BSAVA

JOURNAL OF SMALL ANIMAL PRACTICE

JSAP

Check for updates

ORIGINAL ARTICLE

Clinicopathological features of peripheral odontogenic fibromas in dogs and risk factors for their laboratory diagnosis

J. T. Ambridge*,†,1, E. M. Ambridge‡, H. Jahns*, J. S. McKay†, E. Riccardi† and P. A. Kelly*

*Department of Veterinary Pathology, School of Veterinary Medicine, University College Dublin, Belfield, Dublin, Ireland
†IDEXX Laboratories UK, Grange House, Sandbeck Way, Wetherby LS22 7DN, UK
‡School of Psychology, University of Sussex, Brighton BN1 9RH, UK

[1]Corresponding author email: jacob.ambridge@ucdconnect.ie

Objectives: To explore clinicopathological features of peripheral odontogenic fibromas in dogs and risk factors for their diagnosis.

Materials and Methods: Data of cases with a histopathological diagnosis of peripheral odontogenic fibromas were obtained from a UK-based diagnostic laboratory and retrospectively reviewed. Prevalence amongst all biopsy submissions was assessed using binomial tests and Clopper–Pearson intervals. Age at diagnosis was assessed using *t*-test for independent samples. Lesion location, sex, and neuter status were assessed using χ^2 and post hoc binomial tests. Breed odds ratios were calculated using univariable logistic regression modelling.

Results: The prevalence of peripheral odontogenic fibromas amongst all biopsy submissions was 2.8% (1001 of 35,328, 95% confidence interval [CI]: 2.7 to 3.0). The mean (sd) age was 8.1 (±2.7) years. The most affected quadrant was the rostral maxilla (40.1%). The ratio of maxillary to mandibular lesions was 1.3:1 (95% CI: 1.1 to 1.5), and for cases of multiple peripheral odontogenic fibromas the ratio of maxillary to mandibular lesions was 2.4:1 (95% CI: 1.1 to 5.6). Males had 1.2 times the odds of suffering of peripheral odontogenic fibromas compared to females (odds ratio [OR]: 1.2, 95% CI: 1.1 to 1.4). Neutering was associated with an increased risk of diagnosis (OR: 1.6, 95% CI: 1.3 to 1.9). Breeds with increased odds of peripheral odontogenic fibromas compared to crossbreed dogs included boxers (OR: 3.78, 95% CI: 2.80 to 5.09), border terriers (OR: 3.21, 95% CI: 2.10 to 4.91) and Basset Hounds (OR: 3.18, 95% CI: 1.58 to 6.44). Breeds with increased odds of multiple simultaneous peripheral odontogenic fibromas compared to crossbreed dogs included: Boxers (OR: 12.02, 95% CI: 7.13 to 20.24), border terriers (OR: 5.05, 95% CI: 2.32 to 11.43) and Staffordshire Bull terriers (OR: 2.42, 95% CI: 1.33 to 4.41).

Clinical Significance: Knowledge of clinicopathological features and at-risk breeds for peripheral odontogenic fibroma development can assist clinicians with making a diagnosis. The identification of risk factors provides targets for future research investigating peripheral odontogenic fibroma pathogenesis.

Journal of Small Animal Practice (2023) **64**, 343–349
DOI: 10.1111/jsap.13586

Accepted: 09 November 2022; Published online: 13 February 2023

INTRODUCTION

Canine peripheral odontogenic fibroma/fibromatous epulis of periodontal ligament origin (POF/FEPLO) is a common, benign, gingival lesion in dogs (Murphy *et al.* 2019). Despite the extensive development of odontogenic tumour catagorisation within veterinary pathology over the last half a century, this lesion remains highly contentious in both name and classification. Authors occasionally combine the terms POF and FEPLO and refer to this tumour/tumour-like lesion as POF/FEPLO (Murphy *et al.* 2019). This somewhat unwieldy contraction has come about due to inferences implied by each individual term. Use of the word "epulis" has generally fallen out of favour due to its lack of specificity as to the underlying pathology it describes. For example, canine acanthomatous ameloblastoma, an invasive neoplasm, was historically termed an "epulis", as were foci of gingival fibrous hyperplasia. To remedy this, some authors advocate reservation of the word "epulis" strictly for use within the context of FEPLOs (Uzal *et al.* 2016), however, this approach has yet to be adopted by the wider veterinary community The alternative name for this lesion, peripheral odontogenic fibroma, suggests these lesions are neoplastic in origin, a fact contested by some pathologists (Murphy *et al.* 2019). As a result, neither designation is widely accepted. Further studies investigating the fundamental histogenesis and pathogenesis of these lesions are required before any consensus on terminology within the community is likely to be reached. Peripheral odontogenic fibroma/fibromatous epulis of periodontal ligament origin will be referred to as POF throughout this paper.

In the most comprehensive clinicopathological studies in dogs to date, POF represented 19% to 21% of all oral cavity tumour and tumour-like lesions submitted for histopathological evaluation (Svendenius & Warfvinge 2010, Mikiewicz *et al.* 2019). Macroscopically POF present as variably sized, pink to white, roughened, cauliflower-shaped to nodular, exophytic masses originating from the tooth alveolus. They often displace teeth and can appear aggressive macroscopically, but do not invade bone or metastasise. Lesions can be solitary or multiple; multiple, coalescing, broad-based POF can give a generalised appearance. This generalised form of coalescing POF is anecdotally most common in boxer dogs. It often occurs admixed with the familial form of generalised gingival hyperplasia unique to boxers, potentially lending weight to the argument that POF represent a reactive, rather than neoplastic, process (Burstone *et al.* 1952, Murphy *et al.* 2019). POF most commonly occur in middle aged to older dogs (Fiani *et al.* 2011, Wingo 2018, Mikiewicz *et al.* 2019), and appear to have a propensity for development within the rostral maxilla (Fiani *et al.* 2011). Data regarding sex predisposition for POF diagnosis in the literature is conflicting, with overrepresented males (Fiani *et al.* 2011), overrepresented females (Svendenius & Warfvinge 2010) and no difference in distribution of affected sexes all reported (Wingo 2018). Data regarding breed predisposition are scarce, with rare subjective observations reported which reference breeds as overrepresented (golden retrievers, boxer dogs), but which lack statistical confirmation (Fiani *et al.* 2011, Mikiewicz *et al.* 2019 respectively), often due to small sample sizes.

The present study aimed to explore the epidemiological features of canine POF utilising data obtained from a commercial diagnostic veterinary laboratory that provides diagnostic services to both first opinion and referral practices, largely within the United Kingdom and Ireland. The specific objectives were (1) to characterise the prevalence amongst surgical biopsy submissions, age at diagnosis, and most common position(s) of POF lesions within the oral cavity, (2) to examine the association between sex, neuter status, and breed on risk of POF laboratory diagnosis, (3) to investigate the reported anecdotal predisposition for boxer dogs to show the multiple/multifocal form of POF and (4) to describe the gross appearance of POF.

MATERIALS AND METHODS

Medical record search and data extraction

A search of the medical records database of a UK-based diagnostic laboratory was conducted to identify dogs in which POF were diagnosed by histopathology, during a 158-day period (January 1, 2019 to June 7, 2019). Keyword/trigger phrases used to identify cases were "peripheral odontogenic fibroma", "fibromatous epulis of periodontal ligament origin" and "ossifying fibromatous epulis". Dogs in which any/several of these keyword phrases appeared in the diagnosis or comment as the definitive or primary differential diagnosis were included. Data collected included breed, sex, neuter status, age at diagnosis and position of the lesion within the oral cavity. All identifiers for each case submission were removed and a unique identifier given to each case before analysis.

An additional search was also conducted within the same database and time period for all canine histopathology submissions; breed, sex, neuter status and age at diagnosis data were collected from non-POF submissions to act as a control population for the distribution of the POF population.

Information regarding the size, shape, consistency and colour of POF lesions, alongside the presence or absence of ulceration, patient interference, tooth displacement and pedunculation, were also gathered from the POF population histories to characterise the clinicopathological features most identified by clinicians during submission.

Lesion position in the oral cavity

For classification of tumour location, the oral cavity was divided into four anatomic regions based on oncological surgical principles for mandibulectomy and maxillectomy (Verstraete 2005, Verstraete *et al.* 2019). The rostral aspect of the maxilla and mandible extended from the level of the first incisor tooth to the level of the second premolar tooth. The caudal aspect of the maxilla and mandible was defined as the region of the dental arcade caudal to the second premolar tooth. Rare lesions which were located within the gap between, or spanned, the second premolar and third premolar (i.e., borderline lesions) were not included in the analysis.

Statistical analysis

Commercially available software was used for the statistical calculations (Excel [Microsoft Office Excel 2013; Microsoft Corp.] and IBM SPSS Statistics 27). Both graphical observation and the Shapiro–Wilk test for normality were used to determine data distribution (parametric *versus* non-parametric data). Continuous, normally distributed data were summarised as mean ±sd.

Prevalence amongst biopsy submissions and associated confidence intervals were calculated using a binomial test and Clopper–Pearson interval. The mean age at diagnosis was compared between POF and non-POF submissions using a t-test for independent samples. The distribution of POF within the oral cavity of the sample population was compared to an expected equal distribution between the four regions of the oral cavity (i.e., 25% within each area) using the χ^2 goodness-of-fit test; where a statistically significant result was obtained ($P<0.05$), post hoc analysis using individual binomial test comparisons, with Bonferroni correction for multiple analyses, were conducted amongst the four oral regions. The maxillary to mandibular distribution and rostral to caudal distribution were compared to an expected equal distribution (i.e., 50:50 split) using a binomial test. Sex, neuter status and reproductive status (sex and neuter status combined) distribution of the POF population was compared to non-POF canine histopathology submissions during the same period using the χ^2 test of independence, with post-hoc individual binomial test comparisons and Bonferroni correction for multiple analyses as indicated. Effect size for reproductive status (male neutered *versus* female neutered *versus* male entire *versus* female entire) was calculated using Cramer's V (Cohen 1988). All other effect sizes are given as odds ratios (ORs; Szumilas 2010). An alpha (α) value of 0.05 was selected for all tests (i.e., values of $P<0.05$ were considered statistically significant).

To streamline statistical analysis to the most clinically relevant breeds, breeds were included for analysis if they fulfilled one of two criteria: greater than 500 total submissions during the time period (to include the most common breeds), or greater than 100 total submissions with a POF prevalence amongst all biopsy submissions (within that breed) of more than 5% (thereby including less-common breeds that may be markedly predisposed). Breeds were only included in analysis for "multiple POF" risk if their prevalence for multiple POF was more than 1% of all biopsy submissions within that breed; this lower inclusion threshold was selected due to the comparative rarity of multiple POF cases compared to POF occurrence in general. Breeds could not qualify for multiple POF inclusion on total submission numbers alone. Breeds that did not meet inclusion criteria were combined and categorised as "all other breeds" for analysis. A "crossbreed" category was used as the reference population for OR calculations (O'Neill *et al.* 2020). Univariable logistic regression modelling was then used to identify breeds whose risk of POF diagnosis differed significantly from the reference population (crossbreed dogs), and to calculate the specific OR of POF diagnosis for these breeds compared to the reference population.

Ethical approval was provided by University College Dublin, Animal Research Ethics Committee (AREC E 21 33 Kelly).

RESULTS

Peripheral odontogenic fibromas

Prevalence

There were 1001 confirmed cases of POF diagnosed from 35,328 canine histopathology submissions between January 1 to June 7, 2019; yielding a prevalence for POF of 2.8% [95% confidence interval (CI): 2.7 to 3.0] amongst all biopsy submissions.

Age

The age at diagnosis of POF was available for 982 of 1001 (98.1%) cases. Age distribution within the POF dog population was normally distributed. The mean (sd) age of affected dogs was 8.1 (±2.7) years.

The age at diagnosis was available for 33,255 of 34,342 (96.8%) of non-POF submissions. Age distribution within the non-POF dog population was normally distributed. The mean (sd) age of non-POF submissions was 8.1 (±3.3) years. There was no significance difference in mean age at diagnosis between POF and non-POF submissions.

Position in the oral cavity

"Maxillary or mandibular" lesion position data was available in 627 of 1001 (62.6%) cases; the ratio of maxillary to mandibular lesions was 1.3:1 (95% CI: 1.1 to 1.5, P=0.003). "Rostral or caudal" lesion position data was available in 514 of 1001 (51.3%) cases; the ratio of rostral to caudal lesions was 1.9:1 (95% CI: 1.6 to 2.3, $P<0.001$). Complete lesion position data was available for 465 of 1001 (46.5%) cases. The distribution of POF differed within the four regions of the oral cavity (rostral maxilla, caudal maxilla, rostral mandible, caudal mandible) ($P<0.001$), with the highest proportion (40.1%) located within the rostral maxillary arcade (Fig 1).

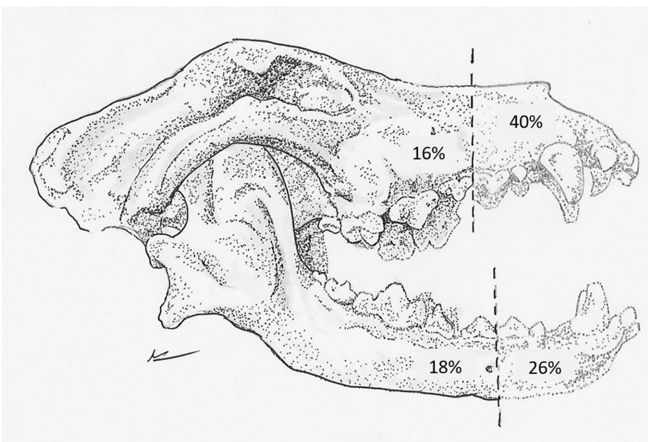

FIG 1. Distribution, as a percentage, of POF/FEPLO in the oral cavities of dogs (n=466)

Table 1. Observed *versus* expected reproductive status distribution of dogs with POF/FEPLO diagnosis (n=883) compared to non-POF/FEPLO diagnoses (n=30,232)

Reproductive status	Expected count	Observed count	Difference in observed *versus* expected count
Male entire	135	108	−27
Male neutered	308	383	75
Female entire	114	66	−48
Female neutered	327	326	−1

Sex, neuter status and reproductive status

Sex data was available for 34,304 of 35,329 (97.1%) of all biopsy submissions. The sex distribution of POF submissions (n=980) differed significantly from non-POF histopathology submissions (n=33,324) during the same period; Males had 1.2 times the odds of suffering POF compared to females (OR: 1.2, 95% CI: 1.1 to 1.4, *P*=0.001). Neuter status data was available for 31,115 of 35,329 (88.1%) of all biopsy submissions. Neutered dogs had 1.6 times the odds of being diagnosed with POF than enire dogs (1.6, 95% CI: 1.3 to 1.9, *P*<0.001). Combined sex and neuter status (i.e., reproductive status) data was available in 31,115 of 35,329 (88.1%) of all biopsy submissions; neutered male dogs were overrepresented and female entire dogs were underrepresented with a small effect size (Cramer's V=0.037, <0.06=small effect size, *P*<0.001) (Table 1).

Breed

Of the 15 breeds that were individually included in the analysis, seven showed increased odds of being diagnosed with any number of POF compared to crossbreed dogs: boxers (OR: 3.78, 95% CI: 2.80 to 5.09, *P*<0.001), border terriers (OR: 3.21, 95% CI: 2.10 to 4.91, *P*<0.001), Basset hounds (OR: 3.18, 95% CI: 1.58 to 6.44, *P*=0.001), flat-coated retrievers (OR: 2.97, 95% CI: 1.57 to 5.63, *P*<0.001), Staffordshire Bull terriers (OR: 2.08, 95% CI: 1.59 to 2.71, *P*<0.001), Lurchers (OR: 2.04, 95% CI: 1.16 to 3.60, *P*=0.014) and Border Collies (OR: 1.54, 95% CI: 1.01 to 2.33, *P*=0.044). Two breeds showed reduced odds of any POF diagnosis compared to crossbreed dogs: Labrador retrievers (OR: 0.63, 95% CI: 0.46 to 0.86, *P*=0.004) and West Highland white terriers (OR: 0.13, 95% CI: 0.03 to 0.54, *P*=0.005) (Table 2).

Descriptive macroscopic features

Information regarding the size, shape, consistency of the lesion, presence/absence of ulceration, pedunculation, tooth displacement or patient interference was noted in 26.5% of submission histories (265 of 1001).

An estimation of size was provided in 85 cases, the vast majority of POF were between 5 and 50 mm in diameter (78 of 85). Gross description of shape was noted in 43 of the cases, with 12 being described as smooth (12 of 43), eight cauliflower-like (eight of 43), six as irregular (six of 43), four as nodular (four of 43), four as rounded (four of 43), three as flat (three of 43), three as dome-shaped/circular (three of 43), one as roughened (one of 43), one as multilobed (one of 43) and one as protruding (one of 43). Pedunculation/narrow-based architecture was documented in 38 of 41 cases. Reported consistencies of POF were provided in 88 cases; with firm, hard or bony being the most common (59 of 88); only six of 88 were noted to be soft or friable. The reported colour of lesions was noted in 37 cases and ranged from pink/gum coloured (18 of 37) to red (eight of 37) to pigmented (eight of 37). Ulceration was commonly reported (23 of 34). Presence or absence of tooth displacement was noted in 12 cases, with 10 confirming tooth displacement; of these, the specific tooth/teeth affected was given in seven cases (six incisors and one premolar). Patient interference or perceived pain were rare (four of 12).

Multiple peripheral odontogenic fibromas

Prevalence

Of the 1001 confirmed cases of POF, 150 dogs had multiple, simultaneous POF, yielding an overall prevalence for multiple POF amongst total biopsy submissions of 0.4% (95% CI: 0.4% to 0.5%).

Table 2. Logistic regression results for breed as a risk factor for POF/FEPLO diagnosis

Breed	Cases	Total	Odds ratio	95% Confidence interval	P value
Crossbreed	126	4717	Base		
Boxer	74	788	3.776	2.8 to 5.09	**<0.001**
Border terrier	28	346	3.208	2.10 to 4.91	**<0.001**
Basset hound	9	112	3.184	1.57 to 6.44	**0.001**
Flat-coated retriever	11	146	2.969	1.57 to 5.63	**0.001**
Staffordshire Bull terrier	101	1873	2.077	1.59 to 2.71	**<0.001**
Lurcher	14	264	2.040	1.16 to 3.56	**0.014**
Border Collie	28	692	1.536	1.01 to 2.33	**0.044**
Golden retriever	24	643	1.413	0.91 to 2.20	0.128
Springer spaniel	34	1011	1.268	0.86 to 1.86	0.227
Shih-tzu	20	614	1.227	0.76 to 1.98	0.403
Cocker spaniel	39	1606	0.907	0.63 to 1.30	0.598
Jack Russel terrier	27	1199	0.839	0.55 to 1.28	0.415
All other breeds	181	9064	0.742	0.59 to 0.93	**0.011**
German shepherd dog	13	678	0.712	0.40 to 1.27	0.249
Labrador retriever	58	3427	0.627	0.46 to 0.86	**0.004**
West Highland white terrier	2	554	0.132	0.03 to 0.54	**0.005**

P<0.05 are considered significant

Age

Age distribution within the multiple POF dog population was normally distributed. The mean (sd) age of affected dogs was also 8.1 (±2.7) years. There was no significance difference in mean age at diagnosis between the multiple POF population and all other submissions in the same period.

Position in the oral cavity

"Maxillary or mandibular" lesion position data was available in 34 of 150 (22.7%) of cases that had multiple POF; the ratio of maxillary to mandibular lesions was 2.4:1 (95% CI: 1.1 to 5.6, *P*=0.026). No significant difference was present between rostral and caudal lesion distribution, or in POF distribution between all four regions of the oral cavity.

Sex, neuter status and reproductive status

The sex distribution of POF submissions with multiple simultaneous POF (n=145) did not differ significantly from all other submissions during the same period. The proportion of neutered dogs which were diagnosed with multiple POF simultaneously was significantly higher than sexually entire dogs (OR: 2.6, 95% CI: 1.6 to 4.2, *P*<0.001). Neutered male dogs were overrepresented and female entire dogs were underrepresented with a small effect size (Cramer's V=0.022, <0.06 = small effect size, *P*=0.02).

Breeds

Four breeds had a prevalence of more than 1% for multiple POF diagnosis, amongst all biopsy submissions within that breed, and thus qualified for inclusion in analysis. Three of these breeds showed increased odds of being diagnosed with multiple simultaneous POF compared to crossbreed dogs: boxers (OR: 12.02, 95% CI: 7.13 to 20.24, *P*<0.001), border terriers (OR: 5.05, 95% CI: 2.32 to 11.43, *P*<0.001) and Staffordshire Bull terriers (OR: 2.42, 95% CI: 1.33 to 4.41, *P*=0.004).

DISCUSSION

This study utilised statistical analysis to examine the clinicopathological features of peripheral odontogenic fibromas (n=1001) diagnosed via histopathological evaluation of samples submitted by first opinion and referral practices. Previous related studies (Svendenius & Warfvinge 2010, Fiani *et al.* 2011, Wingo 2018, Mikiewicz *et al.* 2019) commonly included POF as a small subcategory of tumours within a broader examination of oral lesions, and were often descriptive in nature (i.e., lacked statistical analysis). One study which did benefit from statistical analysis was underpowered (n=47) and was only examining a referral population (Fiani *et al.* 2011). Given that the vast majority of POF are dealt with in a first opinion setting and would rarely, if ever, be referred for specialist care unless there were a concern over more aggressive differential diagnoses, the data from the aforementioned study (Fiani *et al.* 2011) may be self-selecting for more aggressive appearing lesions grossly, which may not be applicable to POF more broadly.

Prevalence data regarding POF within the literature are typically reported as a proportion of oral lesion biopsy submissions (i.e., when a dog develops an oral lesion, what is the prevalence of POF amongst those oral lesions), rather than as a proportion of biopsy submissions for any reason (Svendenius & Warfvinge 2010, Mikiewicz *et al.* 2019). This study examined the prevalence of POF diagnoses amongst all biopsy submissions, not just oral lesion submissions, during a defined time period, and found an overall prevalence amongst those submissions of 2.8% (95% CI: 2.7 to 3.0). The reliance on biopsy submissions as a sampling method likely underestimates the potential prevalence of POFs amongst biopsy submissions as, in practice, an unknown number of grossly diagnosed "epulides" would either be removed and not submitted for histopathological examination or would be left untreated. A large proportion of these epulides would be POF given the prevalence reported amongst oral lesions biopsy submissions in previous studies. An additional limitation of relying on biopsy submissions for diagnosis is that there is a potential selection bias for more aggressive appearing lesions to have an increased likelihood of being submitted compared to more benign appearing lesions. One potential approach to counteract these limitations would be to use a data-mining program and centralised database of first opinion practice medical records to capture all presentations of POF, so that even POF that are identified but not treated, or removed but not submitted for histology, are included in the data. However, the limitation with this approach is that POF are indistinguishable grossly from several other very common lesions (gingival hyperplasia, early-stage canine acanthomatous ameloblastoma), and so definitive diagnosis is not possible without histopathological evaluation; as a result, the investigators would only gain an understanding of "epulis" prevalence, and not POF prevalence specifically.

The age at diagnosis of POF reported in this study (8.1 ±2.7 years) closely resembles previous descriptive studies which included age at POF diagnosis 8.0 ±2.6 years (Mikiewicz *et al.* 2019), 8.5 ±2.9 years (Fiani *et al.* 2011), 8-year mean age ((Wingo 2018) – no standard deviation reported), and there was no significant difference in mean age of POF and non-POF submissions. Interestingly, the age at diagnosis for multiple POF in this study was also 8.1 ±2.7 years, suggesting risk for diagnosis of multiple POF compared to POF generally is not temporal (i.e., "multiple POF" cases are not simply being diagnosed later in the disease process and more likely to develop multiple POF as a result).

The position of POF lesions within the oral cavity revealed a significant predilection for diagnosis within the rostral maxilla, which is consistent with previous reports regarding POF lesion distribution within the oral cavity (Fiani *et al.* 2011). There was a 2:1 rostral to caudal distribution and 1.3:1 maxillary to mandibular ratio, with multiple/multifocal POF presentations having an even greater risk of being diagnosed within the maxilla (2.4:1 maxillary to mandibular ratio). The rostral predilection of POF generally was not mirrored in the "multiple" POF caseload specifically, likely due to underpowering of the "multiple" subcategory for which location was given (n=25) compared to the general POF population (n=514). A predilection for occurrence within the rostral oral cavity is not unique to POF; all of the most common odontogenic lesions (canine acanthomatous ameloblastoma, gingival hyperplasia, POF/FEPLO) appear to occur more commonly in the rostral cavity (Fiani *et al.* 2011). It is not clear whether there is a genuine predilection within the rostral compartments of the oral cavity for odontogenic tumour formation, or if rostral lesions are simply more readily observed by the owner (and consequently presented for investigation and treatment). A prospective study with regular examination of all four quadrants of the oral cavity, over an extended time period and utilising an appropriate number of dogs to ensure sufficient study power, would be required to differentiate these potential causes for overrepresentation of odontogenic tumours and tumour-like lesions within the rostral oral compartment.

Data regarding sex predisposition for diagnosis of POF in the literature is conflicting, with overrepresented males (Fiani *et al.* 2011), overrepresented females (Svendenius & Warfvinge 2010) and no difference in distribution of affected sexes (Wingo 2018) all reported. In this study, POF was diagnosed slightly more often in male dogs compared to female dogs; this sex difference was not detected in the "multiple POF" subcategory, likely due to a combination of the small effect size detected in the POF population generally (and by extension, the anticipated small effect size for multiple POF diagnosis), and relatively small numbers in the "multiple" population (n=145). More notably, neutered dogs were at a significantly increased risk of POF diagnosis compared to unneutered dogs; this increased risk was even more dramatic for "multiple POF" cases. Male neutered dogs were overrepresented and female entire dogs were underrepresented (with a small effect size) in both the POF population generally and the "multiple POF" subcategory. The only other study to date examining both sex and neuter status of POF affected dogs reported a similar over-representation of male neutered dogs and underrepresentation of female entire dogs within a dental referral population, but without the benefit of an effect size calculation (Fiani *et al.* 2011). The manner in which neutering affects POF predisposition is not understood at this stage; a more intimate knowledge of POF pathogenesis, which is notably lacking in the literature, and the role of neutering on potentially implicated pathways is required. Consensus on the fundamental nature of POF, neoplastic *versus* reactive, has yet to be reached within the veterinary community; until POF pathogenesis and histogenesis is better understood, interpretation and understanding of risk factors and their influence remains challenging.

In the current study seven breeds were shown to have increased odds of POF diagnosis compared to crossbreed dogs: boxers, border terriers, Basset hounds, flat-coated retrievers, Staffordshire Bull terriers, Lurchers, and Border Collies all showed variable degrees of increased risk. Two breeds showed reduced odds of POF diagnosis compared to crossbreed dogs: Labrador retrievers and West Highland white terriers. Three breeds had increased odds of being diagnosed with multiple simultaneous POF compared to crossbreed dogs: boxers, border terriers, and Staffordshire Bull terriers. Breeds with increased (and decreased) risk for POF diagnosis in this study do not appear to span a particular body size, morphology or coat type, and so extricating a possible common predisposing factor amongst these breeds is not possible. Currently, except for the present study, there are no publications in the literature which have confirmed breed as a risk factor for POF diagnosis. One study used statistical analysis to attempt to assess the impact of breed on risk of POF diagnosis; the study size was relatively small and so no associations were detected (Fiani *et al.* 2011). Several studies have made subjective observations regarding particular breeds having a possible predisposition for POF diagnosis, including boxers (Mikiewicz *et al.* 2019) and golden retrievers (Fiani *et al.* 2011), but none provided statistically significant evidence for such claims. Notable amongst the results presented in this study was the increased risk of boxer dogs to have a diagnosis of POF compared to crossbreeds; boxers had the highest OR for POF diagnosis amongst all breeds examined, they also had the highest OR for diagnosis of multiple POF by a notable margin. As discussed earlier, the histogenesis of POF (neoplastic *versus* reactive) is not well understood. Boxer dogs are predisposed to gingival hyperplasia, and suffer from a familial, generalised form of the disease (Burstone *et al.* 1952). Commonly this generalised form of gingival hyperplasia appears to occur in tandem with POF development, and the markedly increased risk of boxers (12 times the risk of crossbreed dogs) to be diagnosed with multiple POF identified in this study supports this hypothesis. It could also be argued that this finding lends weight to the claim that POF are reactive rather than neoplastic in origin, although more direct studies into POF pathogenesis are required to confirm or refute this hypothesis (Murphy *et al.* 2019).

The notable discrepancy in reporting rates of gross descriptors by submitting clinicians prohibited statistical evaluation of these features, as the risk of an inherent false negative or false positive during data collection was too high; however, they are included for descriptive purposes. The majority of descriptive, macroscopic features identified during data collection simply confirm the widely accepted appearance of POF documented in numerous textbooks and papers. However, one trait of interest warrants discussion in this study: tooth displacement, and, more specially, which teeth are displaced. While tooth displacement is well documented in POF, the apparent propensity for incisors being, by far and away, most affected is a novel finding. It is possible that POF near incisors are fundamentally different in terms of their development, and so displace teeth more often, although this is considered unlikely. Far more likely, is that this apparent predilection for incisor displacement is a combination of two independent factors (1) the apparent propensity for POF to occur within the rostral oral cavity and (2) the specific anatomy of incisors, having only a single, shallow root and thereby being more prone to instability. Statistical confirmation of this subjective observation would require a larger sample size, specifically relating to tooth displacement, in which submitting clinicians would be required to comment on the absence or presence of tooth displacement and which teeth were affected.

This study of data obtained from dogs diagnosed with a POF revealed an overall prevalence of 2.8% amongst all biopsy submissions, highlighting the relatively high proportion of biopsy submissions for which this single disease entity is responsible. It also characterised the typical age at diagnosis for POF (8.1 ±2.7 years). This study confirms previous observations regarding the propensity for POF to be diagnosed in the rostral maxilla (40.1%), and the maxilla generally (OR: 1.3:1), as well as identifying a previously unreported predilection within the rostral oral cavity (OR: 2:1). This study clarified previous conflicting data regarding sex predispositions for POF diagnosis and found a male to female ratio of 1.2:1. It also highlighted the association between neutering and POF risk (1.6:1) and multiple POF risk (2.6:1), as well as identifying male neutered dogs as particularly predisposed, whilst entire female dogs appeared relatively spared (Cramer's V=0.038=small effect size). Finally, it examined breed related risk, from which two conclusions can be drawn: (1) No common feature is immediately evident across all breeds with increased risk (size, morphology, coat type etc.), suggesting breed related propensity for POF occurrence is multifactorial, or at least more complex than a single genetic defect and (2) boxer dogs have the highest risk of POF diagnosis of any breed, and have a marked predisposition for diagnosis of the generalised/multifocal form of POF, suggesting they would serve as a good model for further POF studies and may have a unique pathway regarding POF pathogenesis.

Acknowledgements

The authors would like to thank Mr. Michael Dixon for his artistic contribution to Fig 1.

Author Contributions

J. T. Ambridge: Conceptualization (lead); data curation (lead); formal analysis (lead); investigation (lead); methodology (lead); project administration (lead); resources (lead); software (lead); writing – original draft (lead); writing – review and editing (lead). **E. M. Ambridge:** Data curation (supporting); formal analysis (supporting); methodology (supporting); writing – review and editing (supporting). **H. Jahns:** Methodology (supporting); writing – review and editing (supporting). **J. S. McKay:** Conceptualization (supporting); supervision (supporting); writing – review and editing (supporting). **E. Riccardi:** Conceptualization (equal); methodology (equal); supervision (equal); writing – review and editing (equal). **P. A. Kelly:** Conceptualization (equal); investigation (supporting); methodology (supporting); supervision (equal); writing – original draft (supporting); writing – review and editing (equal).

Conflict of interest

None of the authors of this article has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

References

Burstone, M. S., Bond, E. & Litt, R. (1952) Familial gingival hypertrophy in the dog (boxer breed). *A.M.A. Archives of Pathology* **54**, 208-212

Fiani, N., Verstraete, F. J., Kass, P. H., *et al*. (2011) Clinicopathologic characterization of odontogenic tumors and focal fibrous hyperplasia in dogs: 152 cases (1995-2005). *Journal of the American Veterinary Medical Association* **238**, 495-500

Mikiewicz, M., Paździor-Czapula, K., Gesek, M., *et al*. (2019) Canine and feline oral cavity tumours and tumour-like lesions: a retrospective study of 486 cases (2015-2017). *Journal of Comparative Pathology* **172**, 80-87

Murphy, B. G., Bell, C. M. & Soukup, J. W. (2019) Veterinary Oral and Maxillofacial Pathology. Wiley-Blackwell, Hoboken, NJ

O'Neill, D. G., Turgoose, E., Church, D. B., *et al*. (2020) Juvenile-onset and adult-onset demodicosis in dogs in the UK: prevalence and breed associations. *Journal of Small Animal Practice* **61**, 32-41

Svendenius, L. & Warfvinge, G. (2010) Oral pathology in Swedish dogs: a retrospective study of 280 biopsies. *Journal of Veterinary Dentistry* **27**, 91-97

Szumilas, M. (2010) Explaining odds ratios. *Journal of Canadian Academy of Child and Adolescent Psychiatry* **19**, 227-229

Uzal, F. A., Plattner, B. L. & Hostetter, J. M. (2016) Chapter 1—Alimentary system. In: Jubb, Kennedy & Palmer's Pathology of Domestic Animals. 6th edn., Vol. **2**. Ed M. G. Maxie. W.B. Saunders, St. Louis, MO. pp 1-257.e2

Verstraete, F. J. M. (2005) Mandibulectomy and maxillectomy. *Veterinary Clinics of North America: Small Animal Practice* **35**, 1009-1039

Eds Verstraete, F. J. M., Lommer, M. J. & Arzi, B. (2019) Oral and Maxillofacial Surgery in Dogs and Cats. Elsevier Health Sciences, St. Louis, MO

Wingo, K. (2018) Histopathologic diagnoses from biopsies of the Oral cavity in 403 dogs and 73 cats. *Journal of Veterinary Dentistry* **35**, 7-17