considered a differential diagnosis in young-adult dogs (especially female springer spaniels) presenting with pyrexia and peripheral and/or internal lymphadenopathy. The suggested breed predisposition in springer spaniels warrants further study.

Conflict of interest

No conflicts of interest have been declared.

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