PAPER

Characterisation and outcome of idiopathic pyogranulomatous lymphadenitis in 64 English springer spaniel dogs

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Objectives: To describe the history, clinicopathological abnormalities, diagnostic imaging findings, lymph node cytological/histological appearance, treatment and outcome of English springer spaniels diagnosed with idiopathic pyogranulomatous lymphadenitis.

Materials and Methods: In this retrospective UK-based multicentre study, 64 dogs were recruited from 10 referral centres, 32 first-opinion practices and three histopathology/cytology laboratories, between 2010 and 2016.

Results: The median age at presentation was 6 years (range: 0.17 to 11.75). Neutered females were frequently affected. Pyrexia (83.8%), peripheral lymphadenomegaly (78.4%), dermatological lesions (72.9%), lethargy (67.6%), hyporexia (54%), diarrhoea (29.7%), coughing (24.3%), epistaxis, sneezing or nasal discharge (21.6%), ocular signs (21.6%) and vomiting (16.2%) were reported in dogs for which the history and physical examination records were available. Popliteal (45.3%), superficial cervical (35.9%) and submandibular (37.5%) lymphadenomegaly were frequently reported. Haematology and serum biochemistry revealed non-specific changes. When undertaken, testing for infectious diseases was negative in all cases. Lymph node cytology, histopathology or both demonstrated mixed inflammatory (27%), pyogranulomatous (24%), neutrophilic (20%) or granulomatous (11%) lymphadenitis. Treatment details were available for 38 dogs, with 34 receiving prednisolone for a median duration of 15 weeks (range: 1 to 28 weeks). A good to excellent clinical response was reported in all but one case. Ten dogs relapsed after discontinuing prednisolone.

Clinical Significance: Idiopathic pyogranulomatous lymphadenitis should be considered as a differential diagnosis for lymphadenopathy and pyrexia in English springer spaniels. The characteristics of the

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disease, absence of identifiable infectious aetiology and response to glucocorticoid therapy suggest an immune-mediated aetiology.

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INTRODUCTION

Pyogranulomatous lymphadenitis refers to inflammation of the lymph nodes, involving inflammatory infiltration by macrophages and neutrophils (Raskin 2016). This type of inflammatory response is often triggered by stimuli such as infectious agents or foreign material (Zumla & James 1996, Greene 2012). Although infectious diseases are strong differentials for pyogranulomatous lymphadenitis, many cases of sterile pyogranulomatous lymphadenitis have been described in young and adult dogs, often associated with cutaneous lesions sharing similar histological or cytological features (Reimann *et al*. 1989, White *et al*. 1989, Jeffers *et al*. 1995, Neuber *et al*. 2004, Bassett *et al*. 2005, Scott & Miller 2007, O'Kell *et al*. 2010, Dandrieux *et al*. 2011, McPartland *et al*. 2016, Fraga-Manteiga *et al*. 2016, Martens 2016). Mineral-associated lymphadenopathy has also been described as an uncommon cause of sterile pyogranulomatous lymphadenitis in which deposition of complex mineral crystals in the peripheral lymph nodes initiates an intense granulomatous inflammation and lymphadenopathy (Day 1996).

In dogs, idiopathic pyogranulomatous lymphadenitis (IPGL) is a diagnosis of exclusion and thus other causes of pyogranulomatous lymphadenitis must be ruled out. In particular, infectious aetiologies must be excluded before starting immunosuppressive treatment. Multiple agents have been identified to cause pyogranulomatous inflammation, including bacteria [*Actinomyces*, *Bartonella* (Pappalardo *et al*. 2000, Pappalardo *et al*. 2001, Saunders & Monroe 2006, Morales *et al*. 2007, Tucker et al. 2014, Drut *et al*. 2014), *Mycobacterium*, *Nocardia* and *Staphylococcus*], fungi (*Aspergillus*, *Blastomyces*, *Coccidioides*, *Cryptococcus*, *Histoplasma*), oomycetes (*Pythium*) and protozoa (*Neospora*, *Toxoplasma*, *Leishmania*) (Mylonakis *et al*. 2005, Greene 2012). Other infectious agents associated with granulomatous and pyogranulomatous lymphadenitis have also been recently reported, such as *Rhodococcus equi* (Bryan *et al*. 2017), *Sporotrichum pruinosum* (Magstadt *et al*. 2018), *Cladosporium* cladosporioides-complex (Spano *et al*. 2018), *Talaromyces helicus* (Tomlinson *et al*. 2011), *Chrysosporium* species (Cook *et al*. 2016), *Scytalidium* (Dunlap *et al*. 2015), *Paracoccidioides brasiliensis* (Headley *et al*. 2017) and circovirus (Li *et al*. 2013).

Several related clinical entities have been described, including "canine juvenile cellulitis," "canine sterile nodular panniculitis" and "sterile idiopathic neutrophilic-macrophagic lymphadenitis." Canine juvenile cellulitis is characterised by cutaneous and/or subcutaneous pyogranulomatous lesions with systemic involvement and pyogranulomatous lymphadenitis (Reimann *et al*. 1989, White *et al*. 1989, Bassett *et al*. 2005, Scott & Miller 2007, Dandrieux *et al*. 2011, Fraga-Manteiga *et al*. 2016, Martens 2016). The onset of the disease can occur from a very early age, the youngest case reported being 4 weeks old (Scott & Miller 2007), although similar cases have been reported in adult dogs (Jeffers *et al*. 1995, Neuber *et al*. 2004, Scott & Miller 2007,O'Kell *et al*. 2010, McPartland *et al*. 2016), and the terms "canine sterile nodular panniculitis" or "sterile idiopathic neutrophilic-macrophagic lymphadenitis" have been used to describe these conditions and their presumed non-infectious aetiology (O'Kell *et al*. 2010, McPartland *et al*. 2016). Additionally, localised foci of sterile pyogranulomatous inflammation within epidural, subcutaneous or intra-abdominal fat have been reported in a few dogs without systemic involvement (German *et al*. 2003, Aikawa *et al*. 2008, Nishida *et al*. 2012). Although the relationship between these different clinical entities remains unknown, the similarities between the clinicopathologic manifestations may suggest a common origin.

IPGL has been recognised for years in several breeds (McPartland *et al*. 2016), including English springer spaniels (ESSs) (Dandrieux *et al*. 2011, McPartland *et al*. 2016, Fraga-Manteiga *et al*. 2016). This disease is characterised by the enlargement of more than one peripheral or internal lymph node, with cytologic examination demonstrating necrosis, and a spectrum of suppurative/neutrophilic, pyogranulomatous or pure granulomatous inflammation. Diagnosis is made by excluding infectious, inflammatory or neoplastic causes. The aetiology is poorly understood, and screening for infectious causes is usually unrewarding. An immune-mediated aetiology has been postulated, because most dogs have a good clinical response to glucocorticoids or other immunosuppressive treatment.

A detailed description of the disease in dogs has not been published. Although a case-series suggested a high prevalence of the disease in ESSs (McPartland *et al*. 2016, Ribas Latre *et al*. 2019), a comprehensive description of the disease in this breed has not been published. Thus, the aim of this retrospective study was to describe the history, clinicopathological abnormalities, diagnostic imaging findings, lymph node histological/cytological and outcome of ESS with IPGL.

MATERIALS AND METHODS

Cases were primarily recruited from 10 referral centres in the UK between 2010 and 2015. A smaller number of cases were also recruited from 22 first-opinion practices, one histopathology and two cytology laboratories. A project outline with a request for cases was published in two veterinary journals (Bexfield *et al*. 2015a, Bexfield *et al*. 2015b) and on the (UK-based) Small Animal Medicine Society (SAMSoc) website (http://www.vetsur-

geon.org/Associations/samsoc/f/64/t/23122.aspx). Clinicians or laboratories who agreed to participate in this study were asked to submit details of signalment, clinical signs, physical examination findings and the location of affected lymph node(s) along with lymph node and cutaneous or subcutaneous lesion cytological and/or histological findings. Additionally, they were requested to submit test results for infectious disease screening on faeces, blood, urine or other body fluids along with the results of all imaging (including the modality used). Information on the drug, dosage and duration of treatment(s) was also submitted along with the response to treatment, adverse effects of treatment and long-term outcome, if available.

Criteria for inclusion in this study were as follows: (1) ESS; (2) lymphadenopathy involving more than one peripheral and/or internal lymph node; (3) lymph node cytology or histology results demonstrating neutrophilic, pyogranulomatous or predominantly granulomatous inflammation. If available, categorical data were collected, anonymised and entered into a spreadsheet (Microsoft Excel). Each category was presented descriptively with percentages. Cases were excluded if an underlying infectious or neoplastic disease was identified. Continuous data including age, treatment dosage and duration of treatment were recorded. For each parameter, median and/or mean ±sd and range were calculated. The age recorded was the age to the nearest month when each dog first presented with clinical signs of IPGL. The relationship of the disease with gender and neuter status was explored using a chi-squared test. For all comparisons, significance was set at $P<0.05$.

RESULTS

Gender and age distribution

Sixty-four ESSs satisfied the inclusion criteria and were included in the study. Ten of these dogs were included in another retrospective study that described canine pyogranulomatous lymphadenitis in several breeds (Ribas Latre *et al.* 2019).

Of our 64 cases, 25 were neutered females, 19 were neutered males, 12 were entire females and eight were entire males (Table 1). The median age at diagnosis was 6 years (72 months) with dogs ranging from 2 months to 14 years (Fig. 1). There was no apparent gender ($P=0.25$) or neuter ($P=0.8$) predisposition in this small sample. However, when the four groups were compared (females, neutered females, males, neutered males), neutered female dogs were statistically over-represented ($P=0.02$).

History and clinical signs

History and physical examination records were available in 37 cases. Information about vaccination status and travel history were not available. The most common clinical signs reported by owners were dermatological abnormalities (n=27; 72.9%), lethargy (n=25; 67.6%) and decreased appetite (n=20, 54%). Reported dermatological abnormalities included single or multiple skin masse(s) (n=8), ulcerated or alopecic skin lesions (n=3), facial swelling (n=2), ventral cervical swelling (n=2), skin erythema (n=2), other localised swelling (n=2), erythematous and pruritic pinnae (n=2) and purulent skin lesions (n=1). Clinical signs suggestive of nasal disease were reported in six cases (16.2%), including nasal discharge (n=4), sneezing (n=2) and epistaxis (n=2). In total, gastrointestinal signs including diarrhoea (n=11), vomiting (n=6), ptyalism (n=2), dysphagia (n=1) and flatulence (n=1) were reported in 21 (56.7%) cases. Respiratory signs were also reported, these included coughing (n=9; 24.3%) and dyspnoea or tachypnoea (n=4; 10.8%). Less frequently reported signs included weight loss, lameness (two cases each; 5.4%) and polydipsia (one case; 2.7%) (Fig. 2).

Table 1. Gender distribution in 64 ESSs diagnosed with IPGL

Gender	Number of dogs	Percentage
Female neutered	25	39.1
Female entire	12	18.8
Male neutered	19	29.6
Male entire	8	12.5
Total	64	100

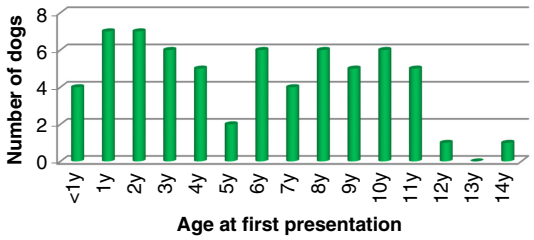

FIG 1. Age distribution in 64 ESSs diagnosed with IPGL

Physical examination

Physical examination on admission revealed pyrexia (range: 39.3 to 40.7°C) in 31 of 37 (83.8%) cases. Peripheral lymphadenomegaly was noted in 29 of 37 cases (78.4%), including popliteal (n=29), superficial cervical (n=24), submandibular (n=23) and retropharyngeal (n=12) lymphadenomegaly (Fig. 3). Jaundice was reported in one dog.

Cardiorespiratory examination and auscultation identified increased inspiratory noise in two dogs, low-grade cardiac murmurs in three dogs, sinus bradycardia in one dog and a cardiac arrhythmia in one dog. Abdominal palpation was abnormal in three dogs, with evidence of abdominal discomfort, splenomegaly or hepatomegaly each identified in one dog (Table 2).

Dermatological abnormalities reported on initial physical examination included: subcutaneous or cutaneous masses (n=8), oral ulcers (n=4), facial swelling (n=2), ventral cervical swelling (n=2), cutaneous pustules (n=2), localised subcutaneous swelling (n=2), otitis (n=2), ulcerated cutaneous lesions on the face (n=1), thoracic limbs (n=1), bridge of the nose (n=1), and prepuce (n=1), alopecic cutaneous lesion with hyperpigmentation and lichenification (n=1), seborrhoea on both pinnae (n=1), and suppurative cutaneous lesion (n=1). Unilateral testicular enlargement was reported in one case (Table 2).

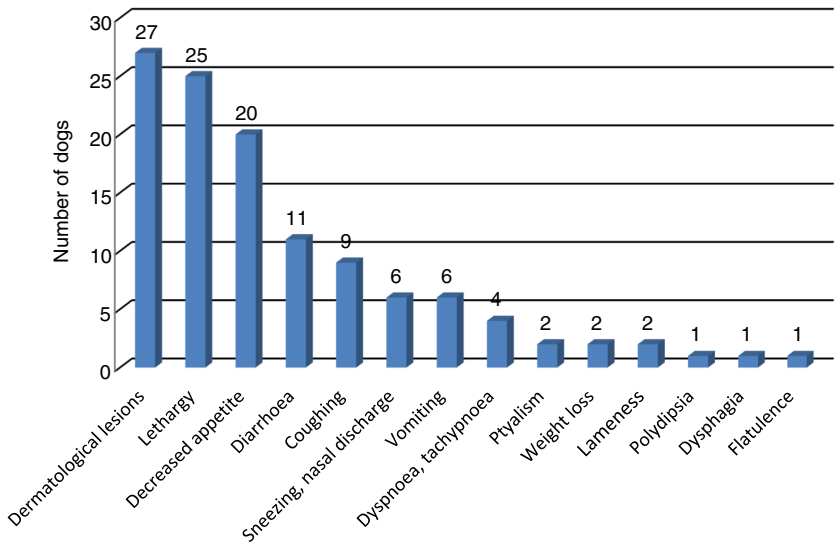

FIG 2. Distribution of clinical signs reported at presentation in 37 ESSs diagnosed with IPGL

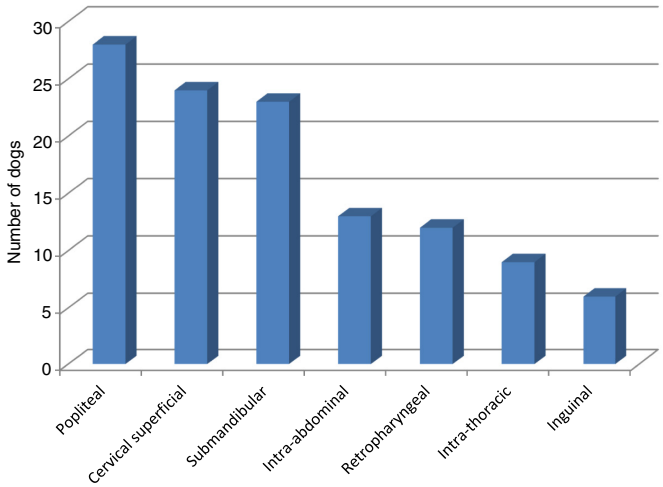

FIG 3. Anatomical distribution of lymphadenopathy in 37 ESSs diagnosed with IPGL

Table 2. Response to treatment in 38 ESSs diagnosed with IPGL

Response treatment modalities	Excellent	Good	Partial	Poor	Total
Prednisolone alone	13	4	0	0	17
Prednisolone+antibiotics*	4	4	1	0	9
Prednisolone+other immunosuppressive drug(s)†	4	2	0	0	6
Prednisolone+other immunosuppressive drug(s)†+antibiotics*	1	1	0	0	2
Antibiotics alone	0	0	0	4	4
Total	22	11	1	4	38

*Metronidazole, doxycycline, amoxicillin/clavulanic acid, enrofloxacin, cephalexin
†Azathioprine and/or ciclosporin

Ophthalmological abnormalities included bilateral conjunctival hyperaemia (n=2), unilateral conjunctival hyperaemia (n=1), unilateral mucopurulent ocular discharge (n=1), uveitis (n=1), and ruptured corneal ulcer (n=1). One dog had absent tear production bilaterally (Table 2).

Orthopaedic examination revealed right pelvic limb lameness in one case and bilateral pelvic limb lameness with bilateral stifle effusion in one case (Table 2).

Neurological abnormalities were identified in five dogs. One dog had head tremor, one dog had unilateral facial nerve paralysis and one dog had unilateral facial paralysis with concurrent neurological abnormalities suggestive of lower motor neuron (LMN) disease in the right pelvic limb. One dog had mandibular paralysis, suggestive of trigeminal nerve disease, and a history of seizures was reported in the remaining dog (Table 2).

Clinical pathology

Haematology and serum biochemistry

Results of complete blood count were available in 34 cases. Abnormalities were documented in 24 cases (70.5%), and were classified as mild-to-moderate by the clinical pathologist. The most commonly encountered haematological abnormality was neutrophilia (n=12), occasionally associated with left shift (n=3), followed by leucocytosis (n=8), monocytosis (n=6), non-regenerative anaemia (n=6), lymphopenia (n=3), leucopenia (n=2), lymphocytosis (n=1), eosinophilia (n=1) and thrombocytosis (n=1).

Results of serum biochemistry were available in 26 cases and abnormal results were noted in 11 (42.3%). These changes included increases in alkaline phosphatase activity (n=8), hypercholesterolaemia (n=4) and hypoalbuminaemia (n=4). Increases in alanine amino transferase activity (n=2), total hypercalcaemia (n=2), total hypocalcaemia (n=1), hyperbilirubinaemia (n=1), hypertriglyceridaemia (n=1) and azotaemia (n=1) were also reported.

Infectious diseases screening

Tests for infectious diseases were undertaken in 18 dogs.

Table 3. Physical abnormalities at presentation in 37 ESSs diagnosed with IPGL

Dermatological abnormalities	Ophthalmological abnormalities	Cardiorespiratory abnormalities	Neurological abnormalities	Palpation abnormalities	Orthopaedic abnormalities
Subcutaneous or cutaneous masses (n=8) Facial swelling (n=2), ventral cervical swelling (n=2), localised subcutaneous swelling (n=2) Oral ulcers (n=4) Ulcerated cutaneous lesions on the face (n=1), forelimbs (n=1), bridge of the nose (n=1), and prepuce (n=1) Cutaneous pustules (n=2) Otitis (n=2) Alopecic cutaneous lesion with hyperpigmentation and lichenification (n=1) Seborrhoea on both pinnae (n=1) Suppurative cutaneous lesion (n=1)	Bilateral conjunctival hyperaemia (n=2) Unilateral conjunctival hyperaemia (n=1) Unilateral mucopurulent ocular discharge (n=1) Uveitis (n=1) Ruptured corneal ulcer (n=1) Absence of tear production bilaterally (n=1)	Low-grade cardiac murmurs (n=3) Increased inspiratory noise (n=2) Sinus bradycardia (n=1) Cardiac arrhythmia (n=1)	Head tremor (n=1) Unilateral facial nerve paralysis (n=1) Unilateral facial paralysis with LMN deficits on the right hind limb (n=1) Mandibular paralysis (n=1)	Testicular enlargement (n=1) Abdominal discomfort (n=1) Splenomegaly (n=1) Hepatomegaly (n=1)	Right hind-limb lameness (n=1) Bilateral hind limb lameness with bilateral stifle effusion (n=1)

IPGL idiopathic pyogranulomatous lymphadenitis, ESS English springer spaniels, LMN lower motor neuron

Serology was performed for *Borrelia burgdorferi* (n=10), *Ehrlichia canis* and *ewingii* (n=5), *Anaplasma phagocytophilum* and *platys* (n=4), *Leptospira* species (n=3), *Brucella canis* (n=1), *Bartonella* species (n=1) and *Leishmania* species (n=1). *Dirofilaria immitis* antigenaemia (n=4), *Babesia* species PCR on whole blood (n=1), *Angiostrongylus vasorum* antigenaemia (n=1), *Mycobacterium* species PCR (n=4) and *Bartonella hanselae* PCR (n=3) on lymph node aspirates or biopsy were also performed. All infectious diseases testing results were negative except for *Leptospira* species serology that was consistent with recent vaccination in one dog (serology positive with a titre of 200 for *L. canicola* and *L. copenhagi*).

Bacterial cultures were negative from a variety of body fluids, including: urine (n=8), faeces (n=4), cerebrospinal fluid (CSF; n=3), blood (n=2), bronchoalveolar lavage fluid (n=2), endotracheal fluid (n=1), joint fluid (n=1) and pericardial fluid (n=1). Bacterial culture from lymph node biopsy was performed in 12 cases and all results were negative.

Cutaneous lesion histology and cytology

Biopsy and cytology results of cutaneous lesions revealed necrotising/pyogranulomatous panniculitis (n=2), pyogranulomatous panniculitis (n=2), pyogranulomatous/granulomatous panniculitis (n=2), pyogranulomatous dermatitis (n=1), granulomatous dermatitis (n=2), pyogranulomatous perifolliculitis (n=1), neutrophilic and necrotising cellulitis (n=1), pyogranulomatous cellulitis (n=1), cellulitis (n=1), panniculitis (n=1) and multiple lipomas (n=1).

Lymph node histology and cytology

In total, 71 lymph nodes were sampled: biopsy and histopathology on 41 (57.7%) and fine needle aspiration cytology on 30 (42.3%). Lymph node cytology and histology results demonstrated a spectrum of necrotising, suppurative/neutrophilic, pyogranulomatous-to-predominantly granulomatous lymphadenitis. Among the main different inflammatory categories, the most common features identified were pyogranulomatous (n=17; 24% of the lymph nodes sampled), followed by suppurative/neutrophilic (n=14; 20%) and granulomatous (n=8; 11%) inflammation. A combination of the different inflammatory features was identified in 19 lymph nodes sampled (27%), including pyogranulomatous/granulomatous lymphadenitis (n=6), pyogranulomatous/necrotising lymphadenitis (n=4), suppurative and necrotising lymphadenitis (n=1), granulomatous, necrotising and sclerosing lymphadenitis (n=1), lymphocytic, suppurative and plasmacytic lymphadenitis (n=1), necrotising, suppurative and pyogranulomatous lymphadenitis (n=1), suppurative/pyogranulomatous lymphadenitis (n=1) and eosinophilic/histiocytic lymphadenitis (n=1). Lymph node cytology or histology results were unremarkable or yielded non-specific findings including lymphoplasmacytic inflammation, reactive hyperplasia, eosinophilic lymphadenitis or necrotising lymphadenitis, in six lymph nodes (7% of lymph nodes). Lymph node analysis also included Ziehl Neelsen (ZN) and Periodic acid-Schiff (PAS) stains on lymph nodes aspirate cytology. Gram stain and examination under polarised light to exclude mineral-associated disease were undertaken on 25 lymph nodes.

Other investigations

Arthrocentesis of multiple joints was performed in two dogs with joint effusion, lameness or both. In these two cases, cytology of the joint fluid revealed sterile neutrophilic inflammation, suggestive of immune-mediated polyarthritis. In one dog, CSF cytology revealed moderate mixed pleocytosis. In another dog, brain MRI was consistent with meningoencephalitis and CSF cytology revealed marked neutrophilic pleocytosis. In the same dog, bronchoalveolar lavage and pericardial fluid cytology revealed pyogranulomatous inflammation. One dog was identified to have

splenic and hepatic nodules, diagnosed by histopathology to be eosinophilic/granulomatous splenitis and eosinophilic, lymphocytic, histiocytic hepatitis, respectively.

Radiography was the most widely used imaging modality (n=21), followed by abdominal ultrasound (n=20). Intra-thoracic lymphadenopathy was diagnosed in five dogs by thoracic radiography. Intra-abdominal lymphadenopathy was detected in nine dogs by abdominal ultrasonography. Intra-abdominal lymph node sampling was undertaken when accessible. Ultrasonographic assessment of the cervical area undertaken in four dogs confirmed the presence of lymphadenopathy in three dogs. Lymphadenopathy was detected in six dogs on CT imaging and in three dogs on MRI.

Distribution of enlarged lymph nodes

Data regarding the type and/or the number of lymph nodes affected was available for 56 dogs. Based on clinical examination and diagnostic imaging, popliteal (n=28; 50%), superficial cervical (n=24; 42.9%) and submandibular (n=23; 41.1%) lymphadenomegaly were frequently reported. Less commonly, retropharyngeal (n=12; 21.4%), intra-thoracic (n=9; 16.1%) and inguinal (n=6; 10.7%) lymphadenomegaly were also identified. Interestingly, intra-thoracic and/or intra-abdominal lymphadenomegaly, with no visible or palpable peripheral lymphadenomegaly, was diagnosed by thoracic and/or abdominal imaging in eight cases (Fig. 3).

The number of enlarged lymph nodes varied. Only one pair of lymph nodes (left and right) was enlarged in most cases (n=25, 44.7%). Two pairs of lymph nodes were enlarged in 15 cases (26.8%), three pairs of lymph nodes in 10 cases (17.9%) and four or more pairs of lymph nodes in six cases (10.7%).

Treatment and outcome

Prediagnosis treatment and outcome

Details about treatment administered before diagnosis were available in 27 cases. Eighteen cases received antibiotics and non-steroidal anti-inflammatory drugs (NSAID). Eight cases received antibiotics alone and one case received antibiotics and a dose of 0.5 mg/kg prednisolone once daily concurrently. Anti-inflammatory drugs used included robenacoxib, meloxicam, carprofen, and tolfedine. Antibiotics used included cephalexin, cefuroxime, doxycycline, amoxicillin clavulanate, metronidazole, amoxicillin, marbofloxacin, enrofloxacin, pradofloxacin, trimethoprim/sulfadimethoxine, clindamycin, spiramycin/metronidazole and oxytetracycline. In most cases, dogs received two or more antibiotics simultaneously. In all cases, there had been no improvement in clinical signs including rectal temperature and lymphadenopathy.

Treatment and outcome after diagnosis

Details relating to medical management were available in 38 cases. Thirty-four (89.5%) of these dogs were prescribed prednisolone, and the remaining four were treated with antibiotics alone, including co-amoxicillin/clavulanate, doxycycline and/or enrofloxacin. Of the 34 cases treated with glucocorticoids, concurrent antibiotics were administered in 12 dogs (35.3%). A variety of other supportive medications were also used, including sucralfate, omeprazole, ranitidine, tramadol, misoprostol, paracetamol, maropitant and mirtazapine. These drugs were administered by primary clinicians based on initial clinical signs.

Data regarding the dose and treatment duration of prednisolone therapy was available in 33 out of 34 cases. The daily dose of prednisolone (mg *per* dog) was available in 20 cases and the exact prednisolone dosage (mg/kg) was available for 13. The mean and median starting doses of prednisolone were 27.5 mg/day (daily dose) or 2 mg/kg/day (exact dosage). Among the 33 dogs with available data regarding prednisolone, three received a constant daily dose, while the dose was tapered in the remaining 30 dogs. The median duration of initial prednisolone treatment was 21 days (range: 2 to 120) and the median duration of the full prednisolone course was 15 weeks (range: 1 to 28) in both groups of dogs receiving constant and decreasing doses. Of the 34 cases that had been given prednisolone, 11 (32.4%) had been given antibiotics at the same time. Among cases which received prednisolone at an immunosuppressive dose, other immunosuppressive treatments were given in eight cases, including doses of 2 mg/kg azathioprine orally once daily (n=7) or 5 mg/kg azathioprine and ciclosporin orally once daily (n=1) (Table 3). Azathioprine and cyclosporine treatment durations were not available in most dogs. Treatment outcome was recorded as partial, good or excellent in the notes from the referring veterinarians.

In dogs treated with prednisolone (n=34), an excellent response was recorded in 22 cases (64.7%), a good response in 11 (32.4%) and a partial response in one (2.9%). Of the four cases that had been given antibiotics only, no improvement was reported in any of them (Table 3).

Relapse was suspected in 10 dogs (10 of 38, 26.3%) with recurrent lethargy, nasal discharge, lymph node enlargement (peripheral or intra-abdominal) and pyrexia. In two dogs, lymph nodes were re-aspirated and cytology results revealed similar features as previously documented. The time of relapse after discontinuation of the glucocorticoids and/or information regarding repeat treatment was not available in three cases. In the remaining seven cases, all dogs relapsed after finishing the course of prednisolone. The median interval till relapse after cessation of prednisolone was 13 weeks (range: 2 to 52 weeks). Re-initiation of prednisolone therapy was recommended in eight cases. Adjunctive immunosuppressants were also recommended in two dogs: a dose of 2 mg/kg azathioprine orally once daily and then every other day in one case, and a combination dose of 2 mg/kg azathioprine orally once daily and 5 mg/kg ciclosporin orally once daily in the other case. One dog (11.1%) was not treated and recovered spontaneously. Two dogs relapsed for a second time at 10 months and 1 year after discontinuation of the second course of treatment (prednisolone and azathioprine, prednisolone alone respectively). No long-term follow-up information was available for these two dogs.

Overall, four dogs were euthanased and one dog died secondary to colonic necrosis and septic peritonitis. Euthanasia was the result of absent or poor response to treatment after multiple episodes of recurrence (n=1), recurrence of the disease after tapering

the dose of glucocorticoids (n=1), onset of monoparesis secondary to development of a lumbar spinal mass (n=1) and worsening of chronic coughing with marked adverse side effects of glucocorticoids (n=1).

DISCUSSION

This retrospective study provides the largest description of IPGL in the ESS. In a multi-breed retrospective study describing the disease in 49 dogs, ESSs appeared over-represented (16 of 49) (Ribas Latre *et al*. 2019). Given the number of cases recruited in this retrospective study over a 5-year time period and given the percentage of ESSs in the previously mentioned study, this breed appears predisposed to IPGL. Therefore, IPGL should be considered as part of the differential diagnosis for lymphadenopathy in all dogs, but particularly in this breed. Further investigations may be required to confirm this assumption. In this study, the median age at the time of diagnosis was 6 years, which compares with a median of 3.75 years reported previously in all breeds (Ribas Latre *et al*. 2019). Neutered female dogs were frequently affected. It remains unclear whether there might be a breed-variant of IPGL in ESSs, or whether a breed predisposition exists in ESSs. The possibility of a true sex predisposition may also warrant further investigations. ESSs with IPGL show many non-specific clinical signs at presentation, similar to those previously reported in all breeds (McPartland *et al*. 2016, Fraga-Manteiga *et al*. 2016), and most appear to show signs of a systemic or multi-organ inflammatory process. Major signs including skin lesions, lethargy and decreased appetite were reported in more than half of the dogs. Diarrhoea, epistaxis, sneezing or nasal discharge, coughing, ocular changes and vomiting were less common. On physical assessment, pyrexia and lethargy were identified in more than three-quarters of the dogs. Although none of these signs were pathognomonic of IPGL, the combination of dermatological lesions, pyrexia and lymphadenopathy should raise suspicion of the disease in this breed.

In this study, peripheral lymphadenomegaly predominantly affected the popliteal, superficial cervical and sub-mandibular lymph nodes. In most cases, only one pair of lymph nodes was enlarged. Although most cases of lymphadenomegaly were identified on physical examination, imaging identified intra-thoracic and/or intra-abdominal lymphadenomegaly with no evident peripheral lymphadenopathy in eight dogs. This finding emphasises that lymph node lesions should not be ruled out based on palpation of peripheral lymph nodes alone. In addition to their usual role in screening for any underlying infectious or neoplastic diseases, thoracic radiography and abdominal ultrasonography appear to be cost-effective first-line imaging modalities for detecting internal lymphadenomegaly.

While coughing or abnormal respiratory patterns were reported in a quarter of cases, thoracic imaging was often of low-yield with respect to identifying the cause of respiratory signs. In our study, thoracic CT revealed abnormalities in two dogs, one with a diffuse bronchointerstitial pattern and the other with a nodular pulmonary pattern. A similar clinical presentation was reported in a 9-month ESS with idiopathic PGL (Fraga-Manteiga *et al*. 2016), but in that case, thoracic radiographs were unremarkable. Similarly, while vomiting and diarrhoea were reported in a quarter of cases, abdominal imaging was frequently unremarkable. Among the 17 dogs with gastrointestinal signs, diffuse small intestinal wall thickening was identified in only one dog, and thickening of the descending colon with altered wall layering was identified in another dog. Although no gastrointestinal disease was identified in our study, lymphoplasmacytic colitis and pancreatitis have previously been described in dogs with sterile nodular panniculitis (O'Kell *et al*. 2010), and could have contributed to the gastrointestinal signs reported by some owners, especially considering that clinicopathological testing and diagnostic imaging are poorly sensitive for both of these diseases. Ptyalism, dysphagia and oral ulcers were reported in four cases. Interestingly, these findings have not been described in previous publications.

There was a combination of pyrexia, abnormalities of multiple organ systems and neutrophilia in most dogs, which may be suggestive of a systemic inflammatory process. Evidence of concurrent inflammatory disease was detected in four cases, including polyarthritis, mild pericardial effusion, bronchial inflammation, splenic and hepatic pyogranulomatous nodules, meningoencephalitis and CSF pleocytosis. However, the relationship between these findings and IPGL remains unclear. Although polyarthritis has been described in dogs with canine sterile nodular panniculitis (O'Kell *et al*. 2010), the relationship between IPGL and other concurrent inflammatory processes requires further investigation.

Before diagnosis, most dogs received either a combination of NSAID and antibiotics or antibiotic therapy alone. In all cases, there was no improvement reported. Following diagnosis, prednisolone was the most commonly used drug, either alone or in combination with ciclosporin or azathioprine. A good to excellent response to treatment was noted in almost all cases. These results are similar to two retrospective studies and one case report of sterile panniculitis, in which the vast majority of dogs were successfully treated with immunosuppressive drugs (Yamagishi *et al*. 2007, O'Kell *et al*. 2010, Santoro & Campbell 2011). The absence of obvious infectious triggers and the good-to-excellent response to glucocorticoids might suggest an immune-mediated aetiology. In our study, patients received long courses of prednisolone, alone or in combination with other immunosuppressive drugs or antibiotics. Relapse(s) occurred in a quarter of cases following cessation of treatment, suggesting the need for long term, and perhaps even life-long, immunosuppressive therapy in some individuals.

Due to the retrospective nature of this study, and because some cases were recruited directly from histopathology laboratories, diagnostic and outcome data were missing in a large number of cases. This may represent the main limitation of our study. Considering the extensive range of possible infectious aetiologies, a further limitation of this study is the absence of systematic infectious disease screening in all dogs. Data regarding travel history was also missing. Considering the low prevalence of infectious diseases in the UK, and the good-to-excellent response to immunosuppressive therapy, an infectious aetiology seems unlikely. Although these conclusions may be applicable to the UK canine population, systemic screening for infectious diseases responsible for pyogranulomatous lymphadenitis is strongly recommended

in other parts of the world. Specific diseases, such as leishmaniasis, need to be systematically ruled out in endemic areas.

In conclusion, although the aetiology of the disease is poorly understood, an immune-mediated process is strongly suspected, and therapy with prednisolone appears effective. The response to immune-suppressive treatment is usually good but long-term courses of immunosuppressive drugs are often required and relapses are frequent.

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Conflict of interest

This study was presented as an abstract at the BSAVA Congress in Birmingham in April 2019. No conflicts of interest have been declared by the authors.

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