“McKinely’s Mysterious Malady”

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Introduction:

Eosinophilic bronchopneumopathy is an incompletely understood disease process, characterized by eosinophilic infiltration of the lung and bronchial mucosa. [1] It typically affects young adults, 4-6 years, but can occur at any age. There appears to be a breed predisposition in Siberian Huskies and Alaskan Malamutes. Though the exact etiology remains unknown, there is more and more evidence indicating that it may be related to a hypersensitivity reaction to airborne allergens. Diagnosis typically relies on history, clinical signs, and evidence of eosinophilia obtained from broncho-alveolar lavage samples or brush cytology. A brush cytology is always performed first, as performing the BAL first can potentially wash away any material of interest. To perform the brush cytology, a small apparatus is fed through an endoscope and down into the trachea or lungs. Once at the area of interest, the apparatus is opened and a small brush extends out to scrape the mucosa, and it is then retracted, pulled back through the scope, and used to make impression smears that are submitted for cytology. In addition, the tip of the brush can be cut and placed in a glass red top if culture is desired. This case will focus on an instance of eosinophilic bronchopneumopathy in a husky mix dog, including the presenting history, diagnostics performed, treatment plan, and eventual outcome.

History and Initial Presentation:

McKinley is an approximately 2 year old, spayed female, husky mix that initially presented to MSU-CVM CVS department on June 8th, ,2020 after the owner noticed a mild cough had grown worse. McKinley had been visiting with the owner's parents in New Orleans the week prior, where it was noticed that she had been picking up and eating acorns. Around the same time she developed a mild cough, which seemed to resolve until the morning of June 8th. At this time, McKinley's coughing episodes became more severe and she began hacking, as if she was

attempting to dislodge something from her throat. She also began producing a clear to yellow tinged foamy substance when she coughed. The owners noted that McKinley appeared worse in the mornings but that she would continually cough throughout the day. She appeared otherwise healthy. McKinley has a history of anxiety, most severe when at the vet, and so had been administered Trazadone (250 mg) in addition to her once daily Fluoxetine (20 mg) that morning to help ease some of her stress.

On presentation, McKinley was bright, alert, and responsive. She was adequately hydrated, and in good condition, with a BCS of 5/9. There was no ocular, aural, or nasal discharge appreciated, and she was deemed neurologically appropriate. All lymph nodes palpated normally and there were no murmurs or arrhythmias appreciated on cardiopulmonary auscultation. A cough was easily elicited when McKinley was pulling against her leash, but not on tracheal palpation. There are several differentials, some of which include: canine infectious respiratory disease complex (aka kennel cough), tracheitis, or pulmonary foreign body, that could have explained her clinical signs. Based on her overall healthy appearance, the owner decided to forgo bloodwork, but did want to have thoracic radiographs performed to help better assess the lungs.

Diagnostics:

Thoracic radiographs were performed, and revealed a diffuse unstructured interstitial pulmonary pattern, which was most severe within the caudo-dorsal lung lobes. The pulmonary pattern was coalescing to alveolar within the right middle lung lobe and cranial subsegment of the left cranial lung lobe. There was also a diffuse bronchial pulmonary pattern with mineralization of the walls of the larger bronchi. There was no foreign material identified, and the unstructured interstitial, coalescing to alveolar, combined with the coughing, led to concern

of pneumonia. McKinley was sent home on Clavamox (250mg) -2 tablets (500mg) by mouth every 12 hours for the next 14 days, and the owners were told to bring McKinley back if she started to worsen.

McKinley returned 2 days later, on June 10, 2020, for a complaint of vomiting. McKinley was also noted to be coughing more. She had not been willing to eat since the previous day (6/9/20), and she vomited for the first time that morning (6/10/20). She had vomited multiple times since then, and it was described as yellow and mucoid with some foam. She vomited after medications were given, vomiting up her Clavamox, Trazodone and Fluoxetine. She had been lethargic and depressed. At this visit, a complete blood count (CBC) and serum chemistry were performed. The CBC revealed a mild leukocytosis, with a moderate eosinophilia and mild monocytosis. The chemistry showed mildly elevated ALP and ALT, and metabolic derangements consistent with vomiting. Due to her anxiety, McKinley was sedated with Dexmeditomidine and Butorphanol and thoracic radiographs were repeated, which showed little change from those taken 2 days prior. She was sent home, and the owner was instructed to continue administering Clavamox, along with oral Maropitant (60 mg; 1 tablet PO q24 for 5 days). Owner was also told that if McKinley had not improved by Friday, she was to be brought back for further evaluation.

McKinley presented for a third time 4 days later on June 14, 2020, to MSU Emergency department for a worsening cough as well as several episodes of regurgitation and general (mild) lethargy. Her appetite had significantly decreased, and when she did attempt to eat, she would almost immediately regurgitate. Initial physical exam on emergency did note harsh lung sounds. McKinley was transferred to Internal Medicine the following day, where a bronchoalveoloar lavage (BAL) was performed, in addition to a Baermann and an occult heartworm test, which

were both negative. Culture of the fluid from the BAL showed Staphylococcus schleiferi, with no respiratory pathogens seen. Cytology of the fluid showed there were approximately 90% eosinophils and 10% nondegenerate neutrophils. There were no atypical cells or etiologic agents identified, and so it was determined that McKinley had eosinophilic bronchopneumopathy.

Pathophysiology:

Eosinophils, so named for the fact that they take up eosin when stained with H&E, are produced from the common myeloid progenitor cells in the bone marrow, under the influence of eosinophilopoietic cytokines, most notably, IL-5[2]. Eosinophils tend to appear predominately in instances of parasitic infection, asthma, or hypersensitivity/allergic reactions. They can rarely be seen as part of paraneoplastic syndrome, especially with mast cell tumors and lymphoma [3]. There are many potential causes for eosinophilia, and it is most commonly first detected via a CBC. As parasites, such as *Filaroides osleri*,[4] and allergies are two of the more common reasons an eosinophilia is found, fecal and BAL are typically the next steps taken diagnostically, especially if the animal also presents with a cough.

Eosinophilic bronchopneumopathy (EBP) is often idiopathic, and diagnosis relies heavily on history, clinical signs, thoracic imaging, and the results of brush border and BAL cytology. It is important to differentiate EBP from another eosinophilic airway disease, known as eosinophilic pulmonary granulomatosis, or EPG. Patients with EBP and EPG may present with almost identical signs, but EPG carries a far graver prognosis. The two can be differentiated based on thoracic imaging or bronchoscopy, as EPG will have pulmonary masses or nodules present, which is typically not the case with EBP.[5] There have been some studies that suggest EPG may be a late stage version of EPB, but no consensus has been reached as of yet.

Though no singular cause of eosinophilic bronchopneumopathy has been identified, it has been hypothesized that it may be a modified Type 1 hypersensitivity reaction. Type 1 hypersensitivity reactions require a primary exposure event, which primes the immune system to recognize the allergen. This initial encounter creates IgE antibodies, that remain in circulation after the allergen is gone. The next time the same allergen is encountered, the IgE reacts and binds to mast cells, leading to degranulation and release of several immune-modulating compounds, such as histamine, cytokines, and eosinophilic chemotactic factors. [6] Additionally, Type 1 hypersensitivity reactions typically involve an up-regulation of CD4+ T-cells, and a down regulation in CD8+ T-cells. CD4+ cells elicit what's known as a Th2, or T-helper 2, response. Th2 cells create a pro-allergic state, and produce IL-4, IL5, and IL-13.[7] These interleukins serve to stimulate B-cells to produce IgE, which activates mast cells, and activated mast cells produce even more IL-4, leading to perpetuation of the hypersensitivity reaction.

A study performed by Clercx, et. al, showed that fluid from bronchoalveolar lavages from dogs affected with eosinophilic bronchopneumopathy had a much greater ratio of CD4:CD8 than healthy dogs. Further testing showed this was because the CD4 levels had increased, while the CD8 levels had dropped in the clinically affected dogs.[8] This is consistent with what is seen in hypersensitivity reactions. This study also evaluated the serum and BAL fluid levels of IgA, IgG, and IgM between the clinically affected and healthy groups and found no significant difference between them. IgE levels were not tested during this project, and the authors freely admit that further study of canine cytokines and chemokines will be necessary to definitively determine if eosinophilic bronchopneumopathy is truly a type 1 hypersensitivity reaction.

The treatment of choice for eosinophilic bronchopneumopathy is oral steroids, and they are often life long. Prednisone is typically prescribed first, and is initiated at 1 mg/kg BID for 1

week, and then dropped to BID every other day for the second week, and finally SID every other day for the third week.[9] Once the lowest functional dose has been found, affected animals are often kept at that dose life long, because the inciting cause is not usually identified, and can therefore be encountered again without the owner's knowledge. As is common with long term steroid use, signs such as muscle wasting, polyuria, polydipsia and lethargy may appear over time. If such signs become severe, it may be prudent to stop steroid administration for roughly 2 weeks, and then test for iatrogenic Cushing's with a low dose dexamethasone suppression test and treat accordingly.

There has been some research exploring the efficacy of inhaled corticosteroids rather than oral, with the hope that less systemic absorption might lessen the side effects, and that placing the steroid directly in the lungs may be more effective at controlling clinical signs. In 3 out of the 8 dogs included in the study, there was poor control of coughing, and exercise intolerance developed after 6 months of inhaled fluticasone monotherapy. In these cases, oral steroids had to be administered, and coughing did subsequently resolve. It was concluded that, while inhaled corticosteroids could achieve decent control initially, the long-term viability is still unclear. Additionally, it was found that the dogs could not be weaned off of inhaled corticosteroids without relapsing.[10] Though there is still much research to be performed, inhaled corticosteroids may be a potential option for owner's that can't give oral medications, or patients who have concurrent disease, such as diabetes or obesity, and for whom oral steroids, and their systemic side effects, may not be ideal.

Treatment and Case Outcome:

After her diagnosis was made, McKinley was prescribed Clavamox (250 mg; 2 tablets by mouth every 12 hours until recheck) for the pneumonia, Fenbendazole (100 mg/mL; 14 mLs

orally every 24 hours for 14 days), in case of worms that may have been missed or dormant, and Omeprazole (20 mg; 1 capsule by mouth every 12 hours until recheck) as a GI protectant, especially as she had been constantly regurgitating. She was also sent home on 0.5 mg/kg of Prednisone orally SID. She was instructed to return in one week for recheck and to adjust her medications as needed. McKinley returned a week later, on June 23,2020, where re-check thoracic radiographs were taken and revealed that the alveolar pulmonary pattern within the ventral aspect of the caudal subsegment on the left cranial lung lobe had resolved. However, there was now a mild, focal, unstructured interstitial coalescing to an alveolar pulmonary pattern within the ventral aspect of the cranial subsegment of the left cranial lung lobe, characterized by air bronchograms and border effacement of the cardiac silhouette. Despite the slow improvement in radiographic signs, owner reported a significant improvement in clinical signs at home. It was decided to continue the Clavamox and Omeprazole as previously prescribed, and to increase the Prednisone dose to 1.1 mg/kg orally SID to help resolution of radiographic signs. Owner was instructed to return in two weeks for re-check.

McKinley presented 2 weeks later, on July 9, 2020 for another re-check. This time, thoracic radiographs showed marked improvement of the unstructured interstitial to alveolar pattern, as well as the bronchiectasis. Owner still reported McKinley was doing well at home, and had not shown any signs of polyuria, polydipsia, or muscle wasting. With the radiographic and clinical signs resolving, it was decided to discontinue the Clavamox and Omperazole, and leave the Prednisone dose where it was. McKinley returned 2 weeks later, on July 23, 2020 for another recheck. Thoracic radiographs were repeated and showed resolution of the interstitial to alveolar pattern. Mild bronchiectasis was still present. It was decided to leave McKinley on her 1.1 mg/kg dose of Prednisone for the next two weeks. After this time, the owner was instructed

to decrease the dose by 20% every 4 weeks until the lowest dose possible that still controlled her clinical signs could be achieved.

Today, McKinley is doing well at home and shows no signs attributable to her eosinophilic bronchopneumopathy. She is currently at a dose of 0.3 mg/kg of Prednisone every other day.

Resources:

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