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Eosinophilic Bronchopneumopathy in Dogs

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Eosinophilic bronchopneumopathy was diagnosed in 23 young dogs. Clinical signs included cough, gagging, and retching in all dogs, dyspnea in 21 dogs (91%), and nasal discharge in 12 dogs (52%). The most common radiographic findings were a moderate to severe bronchointerstitial pattern (68%, 13 of 19 dogs). Bronchoscopic findings included the presence of abundant yellow-green mucus or mucopurulent material (70%, 16 of 23 dogs) and severe mucosal thickening with an irregular or polypoid appearance (52%, 12 of 23 dogs), with partial airway closure during expiration in 3 dogs (13%). Peripheral blood eosinophilia was noted in 14 of 23 dogs (61%). Inflammatory cells in brush or bronchoalveolar lavage fluid cytologic preparations comprised more than 50% eosinophils in 14 of 23 dogs (61%), and 20–50% eosinophils in 6 dogs (26%). Eosinophilic infiltration of the bronchial mucosa was observed in biopsies from 19 dogs and was graded as mild (37%, 7 dogs), moderate (32%, 6 dogs), or severe (32%, 6 dogs). The mean serum immunoglobulin A concentration was almost double that of a population of 20 healthy dogs of various breeds. Oral glucocorticoids were administered on alternate days with progressive tapering of the dose; the dosage at maintenance varied between 0.1 and 1.0 mg/kg every other day. No relationship was found between the duration of clinical signs and the maintenance dosage or the cytologic and histopathologic grades.

Key words: Bronchial mucosa; Bronchoalveolar lavage; Lung; Pulmonary infiltrates with eosinophilia; Respiratory diseases.

Eosinophilic bronchopneumopathy (EBP) is a disease characterized by eosinophilic infiltration of lung and bronchial mucosa that has traditionally been referred to as pulmonary infiltrates with eosinophilia (PIE). PIE is described in humans[1–5] and dogs,[6–10] and includes a range of different diseases that vary in presentation from mild to severe, transient to chronic, and self limiting to sometimes fatal. The diseases are all considered to be manifestations of immunologic hypersensitivity.

In humans, the diseases are divided into categories[1]; however, the terminology is confused and the classifications are imperfect because many of these disorders overlap.[4] In the dog, an attempt to subdivide the diverse disorders collectively referred to as eosinophilic lung disease was proposed by Bauer.[8] Few recent review publications[7–10] exist and isolated cases have been described.[6,11,12]

The causes and mechanisms of pulmonary hypersensitivity are poorly understood in both human and veterinary medicine. Suspected and known causes of pulmonary hypersensitivities in humans and animals include fungi, molds, drugs, bacteria, and parasites, including canine heartworm disease.[8,13] However, in most cases the inciting antigens are not identified. The purpose of this retrospective study was to report the clinicopathologic features and response to treatment in 23 dogs with EBP.

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Materials and Methods

Twenty-three dogs with naturally occurring EBP were evaluated retrospectively. All dogs were client-owned animals presented to the Liège University Veterinary Small Animal Teaching Hospital between 1992 and 1998. All dogs had to meet the following inclusion criteria: presence of complaints such as cough, dyspnea, exercise intolerance, and nasal discharge; physical and radiographic features compatible with disease of the lower respiratory tract; cytologic evidence of bronchial or bronchoalveolar eosinophilic infiltration and presence of eosinophilic infiltrate in bronchial biopsies; as well as exclusion of other specific causes of eosinophilia, such as nonrespiratory causes or a tumoral process. Dog 18 was included despite a lack of histologic lesions because cytology was diagnostic. Historical factors considered were the occurrence and duration of primary complaints (general condition, cough, dyspnea, nasal discharge) and response to previous medications. Clinical evaluation consisted of physical examination, thoracic radiography, bronchoscopy, and, in cases of nasal discharge, rhinoscopy.

Clinical scores were based on general condition (normal attitude and appetite [0], depressed animal and/or decreased appetite [1], unresponsive animal and/or anorexia [2]), cough (frequency: occasional [0], frequent [1], persistant [2]; intensity: weak [0], harsh [1]), gagging (0 or 1), respiratory distress (absent [0], decreased exercise tolerance [1], moderate [2], severe at rest [3]), and auscultatory findings (normal [0], increased sounds [1], abnormal sounds [2]). Nasal discharge (absent [0], serous [1], yellow to green mucus or mucopurulent material [2]) was also assessed. The same examination was repeated after at least 30 days of therapy, and the response to treatment was assessed (absence of symptoms, improvement, no change, or worsening).

Left lateral and ventrodorsal radiographs of the thorax were obtained in 19 dogs. The radiological signs were assessed by 2 of the authors (FS and CC) using a blinded technique. The changes were classified into 3 patterns: interstitial, bronchial, and broncho-interstitial. The severity of radiographic change within each pattern was graded as mild (1), moderate (2), or severe (3). The presence of peribronchial cuffing, alveolar infiltration, and bronchiectasis was also assessed

The minimal clinicopathologic database consisted of a complete blood count. Fecal flotation and Baermann sedimentation were performed in 12 animals to detect parasite eggs or larvae. Three dogs had spent time out of Belgium and Luxembourg during the preceding 3 years, so occult heartworm disease was ruled out using the linked immunosorbent assay antigen test.[a]

All dogs were anesthetized using various anesthetic protocols. A premedication with intramuscular or intravenous administration of medetomidine[b] (10–30 mg/kg) or acepromazine[c] and metadone[d] or

midazolam[e] (2 mg/kg IV) was used. Anesthesia was induced and maintained by IV administration of thiopental[f] up to 5 mg/kg or propofol[g] up to 6 mg/kg for induction, and 0.1–0.2 mg/kg for maintenance. In most dogs, a 5-minute preoxygenation period was used and oxygen saturation was controlled during the procedure. During recovery, the dogs received supplementary oxygen as needed.

In all dogs, bronchoscopic examination was performed using a flexible fiberoptic pediatric bronchoscope[h] with an outer diameter of 4.8 mm. In most dogs, a videoendoscope[i] with an outer diameter of 12 mm was also used to allow video recording of the bronchi. A scoring system was used to define the macroscopic bronchoscopic features: presence of material (no material [0], presence of mucus or mucopurulent material [1], presence of abundant yellow-green mucopurulent material [2]), mucosal changes (no changes [0], congestion [1], thickening of the mucosa [2], severe thickening and irregular aspect [3], polypoid aspect [4]), and airway closure during expiration (no obvious closure [0], exaggerated closure [1], dramatic closure [2]).

A protected catheter brush was inserted into the biopsy channel of the bronchocope to obtain material for cytology. Lobes selected for subsequent lavage were determined by radiographic findings and gross bronchoscopic lesions. One to 3 aliquots of 10–25 mL of 0.9% warmed sterile saline solution were used. Each aliquot was instilled through a 3-way stopcock into the biopsy channel and directly retrieved into a sterile container by low-power pump aspiration. Part of the lavage fluid retrieved was sent directly for microbiological culture in all but 1 case. Another part of the lavage fluid was centrifuged and smears were prepared from the pelletal cells and stained with Wright-Giemsa stain. Alternatively, cytologic preparations were made from the brush samples. In either case, a cytologic grade was assigned, based on determining the percentage of eosinophils by counting inflammatory cells (n = 100) in a good-quality field where maximal numbers of eosinophils were present: no eosinophils (0), 1–20% eosinophils (1), 20–50% eosinophils (2), more than 50% eosinophils (3). Perendoscopic biopsy of the bronchial mucosa was also obtained and fixed in 10% neutral buffered formalin. Hematoxylin and eosin–stained sections were prepared for histopathologic examination. Histopathologic findings were graded as normal microscopic appearance (0), eosinophilic infiltrate with mild inflammatory change (1), eosinophilic infiltrate with moderate inflammatory change (2), eosinophilic infiltrate with severe inflammatory change (3). In the dogs with concomittant nasal discharge, nasal cavities were investigated using a rhinoscope[j] and samples were obtained for bacterial and cytologic examinations (brush or imprint cytology).

In 17 dogs, serum immunoglobulin (IgG, IgM, IgA) concentrations were analyzed using single radial immunodiffusion.[14] These values were log transformed and compared with those obtained in 20 healthy dogs from the same geographic area. This control population was aged 18 months to 9 years, and included 10 males and 10 females of various breeds.

Initial treatment included steroids in all dogs and most dogs received antibiotics concurrently. The animals were treated with antibiotics if indicated by clinical examination, or a positive culture and cytologic evidence of purulent material in the bronchi, or the presence of an alveolar pattern on thoracic radiographs. Antibiotic therapy was administered for 1–8 weeks. The initial choice was amoxicillin clavulanate[k] (12.5–15 mg/kg q12h orally), but antibiotics were eventually changed, on the basis of bacterial cultures and sensitivity, as well as on radiographic and clinical examinations performed on revisit. Oral corticotherapy[l] was initiated in all dogs at a dosage of 1 mg/kg q12h during the 1st week; the same dose was given on alternate days during the 2nd week, and then 1 mg/kg q24h was administered on alternate days during the 3rd week, after which the dose was gradually decreased until maintenance levels were achieved. All animals were treated with fenbendazole[m] (50 mg/kg q24h for 3 days).

Follow-up details were obtained from 22 dogs. Eleven dogs were not examined at the University Clinic, but contact by phone with the owners and the referring veterinarian allowed us to complete the scored questionnaire. In the remaining 11 cases, the animals were reexamined 1–3 times for clinical, blood, and radiographic investigations; in 4 cases, bronchoscopy was repeated.

Statistics and Analysis

Total number, age, sex, weight, and breed of dogs admitted over the same time period were not available for comparison to the animals in this case series. Normality-probability plots and Kolmogorov *D* test for goodness-of-fit to the normal distribution were obtained (Proc UNIVARIATE, SAS[15]) for the variables cytologic and histopathologic grades, age in months, steady-state dosage, and duration of the signs. Spearman rank correlation and chi-squares were used to estimate the linear association relationship between cytologic and histopathologic scores, age, signs, duration, and dosage. A Student's *t*-test for unpaired data was used to compare the log-transformed serum immunoglobulin concentrations in dogs with EBP with those of normal dogs of various breeds. The level of significance was chosen as $P = .05$.

Results

Siberian Huskies accounted for 26% (6) of the dogs. Two Alaskan Malamutes were included. The dogs also included 3 German Shepherd Dogs, 2 Dachshunds, 2 Brittanies, 2 mixed-breed dogs, 1 German Shorthaired Pointer, 1 Briard, 1 Beauceron, 1 Whippet, 1 Labrador Retriever, and 1 Rottweiler. Thirteen dogs were females (1 neutered), and 10 were male (1 neutered). The weights of the dogs varied from 7 to 38 kg (mean ± SD = 24.3 ± 9.3 kg). Age at the time of diagnosis ranged from 9 months to 8 years (mean ± SD = 4.5 ± 2.3 years). Age at disease onset ranged from 6 months to 8 years (mean ± SD = 3.3 ± 2 years) and interval between disease onset and diagnosis was 1 month to 6 years (mean ± SD = 18 ± 17.2 months).

At initial presentation, the most common clinical signs were cough (100%, 23 of 23 dogs), dyspnea (91%, 21 of 23 dogs), and nasal discharge (52%, 12 of 23 dogs). General body condition was normal in 17 cases. Cough was occasional, frequent, or persistant in 13% (3 dogs), 39% (9 dogs), and 48% (11 dogs) of the dogs, respectively. Cough was generally harsh and was always followed by gagging. In dog 21, dyspnea, fatigability, and depression were partly attributed to concomittant congenital heart disease. In early cases, cough with gagging and retching were the only reported clinical signs. Auscultation was normal in 9 dogs (29%), increased lung sounds were noted in 5 (22%), and abnormal lung sounds were present in 9 dogs (29%) (crackles in 7 dogs and crackles and wheezes in 2 dogs). Twelve dogs had nasal discharge; the discharge was serous in 3 and mucus or mucopurulent or yellow or green in 9.

All dogs had diffuse radiogaphic pulmonary lesions (Figs 1, 2). Fifteen of 19 dogs (65%) had a mixed broncho-interstitial pattern (mild, moderate, and severe in 2, 3, and 10 dogs, respectively). Alveolar infiltration was found in 8 of 19 dogs (40%) and peribronchial cuffing in 4 of 19 dogs (21%). Bronchiectasis was seen in 5 dogs (26%) and marked thickening of the bronchial walls occurred in 4 dogs (21%).

Leucocytosis was observed in 11 of 23 dogs (48%) and varied between 15,500 and 47,200 cells/μL (mean ± SD = 25,556 ± 10,279 cells/μL). Neutrophilia was observed in 6 dogs (26%) and varied between 15,312 and 40,592 cells/μL (mean ± SD = 24,159 ± 10,059 cells/μL). Eo-

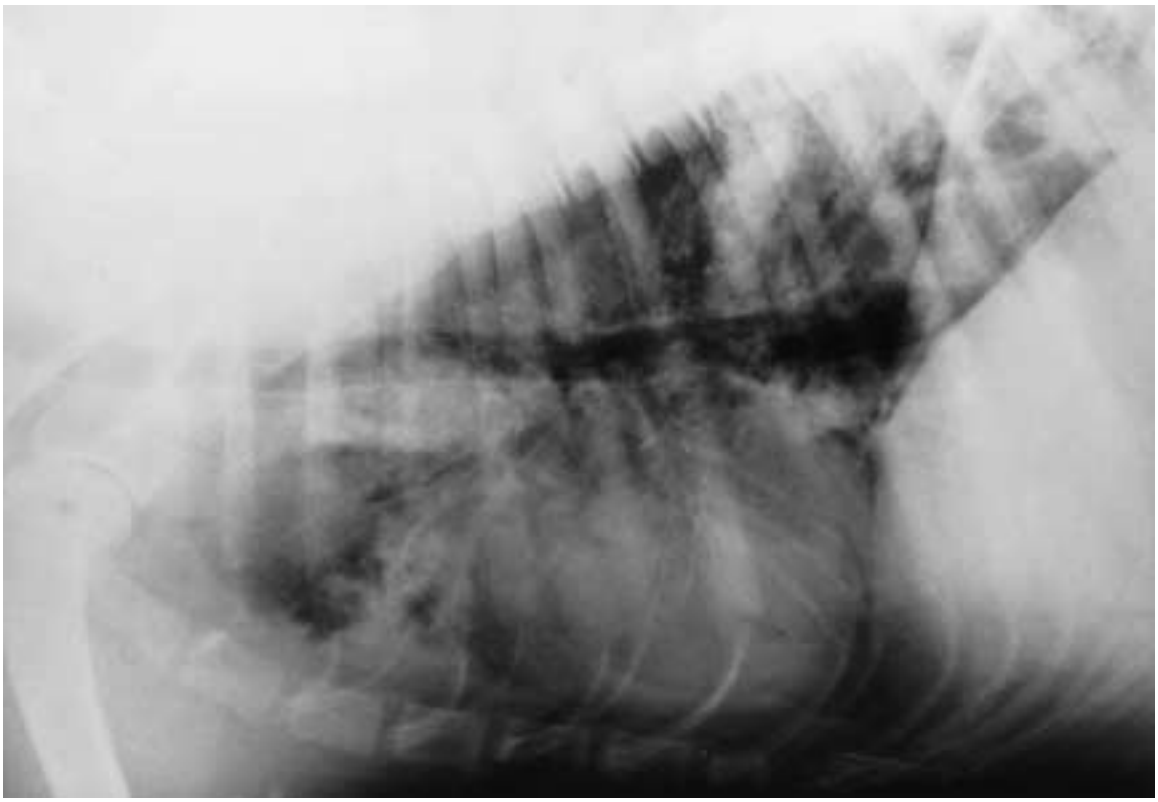

Fig 1. Right lateral projection of the thorax of a dog with eosinophilic bronchopulmonary disease that demonstrates a severe bronchointerstitial pattern. Some peribronchial cuffing and alveolar infiltration are also noted.

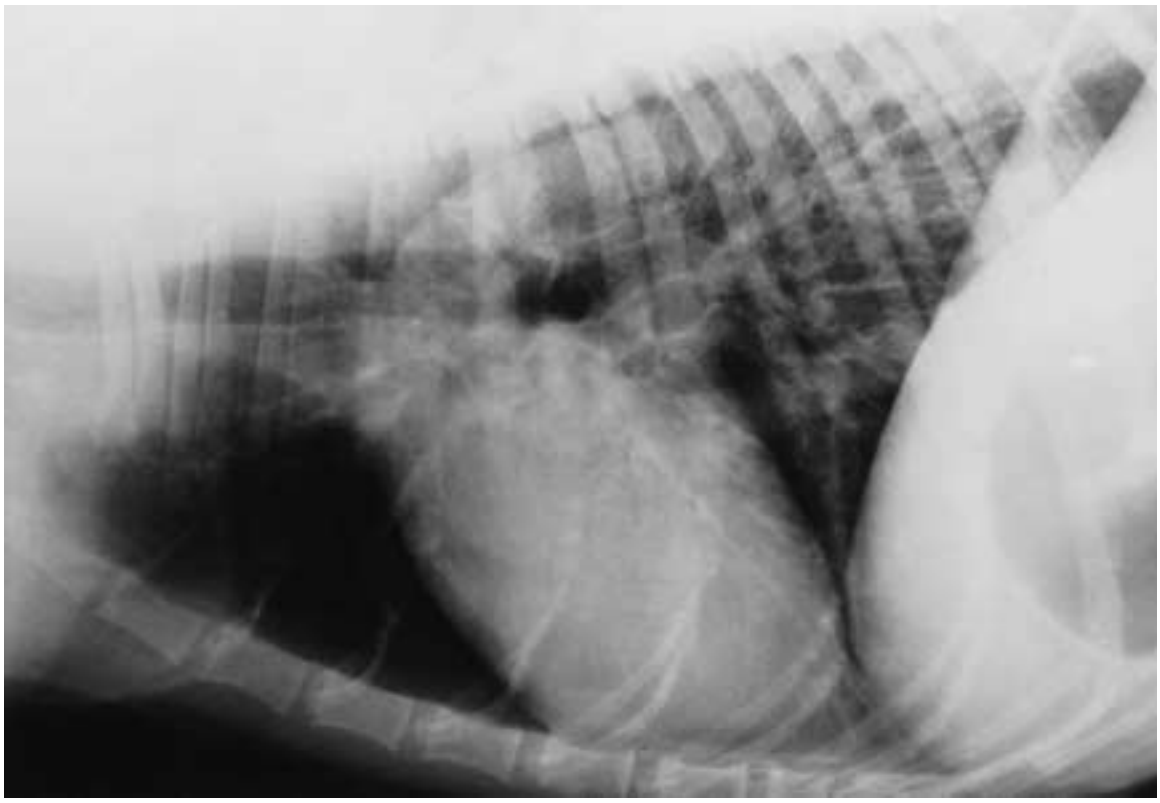

Fig 2. Right lateral projection of the thorax of a dog. The thorax shows a severe bronchointerstitial pattern with the presence of bronchectasis.

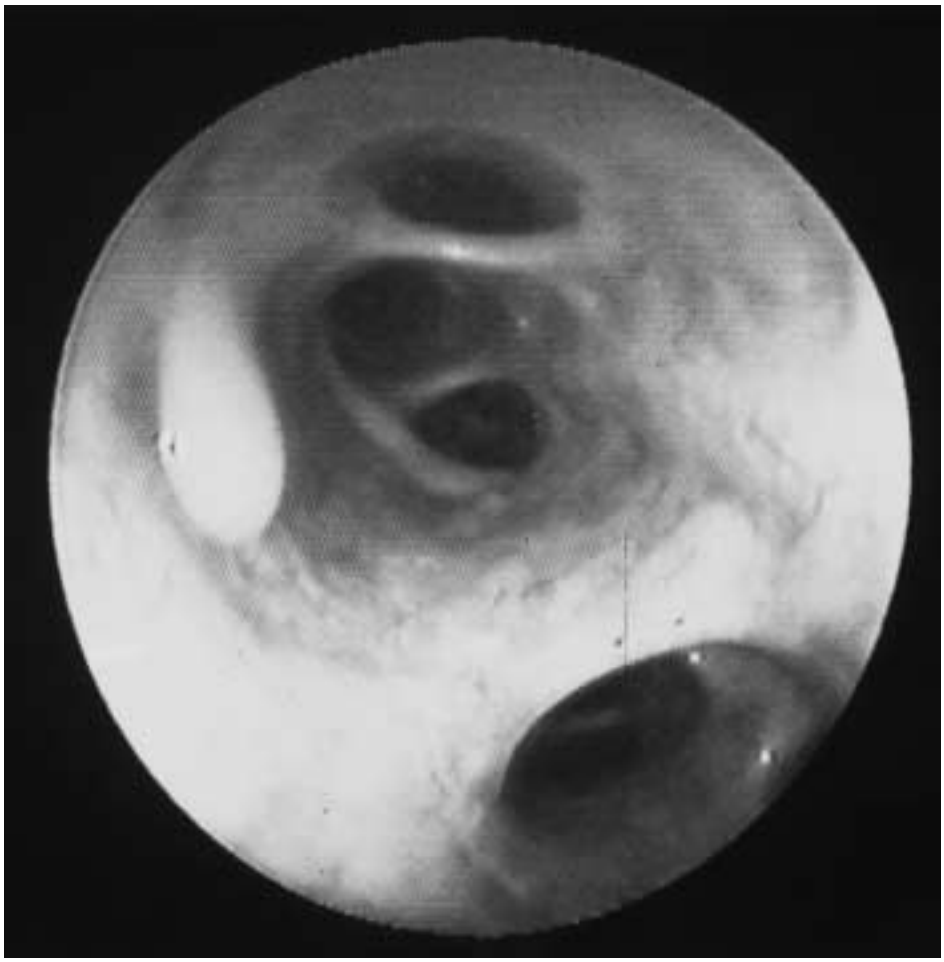

Fig 3. Endoscopic view of the bronchi of a dog with eosinophilic bronchopulmonary disease, showing some thick yellow material.

sinophilia was present in 14 (61%) of the 23 dogs and varied between 804 and 13,038 cells/μL (mean ± SD = 3,358 ± 3,598 cells/μL). Fecal flotation was negative in all but 5 of the 12 dogs tested, in which *Giardia* or *Coccidia* oocysts were detected.

Bronchoscopic findings included the presence of abundant yellow-green mucus or mucopurulent material (70%, 16 of 23 dogs), severe thickening with irregularity or polypoid change to the mucosa (52%, 12 of 23 animals), and exaggerated airway closure during expiration in 8 (35%) animals and virtual closure during expiration in 3 (13%) animals (Figs 3–5). Microbiological cultures from bronchial samples were negative for fungi and mycobacteria, except in 2 of 22 cases where *Aspergillus* species was cultured. Aerobic bacterial cultures were negative in 8 of 22 cases (36%) and yielded *Pseudomonas aeruginosa* as single agent in 3 cases and in combination with *Klebsiella pneumoniae* in another case; *K pneumoniae* in 5 dogs, coupled with *Aeromonas* spp in 2 cases, with *Escherichia coli* in another case, and with *Serratia marcescens* in another case; *Xhantomonas maltophilia* together with *Bacillus* spp in 1 case; and β-hemolytic *Streptococcus* group C associated with *Acinetobacter* in 1 case and with *Proteus mirabilis* and *Citrobacter* in 1 case.

Bronchial brush cytology or cytology from the bronchoalveolar lavage fluid (BALF) were assessed in all cases. The cytologic score was 1 in 3 cases (13%) and 2 in 6 cases (26%), whereas in the remaining 14 samples (61%) 50–90% of the cells were eosinophils. In each case populations of segmented neutrophils, macrophages, and respiratory epithelia with background quantities of mucus were also found (Fig 6). Scattered mast cells were also commonly observed in cytologic preparations. Microorganisms were not identified in any sample.

Histology of bronchial biopsies was assessed in all but 3 cases, but in biopsy the tissue had normal microscopic appearance (grade 0). Biopsies from 7 dogs had evidence of a mild inflammation (grade 1) characterized by edema of the superficial lamina propria with active extravasation of eosinophils from superficial mucosal vessels. Eosinophils were often clustered immediately beneath the respiratory epithelium or were actively migrating through epithelium to the luminal surface. Scattered mast cells were also present in the superficial lamina. The biopsies from 6 dogs (32%) had evidence of moderate inflammation (grade 2), where in addition to the eosinophil infiltrate, numerous plasma cells, lymphocytes, macrophages, and mast cells ewre present within the superficial mucosa (Fig 7). Six dogs (32%) had severe bronchial inflammation (grade 3) with marked thickening of the mucosa. In these biopsies either

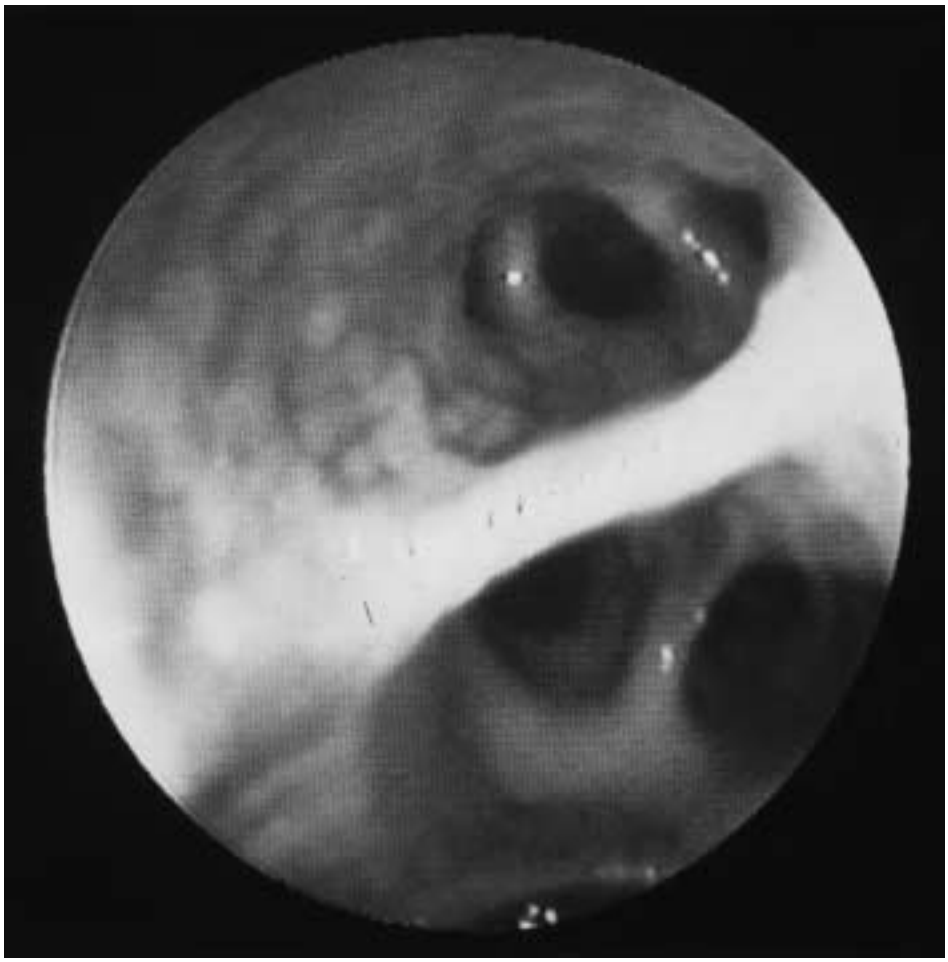

Fig 4. Endoscopic view of the bronchi of a dog with eosinophilic bronchopulmonary disease, showing thickening of the mucosa with an irregular surface.

hyperplasia, squamous metaplasia, or ulceration of epithelium with hyperplasia of glandular elements were present. An intense inflammatory infiltrate extended to the deep margins of the biopsies. This was generally dominated by macrophages and eosinophils, but plasma cells and lymphocytes were scattered throughout. Other changes observed in grade 3 biopsies included microhemorrhage, the presence of hemosiderin-laden macrophages, collagenolysis, and fibrosis.

Rhinoscopy was performed in 10 of the 12 dogs with nasal discharge. The nasal mucosa was normal in 1 animal, congested and edematous in 3 dogs, and mucus or mucopurulent material was also present in 6 dogs. Brush cytology revealed the presence of eosinophils in 4 of the 10 dogs. Bacterial cultures from the nasal cavities were positive in 4 of the 10 dogs and yielded various organisms.

At the time of diagnosis, dogs with EBP had concentrations of serum IgG, IgM, and IgA greater than those in a control group of healthy dogs of various breeds (Table 1). But this difference was significant only for IgA.

Among the 22 dogs available for follow-up, initiation of treatment did not change the clinical signs in 2 dogs, and induced total disappearance of the signs in 5 dogs. In the remaining 15 dogs, cough and dyspnea improved within 1–3 days after initiation of the treatment. Decreased exercise tolerance persisted in 6 dogs. Nasal discharge persisted despite continued treatment in 5 of the 12 animals affected. Moreover, the additional use of intranasal therapy with saline, mucolytics, or vasoconstrictive or corticosteroid agents was not successful in 2 of them. The weight of the dogs increased by 0–20% of the initial value within the 1st month to the 1st 3 years of treatment. Prednisolone dosage at steady-state varied between 0.1 and 1 mg/kg every other day. In 11 dogs, the treatment was discontinued; 3 did not relapse after periods of 1.5 months to 3 years, 3 relapsed immediately, and 5 relapsed within 3 months.

Peripheral blood eosinophil counts returned to normal in all dogs that initially had eosinophilia 1 month after the start of the treatment. Three of these dogs were reevaluated 3 months to 2 years later, and eosinophilia had returned, despite the apparent response to steady-state corticotherapy.

Bronchoscopy was repeated in 4 dogs. In dog 5, 1 month after the start of the treatment, the mucosa was normal, and intrabronchial material was decreased. In dog 19, 2 months after the start of the treatment, the mucosa was thick but the polypoid change was dramatically reduced, and no more material was found in the bronchi. In dog 20, 2 months after the start of the treatment, no material was present and

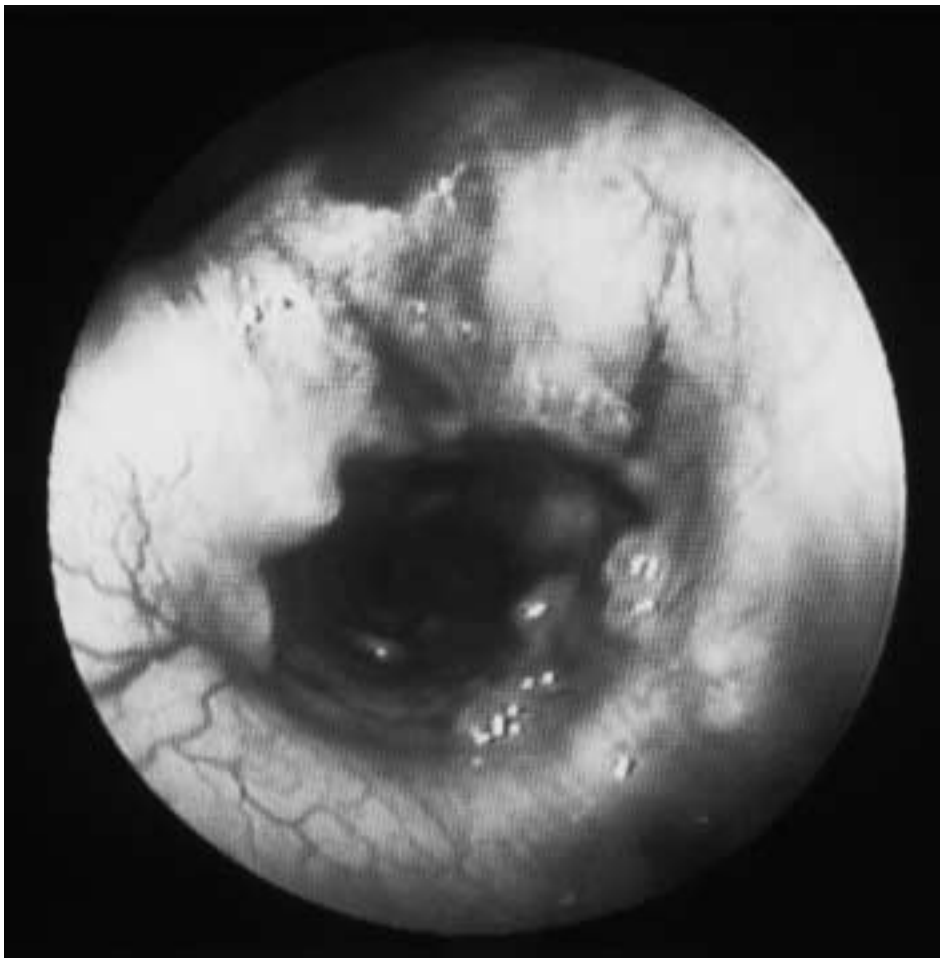

Fig 5. Endoscopic view of a bronchus of a 7-year-old female Dachshund with eosinophilic bronchopulmonary disease showing polypoid aspect, during inspiration. In the same dog, during expiration, airway closure was virtually total.

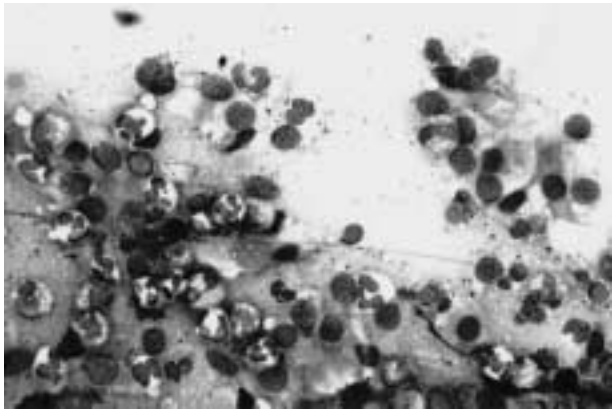

Fig 6. Cytology of a smear prepared from the pelletted cells of bronchoalveolar lavage fluid. The cytological grade, based on determining the percentage of eosinophils by counting inflammatory cells (n = 100) in a good-quality field where maximal numbers of eosinophils were present, was 3 (more than 50% eosinophils). Wright-Giemsa stain. 150×.

the mucosa had returned to normal. Finally, in dog 21, bronchoscopical findings 2 months after the start of the treatment showed a thickened mucosa, but no material. No relationship was found between the duration of clinical signs, age, and the maintenance dosage or the cytologic or histopathologic grades.

Discussion

Siberian Huskies and Alaskan Malamutes were breeds predominantly affected with EBP, but this does not reflect the population distribution in our clinic, where these breeds represent less than 2% of the canine patients (Clercx, unpublished data). Alaskan Malamutes and Siberian Huskies also are among the breeds in which eosinophilic pulmonary granulomatosis has been reported.[16] Eosinophilic pulmonary granulomatosis is a nodular lung disease that shares some features with PIE, such as evidence of pulmonary eosinophilic infiltration and often peripheral eosinophilia, but is differentiated by more severe clinical signs, by the presence of multiple masses of various sizes on thoracic radiography, and by a poorer prognosis.[16–19] However, eosinophilic pulmonary granulomatosis could represent an uncontrollable, progressive form of PIE.

In our series, the mean age at presentation, as well as the

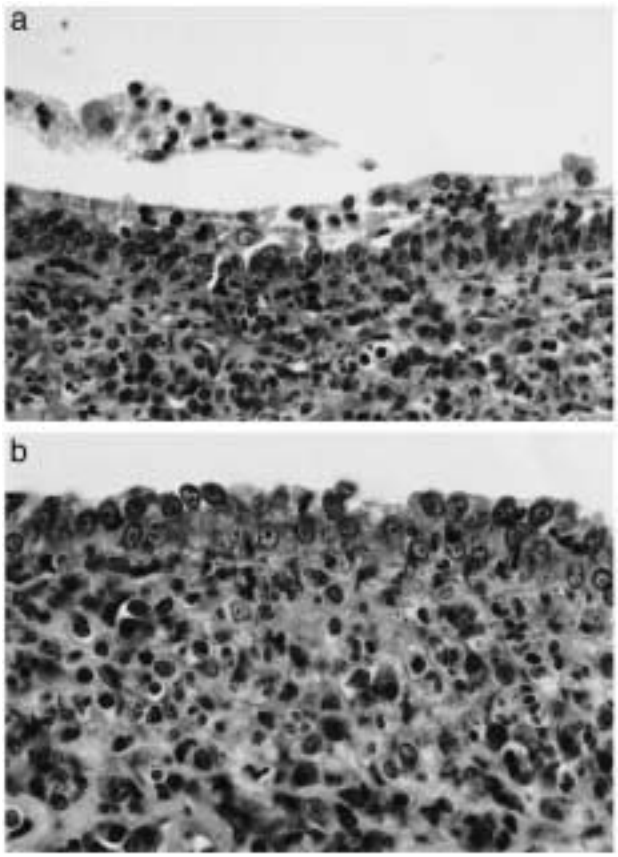

Fig 7. Histopathology of a bronchial mucosal biopsy with moderate inflammation (grade 2) with extravasation of eosinophils from superficial mucosal vessels and migration of these cells through the respiratory epithelium into the bronchial lumen. Eosinophils within the mucosa are accompanied by plasma cells, lymphocytes, macrophages, and mast cells. Hematoxylin and eosin. 187×.

age at the onset of clinical signs, were lower than those previously reported by Corcoran et al,[10] much lower than those reported for classical forms of chronic bronchitis,[20–22] and also lower than those reported in eosinophilic pulmonary granulomatosis.[16–19] It is interesting to note that canine atopic dermatitis, a disease with defined type I hypersensitivity pathogenesis, occurs at a similar age to the dogs in this study.[23]

The clinical presentation of dogs in this series was variable. Usually, the general condition was good and cough was harsh and followed by gagging and retching. In acute cases, gagging and retching were sometimes the main complaint, extending the differential diagnosis to dyspeptic problems. In the more chronic cases, history indicated that the use of cortiocosteroids typically led to temporary relief.

In our series, a mixed moderate to severe broncho-interstitial pattern was most frequently observed on thoracic radiography. The radiographic findings in this study were more severe than those reported in the classical forms of chronic bronchitis, in which a normal appearance or thickened bronchial walls are most commonly found.[20–22] Radiographic findings were also different from those reported in cases of eosinophilic pulmonary granulomatosis in which multiple masses of various sizes, hilar lymphadenopathy, and pleural effusion are reported.[16–19] In 8 of the 19 dogs examined, alveolar infiltration was noticed. In PIE, eosinophilic infiltrates can be limited to the airways or the alveoli or can be present in varying degrees in both structures.[6] In 5 of the 8 dogs with alveolar infiltration, other clinicopathologic findings were eventually compatible with a concomittant bacterial infection. Therefore, it was not possible to determine accurately the number of cases with eosinophilic alveolar infiltration, because alveolar tissue was not available from any of our dogs for histopathologic analysis.

Typical macroscopic bronchoscopic features included the presence of abundant yellow-green mucous or mucopurulent material, severe thickening of the mucosa with irregular or polypoid surface, and airway closure during expiration. Some of these findings, such as thickening and irregularity of the airway mucosa and partial collapse of bronchi during tidal volume expiration, can be considered as a reflection of chronic bronchitis.[21,22] However, the presence of yellow-green mucus or mucopurulent material and polypoid mucosal changes were considered more specific for EBP, although polypoid proliferations have been occasionally described in advanced cases of nonspecific chronic bronchitis.[24]

Bronchial cytologic examination showed the presence of many eosinophils, and other cells including neutrophils, macrophages, and lymphocytes. Although the catheter brush technique has not been specifically invented for cytology, brush cytology provide useful results about bronchial processes, complementary to those obtained by BAL cytology. Although a population of clinically normal dogs apparently exists with relative eosinophil counts in BALF as high as 19%,[25] the percentage of eosinophils observed from the cytologic analysis of the BALF in our dogs was generally much higher. In the few cases where the percentage of eosinophils observed was lower than 20% but higher than 10% (3 cases), eosinophilic infiltration was seen in the bronchial biopsies.

Cytologic and histopathologic grades were not correlated. This could reflect the random choice of 1 single site for

Table 1. Mean (± SD) log serum immunoglobulin levels (mg/mL serum).

	Dogs with EBP at time of Diagnosis (n = 17)	Normal Dogs of various breeds (n = 20)	Normal Laboratory Beagles (n = 10)
Log serum IgG	1.05 ± 0.29	1.02 ± 0.27	0.89 ± 0.16
Log serum IgM	0.07 ± 0.25	−0.55 ± 0.34	−0.06 ± 0.21
Log serum IgA	−0.47 ± 0.33[a]	−0.71 ± 0.25	−0.60 ± 0.25

EBP, eosinophilic bronchopneumopathy; IgG, immunoglobulin G; IgM, immunoglobulin M; IgA, immunoglobulin A.

[a] Significantly different from normal dogs of various breeds ($P = .05$, Student's *t*-test for unpaired data).

mucosal biopsy, as proposed to the more widespread area sampled by the BAL procedure. Of interest was the observation of increased numbers of eosinophils and mast cells in brush cytology samples from the nasal cavity of 4 of the 10 dogs with upper respiratory signs. This may suggest that a similar pathogenic mechanism underlies the lesions that occur at different sites in the respiratory tract in dogs with EBP.

Absolute blood eosinophilia was not always present, even in dogs that were not receiving corticosteroids. Accordingly, and as already reported for PIE, eosinophilia is not a prerequisite for the diagnosis of EBP.[8,10] In some cases of chronic (cryptogenic) pulmonary eosinophilia in humans, peripheral blood eosinophilia was absent in the presence of tissue eosinophilia.[2] In eosinophilic pulmonary granulomatosis, peripheral eosinophilia is generally much higher and may be higher than 20,000/mL, whereas in the dogs of this study, only 1 dog had an eosinophil count over 10,000/mL.[16]

The causes and mechanisms of pulmonary hypersensitivity are poorly understood in both human and veterinary medicine. Type I (immediate hypersensitivity) is probably the most common mechanism of immune injury, but types II, III, and IV also seem to play varying roles.[7–9,26,27] The study of immune-mediated diseases in humans and experimental animals has recently been reshaped by recognition of the fact that 2 subsets of helper T lymphocytes exist (the so-called Th1 and Th2 lymphocytes) that selectively trigger diametrically opposed types of immune response, defined by the ability of these cells to release a unique array of cytokines. Evidence now exists that the Th1/Th2 phenomenon occurs in dogs.[28] Conditions involving type 1 hypersensitivity, such as atopic dermatitis, are typical examples of a Th2-regulated immune response, which drives the immune system towards the synthesis of antibody of the IgE class.[29] A similar mechanism could underlie the bronchopulmonary eosinophilic diseases and is well defined in human asthma[30] and murine models of eosinophilic lung disease.[31]

The role of eosinophils in including the clinical signs of EBP is also poorly understood. Eosinophilic infiltration could be initiated by immunologic reactions between antigen and IgE-coated mast cells. The tissue infiltration of eosinophils may be controlled by soluble chemotactic factors such as interleukin and eotaxin, a recently discovered chemokine with potential importance in the inflammation associated with type I hypersensitivity. Eotaxin is expressed in diseased tissues where eosinophils accumulate, including the lungs of nondomestic animals with hypersensitivity disorders.[32]

Suspected and known causes of pulmonary hypersensitivities in humans and animals include fungi, molds, drugs, bacteria, and parasites.[13] The inciting causes (triggering mechanisms) of such disorders could be somewhat different in Belgium from those in the United States, or other parts of Europe, where a greater prevalence exists of heartworm disease and mycotic and lung parasitic diseases.[7–8,11,16] Indeed, a high incidence of occult heartworm infection occurred in previously reported cases of PIE[6–8,11] and also in dogs with eosinophilic pulmonary granulomatosis.[16–19] In our series, a low incidence of the disease in the study area suggests that EBP was not associated with heartworm. Helminth infections have been established as causes of human pulmonary eosinophilic syndrome,[33] but the fecal parasites found in this study (*Giardia and Coccidia*) were unlikely to be the cause of the disease because they are found in many healthy dogs, and because their elimination did not lead to cessation of the disease. *Aspergillus* can produce a variety of pulmonary lesions including eosinophilic pneumonia.[34] In the United Kingdom, allergic aspergillosis is a common cause of eosinophilic pneumonia in humans, whereas other fungi have rarely been regarded as causative of eosinophilic pneumonia.[4] *Aspergillus* could possibly play a role in canine eosinophilic bronchopulmonary disease because this organism was found in the BALF in 2 dogs. On the other hand, the presence of this organism could also have been incidental.

Various chemical agents have been associated with PIE syndromes of limited or prolonged duration in humans.[34] In dogs, drug exposure can provoke a pulmonary hypersensitivity.[7] Although we are not aware of previous medication in the 23 dogs examined, we cannot exclude the influence of drugs, particularly in the 3 dogs where no relapse was noted after treatment was discontinued.

Because most dogs were treated with antibiotics and steroids at the same time, it is difficult to assess whether bacterial infection of the bronchi or lung plays a major role in eosinophilic bronchopulmonary diseases in dogs.

The role of aeroallergens in EBP is not clear. In our series, skin testing was performed in only 6 dogs, and yielded positive results in 2 (data not shown). It is now known that clinically normal dogs may give positive reactions in the intradermal skin test.[35] Also, the allergens identified by intradermal testing may not be the same as those causing the pulmonary hypersensitivity. This may reflect factors such as a difference of mast cell distribution between the lungs and skin[7] or the route of allergen exposure, and therefore assays for serum allergen–specific IgE may have a role in the diagnosis of canine EBP.

Serum immunoglobulin concentrations were measured on a single occasion, which does not take into consideration possible day-to-day variations, as has been shown for secreted immunoglobulins.[36] In spite of this possible restriction, numerous dogs in this population had elevated serum immunoglobulins, which may reflect the contribution of immunologic mechanisms to the disease pathogenesis. The elevated serum IgA in these dogs could reflect the heightened immune response at the respiratory surface in EBP. However, it does not necessarily rule out a deficiency in mucosal (bronchial) IgA, because serum and mucosal IgA concentrations are poorly correlated in the dog.[36] Dogs with atopic dermatitis also have elevated serum IgG, but may have reduced serum IgA concentration.[37]

The response to steroid therapy was generally very good. In 20 of 22 dogs available for follow-up, cough and dyspnea improved within days of initiating the steroid treatment. The cough totally disappeared in most dogs, but sometimes still occurred after exercise; decreased exercise tolerance sometimes persisted. Nasal discharge was sometimes more refractory to treatment because in 5 of 12 dogs with nasal discharge, this sign persisted despite continued steroid treatment. The maintenance dosage of prednisolone

ranged between 0.125 and 0.5 mg /kg on alternate days, or even less regular administration schedules. In 8 dogs, relapse occurred within months after drug discontinuation, but in 3 dogs, it did not recur up to 2 years after discontinuation.

The patients that responded to treatment were not specifically those in which the time from onset of clinical signs until diagnosis was the shortest. According to Bauer,[8] the younger patients are at the time of the diagnosis, the more difficult they will be to manage. He also noted that they become easier to manage by the time they reach middle age. These observations were not concordant with ours: indeed, the age at the time of diagnosis did not seem to influence the response to treatment. In 1 dog of this series, treatment was irregularly administered after the initial administration, and the dog remained symptomatic with only minimal improvement. This is in agreement with Bauer's[8] observation that the poorest responses to treatment occur in cases that are irregularly treated, with repeated abrupt cessation of high doses of medication without tapering, or with irregular parenteral administration of repository steroid injections.

Therefore, a major goal of management is client education. Because the achievement of total lack of signs is rare, and because therapy is always individualized, the owner must assume significant responsibility and actively participate in the animal's care. Regular oral corticotherapy must be used on alternate days with progressive tapering of the dose, rather than irregular oral or parenteral high doses.

In order to better define the course and prognosis of canine eosinophilic bronchopneumopathies and to offer an appropriate therapy, further studies are needed. Many points need to be addressed; in particular a comprehensive immunologic study of canine cases is lacking and histopathologic examination of lung biopsies would probably allow a better definition of different diseases of the syndrome. The potential role of pneumoallergens is still unclear. Skin testing and serologic detection of allergen-specific IgE should be a routine part of the clinical investigation in order to assess if hyposensitization has a place in the treatment of these diseases. The potential benefits of bronchodilators or other therapies still need to be defined.

Footnotes

[a] Speed Diro, SDI6, BVT, Forlab, Brussels, Belgium
[b] Domitor, SmithKline Beecham Animal Health, Louvain-La-Neuve, Belgium
[c] Combistress, Phenix, Brussels, Belgium
[d] Mephenon, Federa SC, Brussels, Belgium
[e] Dormicum, Roche, SA, Brussels, Belgium
[f] Pentothal, Abbott, Louvain-La-Neuve, Belgium
[g] Diprivan, Zeneca, Destelbergen, Belgium
[h] Fujinon BRO-YP2, Onys SA, Brussels, Belgium
[i] Fujinon E67-FP3, Onys SA, Brussels, Belgium
[j] Optique Hopkins, 27018A, Karl Storz, Anvers, Belgium
[k] Synulox, Smith Kline Beecham, Louvain-La-Neuve, Belgium
[l] Methylprednisolone, Moderin, Upjohn, Puurs, Belgium
[m] Panacur, Hoechst Animal Health Benelux, Brussels, Belgium

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