Idiopathic lymphoplasmacytic rhinitis in 33 dogs

Author:
Remo Lobetti[1]

Affiliation:
[1]Bryanston Veterinary Hospital, Bryanston, South Africa

Correspondence to:
Remo Lobetti

Email:
rlobetti@mweb.co.za

Postal address:
PO Box 67092, Bryanston 2021, South Africa

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Idiopathic lymphoplasmacytic rhinitis (LPR) is recognised frequently in dogs with clinical signs typical of other chronic nasal diseases. The purpose of this study was to determine clinical signs, survey radiographic, rhinoscopic and histologic abnormalities and the response to therapy in dogs with LPR. It was a retrospective study of 33 client-owned animals of various breeds and ages that had been diagnosed with LPR. During the study period, a total of 110 dogs were diagnosed with nasal disease, of which 33 (30%) were diagnosed with idiopathic LPR. The median age was 9 years (range 2.3–17 years) and there were 15 female and 18 male dogs. The majority of dogs showed a mucoid nasal discharge, bilateral stertor and no overt radiographic changes. The most common finding on rhinoscopy was hyperaemic nasal mucous membranes with mucoid material accumulation within the nasal cavity. In all 33 dogs bacterial culture yielded no pathogenic bacteria and fungal culture was negative. Histologically, all 33 dogs showed lymphoplasmacytic infiltration within the nasal mucosa. All 33 dogs were treated with systemic and topical corticosteroids for varying lengths of time and dosing intervals. Eleven dogs were treated with concurrent cyclosporine and three dogs underwent allergy testing followed by desensitisation therapy. The best response was seen in the dogs that underwent desensitisation therapy, followed by those treated with corticosteroids and cyclosporine.

Introduction

Chronic nasal disease can be a common problem in dogs. Clinical signs are a combination of sneezing, nasal discharge, epistaxis, nasal stertor, paroxysmal reverse sneezing, coughing, halitosis, open-mouth breathing, facial deformities, facial pain, discolouration of the nares and exophthalmos (Burgener, Slocombe & Zerbe 1987; Tasker *et al.* 1999). Various diseases of the nasal cavity present with similar clinical signs, and no one sign is pathognomonic for any particular disease (Davidson, Mathews & Koblik 2000), rendering clinical diagnosis difficult (Lobetti 2009).

Common causes of chronic nasal disease in dogs are neoplasia, fungal rhinitis and idiopathic lymphoplasmacytic rhinitis (LPR), also referred to as inflammatory rhinitis (Bolln *et al.* 2003; Davidson *et al.* 2000; Meler, Dunn & Lecuyer 2000; Tasker *et al.* 1999; Windsor & Johnson 2006). Other less common causes include nasal foreign body, rhinitis secondary to dental disease, parasitic rhinitis (*Pneumonyssoides caninum*) and primary ciliary dyskinesia (Lobetti 2009; Pownder, Michelle & Crawford 2006).

Idiopathic LPR, with clinical signs typical of other chronic nasal diseases, is recognised frequently in dogs (Lobetti 2009; Windsor *et al.* 2004). Idiopathic LPR is characterised microscopically by infiltration of lymphocytes and plasma cells into the nasal mucosa, although variable numbers of neutrophils and eosinophils may also be present (Mackin 2004; Windsor *et al.* 2004). Histologically, idiopathic LPR closely resembles human non-polyploid chronic rhinosinusitis (CRS), where nasal tissue infiltration is dominated by lymphocytes and neutrophils, with eosinophilic inflammation being of minor importance (Rudack, Sachse & Alberty 2004; also see Peeters *et al.* 2007).

The aim of this retrospective study was to determine clinical signs, survey radiographic, rhinoscopic and histologic abnormalities and response to therapy in dogs with idiopathic LPR.

Materials and methods

The medical records of dogs that had been assessed for chronic nasal disease between January 2001 and December 2012 were evaluated retrospectively. In all dogs the following results were extracted from the records: history, full nasal and oral examination, survey radiographs of the nasal cavity, nasal culture results, antegrade and retrograde rhinoscopy and nasal biopsy histopathology. For continuity, the work-up was based on the previous study (Lobetti 2009). Additional criteria for inclusion were follow-up assessments and/or telephonic reports for a minimum of 6 months following the initial diagnosis and instituting therapy.

The nasal examination determined the type of nasal discharge, presence of nasal stertor, assessment of nasal patency and presence of facial asymmetry and/or pain. A full oral examination that included periodontal probing for occult dental disease was done under general anaesthesia to exclude the presence of oral masses and dental disease (Lobetti 2009).

Under general anaesthesia, two radiographic views were taken: a rostrocaudal skyline view of the skull to evaluate the frontal sinuses and an intra-oral dorsoventral view to evaluate the nasal cavity. After the radiographs were taken, a sterile swab for bacterial and fungal cultures was taken from each nasal cavity. The nasopharynx and choanae were then examined by retroflexed endoscopy using a flexible fibre-optic scope 7.9 mm in diameter and 1.3 m in length. The dorsal, middle and ventral meatus of both nasal chambers were examined by antegrade rhinoscopy using a 2.7-mm rigid arthroscope (Lobetti 2009). Endoscopy was used to assess the presence of inflammation, haemorrhage, foreign bodies, fungal plaques or masses.

Between five and ten biopsy samples of the nasal turbinate and mucosal tissue were collected from both nasal cavities using flexible 2-mm biopsy forceps. Histological examination of the nasal biopsies was performed on paraffin-embedded sections (6°µm) that were stained with haematoxylin and eosin. Special stains for fungi (Periodic acid-Schiff [PAS]), mycobacteria (Ziehl-Neelsen stain) and bacteria (Gram) were done if deemed necessary (Lobetti 2009).

Bacteria were considered to be normal flora if there was a sparse growth and/or if they were species that have been reported cultured from the nasal passages of normal dogs (Greene & Reinero 2006). Bacteria were considered pathogenic if there was a pure and heavy growth and/or if they were a species of bacteria not previously reported cultured from the nasal passages of normal dogs (Lobetti 2009).

A final diagnosis of idiopathic LPR was made on finding a lymphoplasmacytic infiltration within the nasal mucosa on histopathology, absence of fungi and pathogenic bacteria on culture and resolution of the rhinitis with systemic corticosteroids and/or cyclosporine therapy and/or topical corticosteroid therapy and/or desensitisation therapy without the use of any antibiotic therapy. Response to therapy was based on the degree of resolution of presenting clinical signs.

Results

During the study period, a total of 110 dogs were diagnosed with nasal disease, of which 33 (30%) were diagnosed with idiopathic LPR.

The median age was 9 years with a range of 2.3–17 years. Of the 33 dogs, 15 were female (45%) and 18 male (55%). The most common breeds identified were the dachshund (n = 9, 27%), Yorkshire terrier (n = 6, 18%) and Cocker spaniel (n = 4, 12%). Other breeds affected were German shepherd dog, Pomeranian, Maltese, Jack Russell terrier (two of each) and Staffordshire terrier, Fox terrier, French poodle, Cairn terrier, Rottweiler and Doberman (one of each). When compared with the general hospital population the Yorkshire terrier was significantly overrepresented (odds ratio of 4.55), whereas the dachshund was not.

Twenty-eight dogs (85%) showed a mucoid nasal discharge, 4 (12%) a mucopurulent discharge, and 1 (3%) epistaxis; 19 (57%) were bilaterally and 14 (43%) unilaterally affected. None of the dogs showed any facial deformity. Nasal stertor was bilateral in 23 (70%) dogs, unilateral in 7 (21%) and absent in 3 (9%).

Opacification of the nasal cavity on survey radiographs was bilateral in 6 (18%) and unilateral in 9 (27%) dogs, whilst 18 (55%) dogs showed no opacification. Six dogs (18%) showed trabecular destruction.

Abnormalities observed on antegrade rhinoscopy were hyperaemic nasal mucous membranes in 21 dogs, mucoid material accumulation in 20 dogs, mucopurulent material in 4, mucohaemorrhagic material in 1 and friable mucous membranes in 4. Retrograde endoscopy showed hyperaemic nasal mucous membranes in 2 dogs, mucoid material accumulation in 11, mucopurulent material in 2, mucohaemorrhagic material in 1 and no changes in 17 of the dogs.

No bacteria were cultured in 12 of the dogs and in the other 21 dogs only normal flora was cultured. Fungal culture was negative in all 33 dogs.

Histologically, all 33 dogs showed a lymphoplasmacytic infiltration within the nasal mucosa. In addition, five dogs also showed an eosinophilic infiltration.

All 33 dogs were treated with systemic and topical corticosteroids for varying lengths of time and dosing intervals. In all cases the initial dose of prednisolone was 1 mg/kg orally once a day for a period of 7–10 days, then tapered down to a minimum of 0.5 mg/kg on alternate days. Once the clinical signs resolved, the tendency was to stop the medication. Eleven dogs were treated with concurrent cyclosporine (5 mg/kg orally once a day for a minimum of 4 weeks and then on alternate days at the same dose). Three dogs underwent allergy testing followed by desensitisation therapy, according to standard protocol (Bio-Medical Services, 3921 Steck Avenue, Suite A-101, Austin, Texas, USA). The best response was seen in the three dogs that underwent desensitisation therapy (complete resolution), followed by those that were treated with cyclosporine (marked reduction and duration of signs). In the 19 dogs that were treated with corticosteroids only, the clinical signs were merely controlled and returned once the corticosteroids were discontinued.

Discussion

This study showed that idiopathic LPR is an important cause of chronic nasal disease in dogs and may be more common than previously believed, with clinical signs similar to those of other chronic nasal disorders. Of the total population that was evaluated in this study, idiopathic LPR was diagnosed in 30% of cases, which is higher than the 20% reported in a previous study (Lobetti 2009).

Idiopathic LPR is increasingly being recognised in dogs. The diagnosis is made by the histopathological identification of a lymphoplasmacytic infiltrate within the nasal mucosa and exclusion of other specific causes of chronic nasal disease (Lobetti 2009; Windsor & Johnson 2006). These criteria were applied in this study. Although the aetiology of idiopathic LPR has not been determined, infectious, allergic and immune-mediated mechanisms have been suggested (Windsor & Johnson 2006).

This study showed no predilection regarding sex. Idiopathic LPR tended to affect middle-aged dogs as the median age was 9 years, and the range 2.3–17 years. This is similar to two other studies in which the reported range was 3–10 years (Burgener *et al.* 1987) and 1.5–14 years with a median of 8.5 years (Windsor *et al.* 2004). The median age was not reported in the first study, as there were only five dogs. All three studies suggest that idiopathic LPR is generally a disease of middle-aged to older dogs. The current study showed a predilection toward the dachshund (27%) and Yorkshire terrier (18%), which is similar to a previous study (Lobetti 2009). However, in another study (Windsor *et al.* 2004) the German shepherd dog was overrepresented (27%) compared with the present study (6%).

As with previous studies (Lobetti 2009; Windsor *et al.* 2004), this study showed that idiopathic LPR is commonly a bilateral disease. The most common clinical findings were mucoid nasal discharge and stertor. The finding of mucopurulent nasal discharge in dogs with idiopathic LPR most likely reflects the chronicity of inflammation because bacterial culture of nasal samples often yields minimal to no growth and response to antibiotic therapy is poor (Windsor *et al.* 2004). These last two statements are supported by the present study. In this study, only one dog showed epistaxis. Previous studies have reported epistaxis in 1 out of 15 dogs (Lobetti 2009) and 2 out of 5 dogs (Tasker *et al.* 1999), whilst Windsor *et al.* (2004) reported epistaxis as primary or only complaint in 5 out of 15 dogs with idiopathic LPR.

In this study, the typical radiographic change was opacification of the nasal passages, which is in agreement with previous studies (Burgener *et al.* 1987; Tasker *et al.* 1999). There is some discrepancy in the literature as to the extent of turbinate destruction with chronic inflammatory rhinitis as turbinate loss is usually attributed to neoplasia or aspergillosis (Martin, Meek & Willeberg 1987); however, inflammatory rhinitis has been reported to cause turbinate destruction (Burgener *et al.* 1987; Lobetti 2009; Russo, Lamb & Jakovljevic 2000; Tasker *et al.* 1999). In this study and two previous studies (Burgener *et al.* 1987; Tasker *et al.* 1999), nasal turbinate destruction was uncommon in dogs with idiopathic LPR. Radiography seems to have a low sensitivity in differentiating inflammatory rhinitis from neoplasia or fungal rhinitis (Windsor *et al.* 2004).

The most consistent findings on antegrade rhinoscopy in this study were the finding of hyperaemic nasal mucous membranes and the accumulation of mucoid material within the nasal passages, as had been reported previously (Tasker *et al.* 1999). The most consistent finding on retrograde endoscopic examination of the nasopharynx and caudal nasal cavity in this study was the accumulation of mucoid material, although more than 50% of cases showed no overt abnormalities. Other specific rhinoscopic findings that have been reported include inflammation, excessive mucus and diffuse swelling (Tasker *et al.* 1999; Willard & Radlinksy 1999; Windsor *et al.* 2004), plaque-like lesions (Lent & Hawkins 1992) and mass-like lesions (Willard & Radlinksy 1999).

Histologically, all dogs in this study showed lymphoplasmacytic infiltration within the nasal mucosa, whilst five dogs also showed eosinophilic infiltration. A previous study reported mild inflammation and epithelial changes such as hyperplasia, erosion and lymphocytic exocytosis (Windsor *et al.* 2004). Another study reported epithelial hyperplasia, squamous metaplasia, ulceration and various degrees of submucosal fibrosis (Burgener *et al.* 1987). Neutrophilic infiltration was not evident in this study, as opposed to the study of Windsor *et al.* (2004), which reported neutrophilic infiltration in a large number of dogs and concluded that the neutrophils could have represented chronic inflammation and secondary overgrowth of superficial bacteria. However, only 40% of the dogs in that study had a bacterial nasal culture done. The study by Windsor *et al.* (2004) also reported eosinophilic infiltration in 11% of the dogs, which is similar to the 15% seen in the current study.

In this study, the best response to therapy was seen in the dogs that underwent desensitisation therapy (complete resolution), followed by those that were treated with corticosteroids and cyclosporine (marked reduction and duration of response). In the dogs that were treated with corticosteroids only, the clinical signs were merely controlled and returned once the corticosteroids were discontinued. The study by Burgener *et al.* (1987) reported that four of five dogs improved when treated with prednisone, but the study by Windsor *et al.* (2004) reported a poor response to glucocorticoid treatment. That study, however, concluded that it did have follow-up data on response to therapy for a large number of cases. The use of antibiotics in one study (Windsor *et al.* 2004) was neither effective nor sustained in eliminating clinical signs but helped to reduce the nasal discharge and the type in some dogs, from mucopurulent to serous. It is thus most likely that antibiotics merely reduce

secondary bacterial colonisation without diminishing the nasal discharge caused by idiopathic LPR. In people with CRS and allergic rhinitis the use of topical corticosteroids is more beneficial than antihistamines and antibiotics for achieving symptomatic improvement in children and adults, with systemic corticosteroids indicated in severe cases (Mori *et al.* 2010).

The definitive cause of idiopathic LPR is unknown; chronic inflammatory response to infectious agents, high microbial load, inhaled irritant, pollutant, immune dysregulation and allergens are all presented as hypotheses (Burgener *et al.* 1987; Mackin 2004; Windsor *et al.* 2004). An immune-mediated (rather than irritant or allergic) pathogenesis has also been suggested (Burgener *et al.* 1987), but poor glucocorticoid response in most dogs with idiopathic LPR does not support this hypothesis (Windsor *et al.* 2004; also see Peeters *et al.* 2007). Although rhinitis is a common manifestation of allergy in humans, there is little reported evidence of allergic rhinitis in dogs. Upper respiratory tract signs have been described as signs of allergy in only two reports (Patterson & Harris 1999; Willemse 1984), both of which focused on the predominance of allergic dermatitis and conjunctivitis. In this study, the management of the disease with corticosteroids and cyclosporine would imply that the underlying pathogenesis of idiopathic LPR would be either allergic or an immune-mediated disease. Complete resolution of clinical signs with desensitisation therapy would support an underlying allergic pathogenesis, but no conclusion can be drawn as only three dogs underwent desensitisation therapy in this study. Possible further evidence of an allergic aetiology would be that anti-inflammatory doses rather than immune-suppressive doses of corticosteroids were used in this study. Based on this study, it seems that idiopathic LPR needs to be managed with long-term corticosteroids and cyclosporine therapy if the underlying triggers are not identified and suppressed with desensitisation therapy.

In humans, the predominating inflammatory cell type in most cases of CRS is the eosinophil (Hamilos & Lund 2004). In non-allergic CRS, the cytokine profile in sinus tissue is that of a partial T helper type 2 (Th2) immune response with production of interleukin 5 (IL-5) and IL-13 but little production of IL-4 (Hamilos & Lund 2004). In seasonal and perennial allergic rhinitis in humans, the profile of T-cell cytokines in nasal tissue or mucus fits the classic Th2 profile, with production of IL-4, IL-5 and IL-13 (Hamilos & Lund 2004; also see Peeters *et al.* 2007). Thus, in humans, CRS is considered an inflammatory rather than an infectious disease, as microbes found in the nasal cavity play a role in initiating or perpetuating mucosal inflammation (Shin *et al.* 2004; also see Mercier 2012 *et al.* 2012). However, it has been shown that IL-5 is not produced by T cells in CRS (Peeters *et al.* 2007; Riechelmann *et al.* 2005; Rudack *et al.* 2004). Although IL-5 is known to play a critical role in antigen-induced tissue eosinophilia (Matsumoto *et al.* 2003), eotaxins are more important than IL-5 for eosinophil-selective chemo-attraction (Rothenberg & Hogan 2006) and IL-5 alone does not promote tissue accumulation of eosinophils (Yang *et al.* 2003). A recent study showed that there was an increase in IL-5 transcription in nasal tissue of dogs with idiopathic LPR, which might reflect a type I hypersensitivity response (Th2 immune response) occurring within the nasal mucosa (Peeters *et al.* 2007). In addition, the amount of eotaxin-2 and eotaxin-3 gene transcription was not increased in tissue from dogs with idiopathic LPR. This could account for the lack of a significant eosinophilic infiltration within the nasal mucosa of dogs with idiopathic LPR, despite increased IL-5 messenger ribonucleic acid (mRNA) expression (also see Peeters *et al.* 2007).

The innate immune system of the sinonasal mucosa plays a major role in upper airway immunity (Ooi, Wormald & Tan 2008). Recognition of conserved structures present on bacterial, fungal, viral and protozoal organisms is possible by pattern-recognition receptors, which are expressed by a wide range of immune and non-immune cells such as respiratory epithelial cells (Sha *et al.* 2004). The two best-characterised classes of pattern-recognition receptors are the Toll-like (TL) receptors and the nucleotide-binding oligomerisation domain (NOD)-like receptors. A recent study showed that both the TL and NOD receptors are expressed in the nasal mucosa of normal dogs and that dysregulation of the genes encoding these receptors may contribute to development of idiopathic LPR (Mercier *et al.* 2012).

Conclusion

This study concluded that the Yorkshire terrier appears to be predisposed to idiopathic LPR and that desensitisation therapy and cyclosporine together with corticosteroids give the best long-term outcome.

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Competing interests

The author declares that he has no financial or personal relationship(s) which would have inappropriately influenced the writing of this article.

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