

Paper

Histopathology inflammation scoring and classification in 34 dogs with inflammatory nasal disease

A. R. R. Furtado, F. Constantino-Casas

The aims of this study are to suggest a histological classification and a scoring system (0–12) for dogs with inflammatory nasal disease, and to compare and determine statistical associations between histopathology findings and lymphoplasmacytic rhinitis (LPR) or aspergillosis. Twenty-one LPR cases and 13 aspergillosis cases were reviewed and classified at the Queen's Veterinary School Hospital of the University of Cambridge. Statistical analysis was performed using SPSS V.17 and the level of significance accepted was $P < 0.05$. The suggested classification includes the name of the two most common inflammatory cells found, duration of disease, lesion distribution, severity of epithelial and goblet cell hyperplasia and presence of oedema and fungi. The inflammation score was calculated according to the number of inflammatory cells present, and revealed that half the cases had moderate nasal inflammation and that most of the cases (67.6 per cent) were lymphocytic rhinitis. As far as the statistical associations were concerned, only fungal presence was proven to be associated with aspergillosis ($P = 0.04$). The two conditions were found to have similar histological appearance. Implying that the histological diagnosis can sometimes be difficult and that the clinician should always consider the results from other diagnostic tests to reach a final diagnosis.

Introduction

Respiratory system diseases are considered to be common and important causes of morbidity and mortality in animals and humans, mainly because the respiratory tract is in direct contact with the physical environment and is exposed to airborne micro-organisms, such as viruses, bacteria, fungi and parasites.

Nasal disease in dogs can be a result of several conditions like neoplasia, inflammation, infection (primarily fungal), trauma, foreign body or, less commonly, parasitic infestation (Miles and others 2008). Determining the underlying cause in dogs with nasal disease can be challenging and frustrating, often necessitating multiple diagnostic procedures at substantial cost to the client (Miles and others 2008).

Diagnostic tests are obviously required to confirm the presence of these respiratory diseases, however, respiratory medicine is considered to be an underdeveloped subspecialty in veterinary medicine; most of the commonly available tests are used to point the clinician in the right direction, and to rule out the presence of other potentially confounding disorders (Padrid 2007). Nowadays, there are several ancillary diagnostic tests that help the clinician reach a correct diagnosis of inflammatory nasal disease, nevertheless, the most important ones are still MRI, CT and rhinoscopy with subsequent biopsy and histopathology of nasal mucosa.

Histopathology plays an important role in the diagnosis of inflammatory nasal diseases, since it is possible to detect inflammation and fungal hyphae even when these changes cannot be seen on rhinoscopy. All the biopsies should be fixed in 10 per cent formaldehyde (10 per cent neutral buffered formalin), and stained using H&E which shows inflammatory cells and some types of fungi, such as dermatophytes (Pérez and Carrasco 2000, Mackin 2004). However, most of the potentially pathogenic species of fungi are poorly stained with this technique, so special staining techniques are needed, such as periodic acid-Schiff (PAS), Gridley technique or the silver methenamine techniques (Pérez and Carrasco 2000).

First described in 1987 (Burgener and Slocombe 1987), idiopathic lymphoplasmacytic rhinitis (LPR) is characterised by the histopathological appearance of inflammation of the nasal mucosa dominated by lymphocytes and plasma cells (Day 2009). Because dogs with LPR may have neutrophilic inflammation of the nasal mucosa in addition to the characteristic lymphoplasmacytic infiltration, less specific terms, such as chronic rhinitis, chronic inflammatory rhinitis and idiopathic chronic rhinitis, have also been used to identify this condition (Mackin 2004, Windsor and others 2004, Hawkins and others 2008).

Mycotic rhinitis cases in the dog are usually caused by *Aspergillus fumigatus* and rarely by *Aspergillus niger*, *Aspergillus nidulans* and *Aspergillus flavus* (Harcourt-Brown 2006, Ferreira and others 2007). Histological identification of fungal hyphae in biopsy specimens has traditionally been used to confirm the diagnosis of mycotic rhinitis; nevertheless, it does not identify the precise fungal agent present (Mathews and others 1998, Blanco and García 2000, Johnson and others 2006).

Another study (Peeters and others 2005) suggested that nasal aspergillosis in dogs is not associated with mucosal invasion, thus, histological evidence of disease may not be obtained in all cases, and detection of plaques during rhinoscopy, along with histological examination of plaque material, is of critical importance in confirming the diagnosis (Johnson and others 2006).

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A. R. R. Furtado, DVM, MRCVS
Vets Now Referrals, 36 Warren Road,
Chatham, Kent ME5 9RD, UK
F. Constantino-Casas, MVZ, PhD,
MRCVS
Department of Veterinary
Medicine, University of Cambridge,

Cambridge, UK, CB3 0ES
E-mail for correspondence:
ritarfurtado@gmail.com
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Another point that should be taken into consideration is that the presence of fungal elements does not rule out other underlying problems, such as nasal foreign bodies or neoplasia (Lorenzi and others 2006).

As the inflammatory cellular response to *Aspergillus* species is primarily neutrophilic, a large number of moderately lytic neutrophils is usually seen, and many samples show bacterial phagocytosis due to secondary bacterial infection (Lorenzi and others 2006).

The aims of this study are to propose a histologic nasal inflammation scoring system based on the degree of inflammatory cell presence on nasal mucosa samples, to suggest a more objective method to histologically classify rhinitis and, finally, to determine statistical associations between the histopathology findings of the two most common inflammatory nasal diseases: LPR and aspergillosis.

Materials and methods

Thirty-four histopathology tissue samples from dogs with inflammatory nasal disease were blind-reviewed at the pathology laboratory of the Queen's Veterinary School Hospital of the University of Cambridge. A single pathologist reviewed the samples, and a Nikon Eclipse 50i light microscope was used to view the slides. The samples were later compared with the final diagnosis previously made by several different pathologists of the same department.

The cases included 21 cases of LPR, diagnosed on the basis of CT, MRI, rhinoscopy and histopathology findings, and 13 cases of aspergillosis, confirmed by at least three positive ancillary tests, such as radiography, CT, MRI, visualisation of fungal colonies via rhinoscopy, serology, culture and histopathology. Dogs were excluded from the study if the final diagnosis was foreign body, parasitic infection, trauma or neoplasia, or if nasal disease was not present.

Nasal biopsy specimens were taken during rhinoscopy at the same hospital and were stained with H&E and PAS. Necrotic and haemorrhagic areas were excluded from the estimation, and only mucosa and submucosa were assessed.

For all the samples, the proportion of each inflammatory cell type (lymphocytes, neutrophils, plasma cells and eosinophils) was estimated in a semiquantitative manner in three random fields at 40× magnification. Macrophages were excluded from the study since they were rarely seen in the samples.

The cell presence was estimated for each cell type and was classified as either (a) not present; (b) mild: 100–200 cells per 3 high-power fields (HPFs, 40×) and a mucosal surface with at least 10 intraepithelial cells per 3 HPFs; (c) moderate: 201–300 cells per 3 HPFs and 11–20 intraepithelial cells per 3 HPFs; or (d) severe: more than 300 cells per 3 HPFs, with more than 20 intraepithelial cells per 3 HPFs and lymphoid aggregates. This classification was then converted into a numerical score, and it was established that not present would be 0, mild would be 1, moderate would be 2 and severe would be 3.

The numbers for each cell type were then totalled and a final score from 0 to 12 was given. It was then stipulated that from 0 to 3 the inflammation was classified as mild; from 4 to 6 was moderate and more than 7 was severe inflammation (see Table 1 for examples of scoring).

In cases with only one or two types of inflammatory cells present, this form of the scoring system was not applied. Instead, the cell presence for the individual inflammatory cell types present in the sample were classified as mild, moderate and severe according to the criteria described above; the overall grade of the sample was given as the highest score for any one of the individual cell types present (see Table 1, samples 4 and 5).

The epithelial hyperplasia and goblet cell hyperplasia were classified as normal, mild if focal thickened epithelium was found, moderate if

multifocal thickened epithelium was present and severe if diffuse thickened epithelium was seen. Mucosal oedema was classified as normal if not present, mild if it was present in less than 20 per cent on three random fields, moderate if present between 20 and 40 per cent, and severe if present in more than 40 per cent.

Fibrosis within the submucosa and the presence of epithelial ulceration were classified as present or absent.

Fungi (hyphae, PAS-positive organisms) were considered as present or absent. The duration of the lesions was classified as acute, subacute and chronic. It was considered acute when neutrophils, eosinophils and oedema were the predominant findings; subacute if neutrophils, eosinophils, lymphocytes and plasma cells were present concomitantly with variable degrees of epithelial hyperplasia, and chronic if there were predominantly plasma cells and lymphocytes and few neutrophils and eosinophils, with variable degrees of epithelial hyperplasia.

The distribution of the inflammatory lesions was categorised as diffuse, when inflammatory changes were seen through the entire sample, or localised when only some parts of the specimen analysed had inflammatory cell infiltration (Box 1).

The suggested histopathology classification was based on the most frequent inflammatory cell type present in the samples given. The classification included the name of the most frequent cell type; the second most frequent cell type; the duration of the disease; distribution; severity of epithelial and goblet cell hyperplasia; a reference to the presence of oedema and fungi.

Statistical analysis of the data was performed using SPSS V.17. The histopathology variables were all cross-tabulated with the variables LPR and aspergillosis, and for each cross-tabulation, non-parametric tests were used. The level of significance accepted for all the cross-tabulations was $P < 0.05$. The Pearson's χ^2 test was used to test for row and column independence, however, in some cases it was not possible to apply this test because there were not enough criteria. In these cases, the Fisher's Exact Test of independence was used to obtain the exact P value for a single 2×2 contingency table. The cases in which it was not possible to calculate an exact P value with the Pearson's χ^2 or Fisher's exact test, the Monte Carlo method was used, which provides an unbiased estimate of the exact P value of Pearson's χ^2 without the requirements of the asymptotic method.

BOX 1: Histopathology guidelines for the evaluation of inflammatory nasal diseases

- Classification according to the number of
 - Neutrophils
 - Lymphocytes
 - Plasma cells
 - Eosinophils
 } Not present (0)
Mild (1)
Moderate (2) → (0–12)
Severe (3)
- Total Inflammation score (0–12)
 - 0–3—Mild inflammation
 - 4–6—Moderate inflammation
 - ≥7—Severe inflammation
- Epithelial and goblet cell hyperplasia
 - Mild, moderate and severe
- Oedema presence
 - Mild, moderate and severe
- Fibrosis within the mucosa
 - Present or absent
- Epithelial ulceration
 - Present or absent
- Fungal hyphae
 - Present or absent
- Duration of the disease
 - Acute
 - Subacute

TABLE 1: Final inflammation score

	Neutrophils	Lymphocytes	Plasma cells	Eosinophils	Final score	Grade
Sample 1	1	1	1	0	3	Mild
Sample 2	1	2	2	0	5	Moderate
Sample 3	3	3	2	3	11	Severe
Sample 4	0	3	0	0	3	Severe lymphocytic infiltration
Sample 5	0	2	1	0	3	Moderate

Results

Population

Thirty-four dogs were included in this study. Twenty-nine dogs (85.3 per cent) were purebred, including four labrador retrievers, four jack russell terriers and three dachshunds. Five (14.7 per cent) of the 34 dogs were crossbreed dogs. The dogs' ages included in this study ranged from 18 months to 13 years old (mean, 6.43 years; sd, 3.45 years). There were 23 male dogs (67.6 per cent; 14 castrated and 9 entire) and 11 female dogs (32.4 per cent; 7 spayed females and 4 entire). Bodyweight ranged from 7.1 kg to 46 kg (mean, 24.08 kg; sd, 10.7 kg).

Inflammatory cell presence

Lymphocytes

Lymphocytes were found in all (100 per cent) the 34 cases from which histopathology was carried out. Five cases (14.7 per cent) were found to have a mild lymphocytic infiltration, nineteen cases (55.9 per cent) had a moderate presence and 10 cases (29.4 per cent) were classified as severe infiltration.

These results were table-crossed with LPR and aspergillosis cases, but no statistically significant associations were found ($P=0.30$, 99% CI (0.287 to 0.311)). Nevertheless, the moderate presence of lymphocytes was the most common finding in LPR (66.7 per cent), while in aspergillosis, moderate (38.5 per cent) and severe (38.5 per cent) infiltration were the most common findings.

Plasma cells

Plasma cells were found in 30 patients (88.2 per cent) out of the 34 reported cases; the other four cases did not show plasma cell infiltration. The most common feature seen was the moderate infiltration of plasma cells (52.9 per cent), followed by severe (23.5 per cent) and mild infiltration (11.8 per cent).

LPR and aspergillosis groups were cross-tabulated with the plasma cell infiltration results, however, no associations were shown to be statistically significant ($P=0.23$, 99% CI (0.223 to 0.245)). It was seen, however, that the most frequent feature in LPR was moderate infiltration (66.7 per cent), while in cases of aspergillosis, moderate and severe infiltration were the most common findings.

Neutrophils

Neutrophils were seen in 28 dogs (82.4 per cent). Twelve cases (35.3 per cent) had a mild presence of neutrophils, 10 had a moderate presence (29.4 per cent) and 6 had severe infiltration (17.6 per cent). These results were cross-tabulated with LPR and aspergillosis cases, but no associations were shown to be statistically significant ($P=0.06$, 99% CI (0.053 to 0.065)). Nonetheless, it was noticed that mild neutrophilic infiltration was the most common finding in LPR (47.6 per cent) and moderate infiltration was most commonly seen in aspergillosis (46.2 per cent). Additionally, it was noticed that severe neutrophilic infiltration was more frequently seen in aspergillosis (30.8 per cent) than in LPR cases (9.5 per cent).

Eosinophils

Thirty-three cases (97.1 per cent) were reported to be normal, and only one (2.9 per cent) was classified as having moderate eosinophilic infiltration. This case belonged to the LPR group, but no statistically significant association was found ($P=1.0$).

Inflammation score

The inflammation score was given by the infiltration level of neutrophils, lymphocytes, plasma cells and eosinophils. The grade ranged from mild to severe, since no sample was found to be completely normal.

All the samples had more than two cell types present. Totally, 5 (14.7 per cent) out of the 34 cases were classified as having mild inflammation, 17 (50 per cent) as moderate and 12 (35.3 per cent) as severe. The results were cross-tabulated with the LPR and aspergillosis cases, but no associations were proven to be statistically significant ($P=0.46$, 99% CI (0.444 to 0.469)). Nevertheless, it was seen that most of the LPR cases had a moderate grade of inflammation, while aspergillosis cases had most samples classified as moderate or severe (Fig 1).

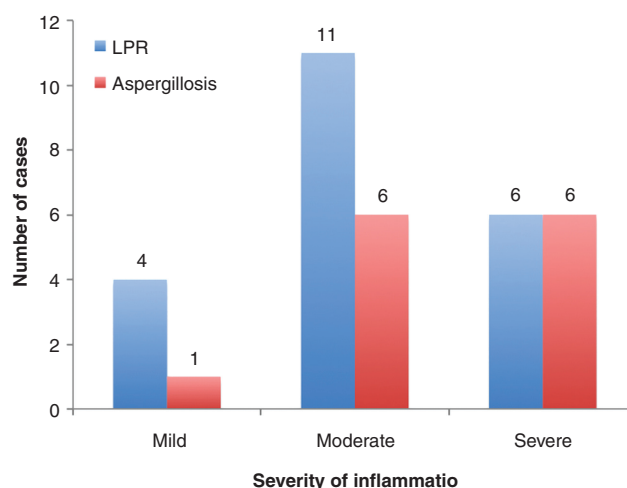


FIG 1: Distribution of severity of inflammation according to lymphoplasmacytic rhinitis and aspergillosis

Epithelial and goblet cell hyperplasia

Epithelial cell and goblet cell hyperplasia were visualised in 24 (70.6 per cent) out of the 34 cases. Epithelial cell hyperplasia was classified as moderate in 13 cases (38.2 per cent), mild in eight cases (23.5 per cent) and severe in three cases (8.8 per cent). The cross-tabulation of epithelial cell hyperplasia with LPR and aspergillosis groups did not show any statistically significant associations ($P=1.00$).

Goblet cell hyperplasia was classified as mild in 17 cases (50 per cent) and moderate in 7 cases (20.6 per cent); no cases with severe goblet hyperplasia were found. LPR and aspergillosis cases were cross-tabulated with goblet cell hyperplasia, however, no association was shown to be statistically significant ($P=0.58$, 99% CI 0.570 to 0.596).

Oedema

Oedema in the samples was another feature considered, and its presence was identified in 24 cases out of 34 (70.6 per cent). The presence ranged from mild to severe, with 8 cases classified as mild (23.5 per cent), 15 as moderate (44.1 per cent) and only 1 (2.9 per cent) as severe. These results were cross-tabulated with LPR and aspergillosis, but no statistical association was found ($P=0.06$, 99% CI 0.054 to 0.066).

Fibrosis within the submucosa, and the presence of epithelial ulceration

The presence of fibrosis within the mucosa and epithelial ulceration was not seen in any sample analysed in the present study.

Fungi

The presence of fungi was only reported in four (11.8 per cent) cases. Although not all aspergillosis cases had fungal present in the samples taken, this finding was proven to be associated with aspergillosis ($P=0.04$, 99% CI 0.037 to 0.048) (Table 2).

Duration and distribution of the inflammation

As far as the duration of the inflammation was concerned, three categories were made: acute, subacute and chronic. The most frequent feature was subacute inflammation which was present in 28 samples out of the 34 analysed (82.4 per cent), followed by chronic inflammation that was seen in 4 (11.8 per cent) cases and acute inflammation with only 2 cases (5.9 per cent).

TABLE 2: Cross-tabulation between fungi presence and inflammatory nasal diseases

	Fungi presence		Total
	Absent	Present	
LPR (%)	20 (95.2)	1 (4.8)	21 (100)
Aspergillosis (%)	10 (76.9)	3 (23.1)	13 (100)
Total (%)	30 (88.2)	4 (11.8)	34 (100)
LPR, Lymphoplasmacytic rhinitis			

TABLE 3: Histopathology classification

Rhinitis	Duration	Distribution	Cell hyperplasia	Oedema	Fungi
Lymphoplasmacytic	Subacute	Diffuse	Moderate goblet cell hyperplasia and mild epithelial hyperplasia	Moderate	Absent
Neutrophilic	Subacute	Diffuse	Severe epithelial hyperplasia and mild goblet cell hyperplasia	Mild	Absent
Plasmalymphocytic	Chronic	Diffuse	Moderate epithelial and goblet cell hyperplasia	Mild	Present

These results were distributed according to LPR and aspergillosis cases. It was seen that the only two acute inflammation cases belonged to the aspergillosis group (15.4 per cent), however, the most predominant feature in this group was subacute inflammation (69.2 per cent). Nineteen LPR cases (90.5 per cent) were reported to have subacute inflammation, and two (9.5 per cent) to have chronic inflammation; in this group, no sample was assessed to have acute inflammation present.

The inflammatory distribution was analysed in all the 34 samples, and it was noticed that all of them presented as diffused inflammation, with no samples having only localised or focal inflammation present.

Histopathology classification

Since the proposed histopathology classification included the name of the most frequent cell, it was seen that 23 (67.6 per cent) out of the 34 samples had lymphocytes as the most common cell type, 7 (20.6 per cent) samples showed more neutrophils and 4 (11.8 per cent) samples showed more plasma cells. The epithelial and goblet cell hyperplasias were included in the final histopathology classification, showing the name of the cell most frequently found. Examples of this classification are shown in Table 3.

Discussion

The proposed histopathology classification of inflammatory nasal disease proved to be descriptive, providing a more accurate and more informative morphologic diagnosis to the clinician.

The histological results showed that the majority of cases had lymphocytic and plasma cell infiltration regardless of the pathology. Neutrophilic inflammation was also frequently present, and since it is characteristic of a catarrhal and purulent rhinitis (Mathews 2004), it may suggest that LPR and aspergillosis are associated with acute or subacute inflammation.

Moderate eosinophilic infiltration in the nasal mucosa was present in one case. The literature reports cases of eosinophilic infiltration in patients with allergic rhinitis (Terada and others 2001) in humans and dogs (Meler and others 2008), related to tobacco smoke. While this was taken into consideration for the particular samples in this study, no further studies, such as allergy testing, were found in the literature that would confirm this hypothesis.

The proposed inflammation scoring system, given according to the number of cells present, may be an excellent means with which to objectively assess mucosal histologic inflammation. To the authors' knowledge, there are no studies reporting the types of cells present in the nasal mucosa in healthy samples since all dogs submitted for a rhinoscopy and biopsies have clinical signs compatible with nasal disease.

It was confirmed that LPR and aspergillosis were of similar histopathologic appearance, and although not statistically significant it was found that aspergillosis was more frequently seen in cases that had higher scores (moderate to severe inflammation).

Epithelial and goblet cell hyperplasia were seen more frequently in LPR cases, however, no statistical association was found between these variables. In order to reach conclusive results, further studies are needed to show if there is any association between these characteristics and this specific nasal pathology.

The association between fungal presence and aspergillosis was shown to be statistically significant ($P=0.04$). Although histologic evidence of aspergillosis is often used as a diagnostic criterion (Mathews and others 1998), one study (Peeters and others 2005) showed that given the superficial nature (no mucosal invasion) of fungal hyphae in dogs with nasal aspergillosis, detection of fungal hyphae in the nasal cavity was not always to be expected as was observed in the present

study. It is therefore important for the clinician to consider aspergillosis as a differential even when fungi are apparently absent from the sample.

Another important finding was the presence of fungi in one LPR sample. The authors' point of view is that this can be due to the fact that a small number of fungi can be part of the normal flora of the nose. Furthermore, the authors also believe that it can also be the result of a misdiagnosed LPR.

Most of the cases in both pathologies were classified as subacute, and all the cases had diffuse inflammation present throughout the samples. This result is in agreement with the literature (Mackin 2004) where it is reported that the histopathologic changes in LPR are typically diffuse and distributed throughout the nasal cavity. Although in aspergillosis the fungal plaques are localised, in this study it was shown that the inflammation was more frequently diffuse.

To the authors' knowledge, this type of detailed and systematic histopathology classification has not been published in any other study. Classification of nasal inflammatory diseases into distinct categories based on the predominant inflammatory cell and cell hyperplasia has been arbitrary (Mackin 2004), for example, cases of LPR may not have lymphocytes or plasma cells as the most prevalent type of cell. This classification will, therefore, give more information about the type and cause of inflammation present giving an indication to the clinician about the stage of the disease and possible pathogenesis of the rhinitis in order to discuss therapy, progression and prognosis.

The two conditions were found to have similar histological appearance and only differed significantly in terms of fungal presence. This implies that the histological diagnosis can sometimes be difficult and that the clinician should always consider the results from other ancillary diagnostic tests, such as rhinoscopy and MRI, to reach the final diagnosis. Both diseases induce inflammation reaction on the nasal mucosa, however, if the sample is not representative, or if commensal fungi are present in the sample, the histopathology diagnosis can be misleading.

Further studies with a larger sample size should be made in order to confirm the statistical associations that were presented by this study. Since the nasal cavity is always in contact with bacteria, virus, pollen, dust, conidia of *Aspergillus* species and parasites, it would also be of interest to test the inflammation score in healthy animals in order to establish if a certain grade of inflammation should be considered normal by the histopathologist or clinician. In addition to this, it is important that other studies carried out by different histopathologists confirm the homogeneity of the results using this score to assess if it should be considered an important diagnostic tool for inflammatory nasal disease in the future.

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