https://doi.org/10.17221/136/2020-VETMED

Pulmonary eosinophilic granulomatosis in a dog

Carlos Fernando Agudelo, Ladislav Stehlik, Zita Filipejova, Benicie Koskova, Marie Sterbova, Michal Crha*

Small Animal Clinic, University of Veterinary Sciences Brno, Brno, Czech Republic

**Corresponding author: cagudelo@vfu.cz*

Citation: Agudelo CF, Stehlik L, Filipejova Z, Koskova B, Sterbova M, Crha M (2022): Pulmonary eosinophilic granulomatosis in a dog. Vet Med-Czech 67, 150–155.

Abstract: A two-year-old female Prague Ratter dog was presented for evaluation of cough, exercise intolerance and worsening dyspnea. A previous treatment with antibiotics did not resolve the clinical signs. A diagnostic approach revealed peripheral eosinophilia, endoscopic bronchial changes, and bronchoalveolar lavage with eosinophilic inflammation. Thoracic radiographs revealed a solitary mass and bilateral interstitial lung pattern. These radiographic findings were confirmed by computed tomography and ultrasound-guided biopsy of the lung mass. Treatment with prednisolone and azathioprine was initiated. Two months afterwards, the granuloma was no longer detectable radiographically. All medication was gradually discontinued after nine months and currently, after almost three years, the dog remains free of clinical signs.

Keywords: allergy; bronchoalveolar lavage; eosinophilia; immunosuppression; tomography

The terms "eosinophilic pneumonia" (EP) and "pulmonary eosinophilia" loosely encompass a broad range of infectious and noninfectious pulmonary conditions that involve infiltration of the eosinophils into the lungs, often with accompanying peripheral blood eosinophilia (Akuthota and Weller 2012; Reinero 2019). A few studies have carefully tackled the spectrum of eosinophilic lung diseases (among other interstitial diseases) in dogs and cats, and suggest a classification based on haematology, diagnostic imaging, bronchoscopy, bronchoalveolar lavage (BAL) and cytology findings (Johnson et al. 2019; Reinero 2019). According to these data eosinophilic lung diseases can be roughly divided in eosinophilic bronchitis (EB), eosinophilic bronchopneumopathy (EBP), EP and pulmonary eosinophilic granulomatosis (PEG). Moreover, there may be some controversy about whether PEG is a form of EP (Reinero 2019). It is unclear whether these various forms of pulmonary eosinophilia share the same etiopathogenesis or represent distinct disease processes (Reinero 2019). The characteristics of PEG among others include more severe clinical signs, nodular infiltration obliterating the normal lung architecture, airway eosinophilia and in general, a poor response to therapy (Neer et al. 1986; Moon 1992; Akuthota and Weller 2012; Mesquita et al. 2015; Johnson et al. 2019; Reinero 2019).

The most common identifiable cause of PEG is parasitic infection, especially heartworm disease (Moon 1992; Johnson et al. 2019). Dogs or cats of any age may be affected, although it is more common in dogs less than three years of age and predominately females (Sykes et al. 2001; Wallace et al. 2012). Rottweilers, Siberian Huskies and Alaskan Malamutes may be more likely to develop EP than other breeds (Moon 1992; Sykes et al. 2001; Wallace et al. 2012; Katajavuori et al. 2013; Adamama-Moraitou et al. 2015). It is possible that antigenic sources can trigger a hypersensitivity reaction, such as bacteria, fungi, parasites, inhaled allergens or drugs (Akuthota and Weller 2012) and neoplasia (Fina et al. 2014). One study reported PEG secondary to mediastinal lymphoma (Wallace et al. 2012).

Supported by the Internal Creative Agency of the University of Veterinary Sciences Brno (Project No. FVL/Crha/ITA2019).

https://doi.org/10.17221/136/2020-VETMED

The clinical presentation usually involves slowly progressive respiratory signs with a chronic cough, difficulty in breathing, and exercise intolerance. Diffuse bilateral crackles can be auscultated in the lungs on physical exam. Exercise exacerbates the coughing and results in dyspnea (Waddle et al. 1992). Diagnosis is based on the signalment, history, clinical signs, diagnostic imaging, bronchoscopy, BAL and lung biopsy. Radiographs show one or multiple pulmonary nodules and/or masses of variable location and size (DeNault 2000; Fina et al. 2014; Reinero 2019). An alveolar pattern and lung consolidation with or without hilar lymphadenopathy may also be found (DeNault 2000). Other findings include pleural fissure lines, and in rare cases cranial mediastinal and intratracheal masses (Fina et al. 2014). Computed tomography (CT) can aid in the diagnosis of PEG. Interestingly, the CT findings for PEG were very similar to those in some cases of EBP, where nodules, diffuse bronchiectasis and bronchial obstruction by fluid or tissue were also found (Katajavuori et al. 2013; Fina et al. 2014).

The final diagnostic test that can be performed is a lung aspiration or lung biopsy that will predominantly show eosinophilic inflammation with or without other inflammatory cells (Akuthota and Weller 2012; Johnson et al. 2019; Reinero 2019). It is important to perform heartworm and faecal examination to rule out parasitic lung disease (DeNault 2000). To the authors' knowledge this patient is among the first cases to describe complete remission from PEG in a dog.

Case presentation

A two-year-old female Prague Ratter dog was presented to the Small Animal Clinic at the Faculty of Veterinary Medicine, University of Veterinary Sciences Brno, Czech Republic for worsening of acute onset of cough, tachypnea, fever and mixed dyspnoea that had lasted one week. The dog was initially unsuccessfully treated in another practice with antibiotics.

Clinically the dog was mentally depressed, the mucous membranes were pink and mild expiratory restrictive dyspnea and tachypnea were present. On auscultation there were increased bronchovesicular sounds on both sides. The temperature was normal. Possible differential diagnoses pointed to several lower respiratory tract diseases of a diverse aetiology including inflammatory, infectious, neoplastic, bleeding, parasitic, degenerative, and immune-mediated diseases (i.e., EBP). An initial database and diagnostic tests to narrow the differential diagnoses included thoracic radiographs, a complete blood count (CBC) and serum chemistry screen.

The thoracic radiographs showed a bilateral interstitial pattern and a well-marginated soft-tissue opacity mass in the cranial right lung lobe (Figure 1). The possible causes that were contemplated were granulomatous pneumonia, primary and metastatic pulmonary neoplasia, immune-mediated pulmonary disease, pulmonary thromboembolism, and pulmonary haemorrhage. A lung ultrasound dis-

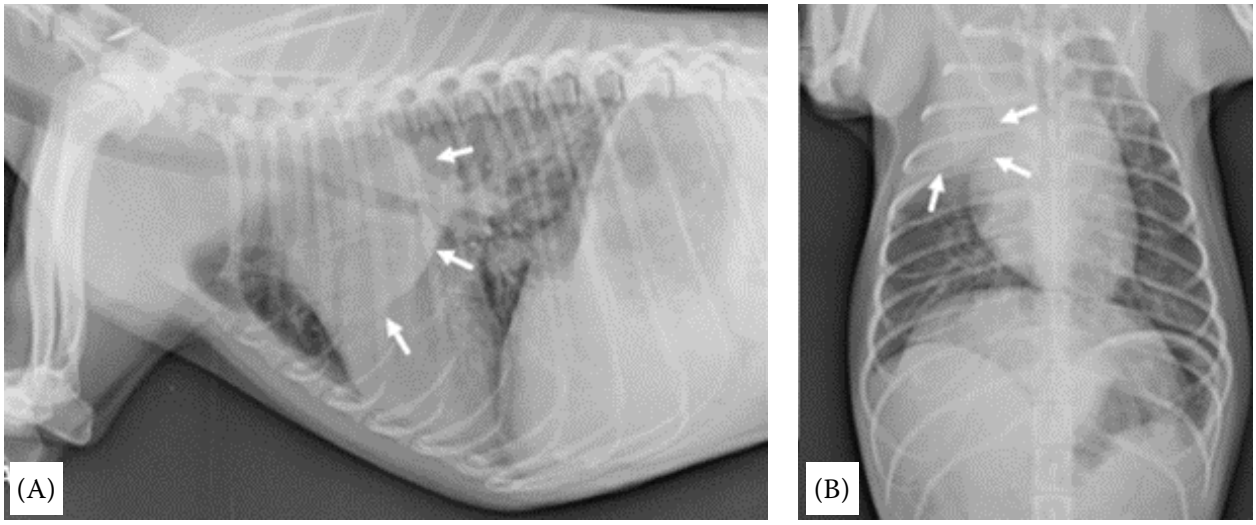

Figure 1. Right laterolateral (A) and ventrodorsal (B) view of the thorax
A well circumscribed soft-tissue opacity mass is observed in the right cranial lung lobe (arrows). There is also unstructured interstitial pulmonary pattern in the caudal lung lobes

https://doi.org/10.17221/136/2020-VETMED

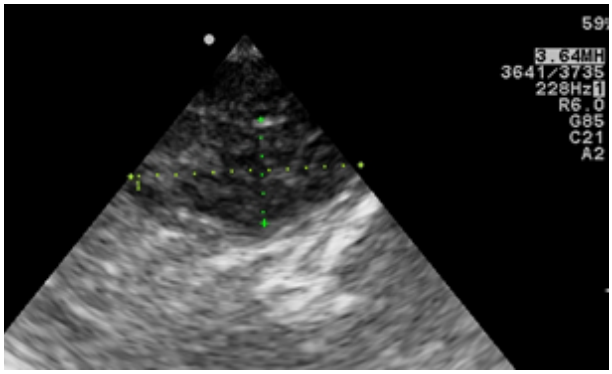

Figure 2. Ultrasound of the affected right cranial lung lobe (sector transducer, 2–5 MHz)
There is a well-defined hypoechoic mass of 1.9 × 2.5 cm in size

played an approximately 2 cm round hypoechoic mass-like lesion on the right hemithorax at the right cranial lung lobe (Figure 2).

The CBC showed normal leukocyte count with eosinophilia (2.18 × 10^9/l, reference range: 0–0.6 × 10^9/l); biochemistry was unremarkable. Differential diagnoses for the eosinophilia in this dog included reactive eosinophilia secondary to allergic, parasitic, infectious, or neoplastic disorders, EBP, eosinophilic granulomatous disease, dirofilariosis and idiopathic eosinophilic disorders such as hypereosinophilic syndrome (HES).

The faecal examinations (flotation and sedimentation), Knott's test for microfilaria and enzyme-linked immunosorbent assay (ELISA) serology to *Dirofilaria immitis* and *Angiostrongylus vasorum* (IDEXX Laboratories, Inc, Westbrook, Maine, USA) were negative.

The patient was hospitalised for a bronchoscopy and CT. The patient underwent general anaesthesia, positioned in sternal recumbency and a whole-body scan was performed (LightSpeed 16; GE Healthcare, Milwaukee, WI, USA). Non-ionic iodinated contrast agent (Xenetix 350; Guerbet, Roissy CdG Cedex, France) was applied at a dose of 700 mgI/kg using a power injector (MCT Plus; Medrad, Indianola, PA, USA).

A mass lesion was confirmed in the right cranial lung lobe with evidence of an interstitial pathology in all the lung lobes. There was no contrast enhancement of the mass in the right cranial lung lobe (Figure 3).

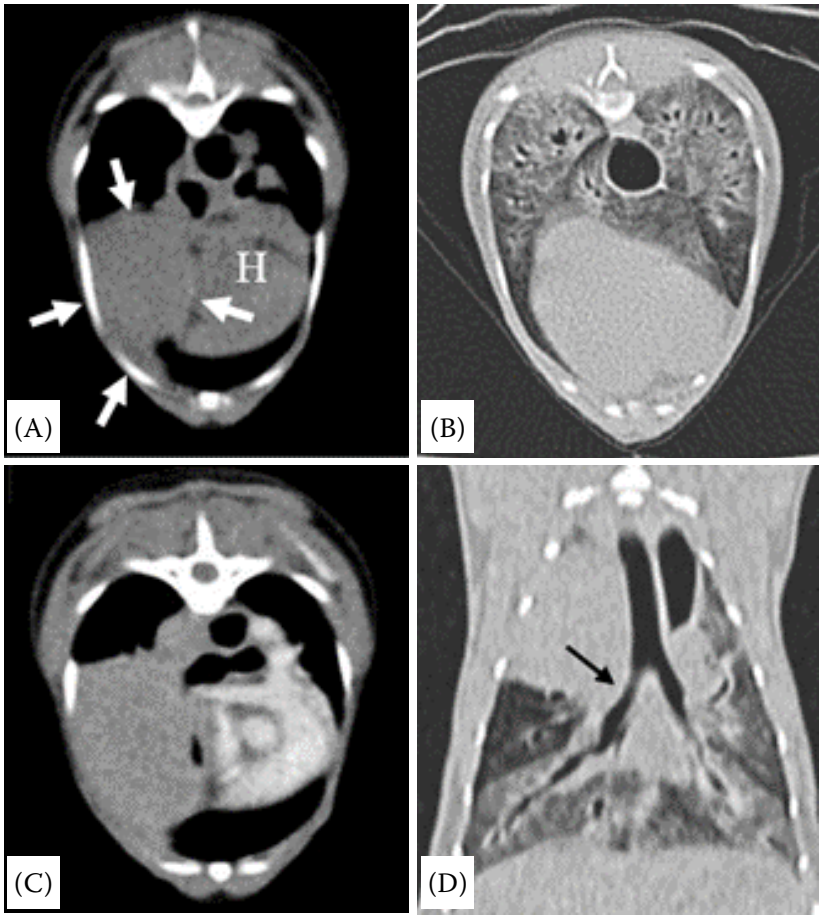

Figure 3. Computed tomographic images of the thorax
(A) Pre-contrast transversal CT image in a narrow soft-tissue window (WW350, WL40) showing a soft tissue attenuating mass (white arrows; 43 HU) in the right cranial lung lobe at the level of the heart (H). (B) Pre-contrast transversal CT image in a wide window (WW2000, WL400) showing the increased density of the caudal and accessory lung lobes, a ground-glass appearance. (C) Contrast enhanced transversal CT image in a narrow soft-tissue window (WW350, WL40) at the same level as in (A). There is only mild contrast enhancement of the mass (61 HU). (D) Dorsally reformatted pre-contrast CT image in a wide lung window (WW2000, WL400). The mass in the right cranial lung lobe mildly deviates the trachea to the left (arrow). The right caudal bronchus has an irregular diameter (parts of narrowing and dilation resembling bronchiectasis) and there is an increased, ground-glass appearance of the remaining lung lobes

https://doi.org/10.17221/136/2020-VETMED

A bronchoscopy also was performed in sternal recumbency with a flexible endoscope (Olympus bronchoscope BF-PE; Olympus, Tokyo, Japan). There was an intraluminal mass lesion in the right cranial lobar bronchus, mild presence of mucous secretion and a mild erythema in the distal trachea and in both mainstem bronchi (the right bronchus more affected than the left). Warmed sterile saline (2–3 ml/kg body weight) and air were injected through the biopsy channel into the airway for all left and right lobar bronchi. Further, an ultrasound-guided fine-needle aspirate of the mass was performed revealing a large presence of eosinophils. The cytological examination of the bronchial lavage specimens stained with a Wright Giemsa and a Gram stains showed an average of approximately 60% of eosinophils, macrophages 15%, lymphocytes 15% and neutrophils 10%. The ultrasound-guided fine-needle aspiration samples of the cranial right lung lobe showed 43% lymphocytes, 27% neutrophils, 18% eosinophils, 7% mastocytes and 2% plasmocytes. No infectious agents were identified on the cytological examination and subsequent quantitative bacterial and fungal culture. The above-mentioned changes suggested the presence of an eosinophilic granuloma.

Treatment with prednisolone (Prednicortone 1 mg/kg p.o., b.i.d.; LelyPharma B.V., Lelystad, The Netherlands), azathioprine (Imuran 2 mg/kg p.o., s.i.d.; Aspen Pharma Trading Limited, Dublin, Ireland) and famotidine (Famosan 0.5 mg/kg p.o., s.i.d.; Pro. Med Cs, Prague, Czech Republic) was initiated. The clinical signs started improving after two days of therapy. Within two months, the granuloma was no longer detectable by ultrasound or radiographs (Figure 4). The repeated CBC were normal with the eosinophil counts 0.25×10^9/l. After eight months of therapy the residual radiographic abnormalities were minimal (mild bronchial pattern). All the medication was gradually tapered and stopped after nine months. Twelve months after diagnosis the patient came in for regular vaccinations (canine distemper virus CDV, infectious canine hepatitis CAV-1, canine parainfluenza CPiV, canine parvovirus CPV leptospirosis: *Leptospira canicola, L. grippotyphosa, L. icterohaemorrhagiae,* and *L. pomona*). Five minutes after the vaccination the dog started having facial angioedema, skin erythema and laboured respiration. The patient received oxygen therapy and a single dose of dexamethasone (Dexadreson 0.2 mg/kg i.m.; Intervet International B.V.. Boxmeer, The Nethrelands) was administered.

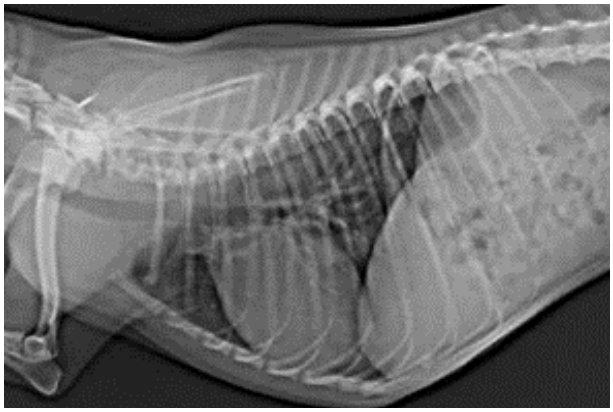

Figure 4. Follow-up radiographs of the patient after eight months of treatment showing resolution of the mass and a mild bronchial pattern in the caudal lung lobes

After two hours, the clinical signs resolved. At the time of writing the manuscript, the dog remains disease-free for almost three years.

DISCUSSION

Canine PEG is one important aetiology of interstitial lung diseases (ILD) in dogs and cats and is currently considered a rare disease, where the aetiology remains obscure with poor prognosis due to rapid relapses (Reinero 2019). Efforts to unify a classification that contemplates eosinophilic lung syndromes among other ILD have been made (Johnson et al. 2019; Reinero 2019); the readers are encouraged to review the cited literature for a more comprehensive understanding. We reached a diagnosis after filling the criteria for PEG as described elsewhere (Johnson et al. 2019; Reinero 2019), including the radiographic, ultrasound and CT detection of a lung mass, peripheral eosinophilia without leukocytosis in CBC, a higher number of nucleated cells and eosinophils in BAL fluid. Other findings reported for dogs with eosinophilic disease (Johnson et al. 2019) such as mucous erythema and secretion in the airways, airway collapse and radiographic infiltrates and bronchiectasis were also diagnosed. However, not all dogs with PEG will show eosinophilia on CBC (Sykes et al. 2001; Reinero 2019). Initial antibacterial therapy in this case may have helped to rule out a bacterial infection as a source of eosinophilia in spite of a history of possible infection-like signs like fever, inappetence, or dyspnoea. Also, a possible correlation with bacterial or fungal infections and parasitic

https://doi.org/10.17221/136/2020-VETMED

infestations appears unlikely (Katajavuori et al. 2013) due to the results of different tests.

The pathophysiology of EP is currently unclear; however, the literature suggests increases in cytokine responses from T-helper type 2 lymphocytes (predominantly IL-5, IL-10, and IL-13) and low IL-2 and IFN-g responses in type 1 cells (Pornsuriyasak et al. 2014). Besides there may be a connection among pulmonary eosinophilia and other systemic manifestations of allergic disease in human beings (Campos and Pereira 2009) and we hypothesise the same situation in our patient based on the literature reports (Sykes et al. 2001). A very low number of human beings vaccinated against influenza have developed ILD and at least 50% of them had pre-existing respiratory disorders (Pornsuriyasak et al. 2014). Interestingly, some of the patients reported respiratory failure due to EP. It is possible that the PEG of our report may have been a possible manifestation of systemic immune process because the same dog had an anaphylactoid reaction to a normal vaccination after one year of PEG remission.

Thoracic radiographs in our patient demonstrated interstitial pattern and a large mass, which also has been reported in literature. Also, bronchial and alveolar pattern and bronchiectasis can be found in radiographs (Johnson et al. 2019) (Figure 1). Other differential diagnoses for pulmonary nodules seen on radiographs would also be fungal diseases or a metastatic neoplasm (DeNault 2000) and for this reason, an ultrasound-guided lung biopsy and bronchoscopy with BAL were necessary to make a definitive diagnosis. For the same reasons, a CT scan was also performed showing a wider variety of CT features that have been previously described in PEG patients including nodular parenchymal lesions and bronchiectatic airways identified within the masses (Katajavuori et al. 2013; Reinero 2019). The bronchoscopy findings were similar to those reported in a meta-analysis where all dogs with intraluminal bronchial masses were diagnosed with PEG (Reinero 2019).

Other differential diagnoses for eosinophilic lung disease are acute or chronic allergic bronchitis, diffuse infiltrative neoplasm, mononuclear granulomatous disease such as systemic lupus erythematosus, infectious diseases like rickettsiosis, atypical bacterial, protozoal, fungal, parasitic, or secondary bacterial infection due to a foreign body (Confer et al. 1983), however, most of them were ruled out.

The mainstay of treatment of chronic EP is using glucocorticoids (Waddle et al. 1992; Reinero 2019). Prednisone at 0.5 mg/kg to 2.2 mg/kg orally s.i.d. or b.i.d. over a three- to four-week period is usually adequate to control clinical manifestations of the granulomas and strikingly, spontaneous remission has been also reported (Adamama-Moraitou et al. 2015).

The excellent response to glucocorticoids in the dog reported herein is typical of human patients with chronic EP, where the thoracic radiographs resulted in normal readings within three to six weeks after initiation of therapy (Waddle et al. 1992). Treatment may be continued for several months to over a year according to the clinical, haematological and imaging diagnostic findings. As PEG carries a more guarded prognosis than other eosinophilic lung syndromes (Johnson et al. 2019; Reinero 2019) other immunosuppressive drugs may be used in combination with glucocorticoids (Waddle et al. 1992; Katajavuori et al. 2013). This also allows the dosage of steroids to be minimised, which is a benefit. In this case, azathioprine was used to reduce the doses of prednisolone and prevent side effects (Katajavuori et al. 2013). Interestingly, inhaled steroids have not been very useful in controlling clinical signs associated with PEG (Reinero 2019) so we did not elect to use that option. In contrast to previous reports and in accordance to our case (more than 55 months), prolonged survival has been documented in dogs with PEG (Johnson et al. 2019).

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

Adamama-Moraitou KK, Soubasis N, Pardali D, Psalla D, Papazoglou LG, Prassinos NN, Anagnostou TL, Rallis TS. Recurrent intraluminal eosinophilic tracheal granuloma in a Siberian Husky. Vet Q. 2015 Jun;35(2):116-22.

Akuthota P, Weller PF. Eosinophilic pneumonias. Clin Microbiol Rev. 2012 Oct;25(4):649-60.

Campos LEM, Pereira LFF. Pulmonary eosinophilia. J Bras Pneumol. 2009 Jun;35(6):561-73.

Confer AW, Qualls CW Jr, MacWilliams PS, Root CR. Four cases of pulmonary nodular eosinophilic granulomatosis in dogs. Cornell Vet. 1983 Jan;73(1):41-51.

https://doi.org/10.17221/136/2020-VETMED

DeNault L. A case report: Pulmonary infiltrates with eosinophilia in a canine. Iowa State Univ Vet. 2000;62(1): 20-2.

Fina C, Vignoli M, Terragni R, Rossi F, Wisner E, Saunders JH. Computed tomographic characteristics of eosinophilic pulmonary granulomatosis in five dogs. Vet Radiol Ultrasound. 2014 Jan-Feb;55(1):16-22.

Johnson LR, Johnson EG, Hulsebosch SE, Dear JD, Vernau W. Eosinophilic bronchitis, eosinophilic granuloma, and eosinophilic bronchopneumopathy in 75 dogs (2006–2016). J Vet Intern Med. 2019 Sep;33(5):2217-26.

Katajavuori P, Melamies M, Rajamaki MM. Eosinophilic pulmonary granulomatosis in a young dog with prolonged remission after treatment. J Small Anim Pract. 2013 Jan; 54(1):40-3.

Mesquita L, Lam R, Lamb CR, McConnell JF. Computed tomographic findings in 15 dogs with eosinophilic bronchopneumopathy. Vet Radiol Ultrasound. 2015 Jan-Feb; 56(1):33-9.

Moon M. Pulmonary infiltrates with eosinophilia. J Small Anim Pract. 1992 Jan;33(1):19-23.

Neer TM, Waldron DR, Miller RI. Eosinophilic pulmonary granulomatosis in two dogs and literature review. J Am Anim Hosp Assoc. 1986 Nov;22(56):543-99.

Pornsuriyasak P, Suwatanapongched T, Klaewsongkram J, Buranapraditkun S, Rotjanapan P. Acute respiratory failure secondary to eosinophilic pneumonia following influenza vaccination in an elderly man with chronic obstructive pulmonary disease. Int J Infect Dis. 2014 Sep; 26:14-6.

Reinero C. Interstitial lung diseases in dogs and cats part II: Known cause and other discrete forms. Vet J. 2019 Jan; 243:55-64.

Sykes JE, Weiss DJ, Buoen LC, Blauvelt MM, Hayden DW. Idiopathic hypereosinophilic syndrome in 3 Rottweilers. J Vet Intern Med. 2001 Mar-Apr;15(2):162-6.

Waddle JR, Giger U, Evans S. Chronic eosinophilic pneumonia in a dog. Can Vet J. 1992 Feb;33(2):126-8.

Wallace M, Lathan P, Brinkman-Ferguson E. What is your diagnosis? Hypereosinophilia in a dog with multicentric B-cell lymphoma. J Am Vet Med Assoc. 2012 May 1; 240(9):1063-5.

Received: June 24, 2020
Accepted: October 8, 2021
Published online: January 18, 2022