Case Report

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Treatment of feline asthma with ciclosporin in a cat with diabetes mellitus and congestive heart failure

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Abstract

A 5-year-old domestic shorthair cat that had been previously diagnosed with diabetes mellitus was presented for episodes of coughing and respiratory distress. Diagnostic testing revealed congestive heart failure secondary to hypertrophic cardiomyopathy and concurrent asthma. All clinical signs and eosinophilic airway inflammation resolved with oral ciclosporin while the cat was concurrently receiving medications for treatment of heart failure (furosemide and enalapril). Ciclosporin should be considered for treatment of feline asthma in patients with concurrent diseases (eg, diabetes mellitus, severe heart disease) that may contraindicate use of oral glucocorticoid therapy.

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Feline asthma is a common disorder of the lower airways resulting in airway eosinophilia and reversible bronchoconstriction.[1] Current traditional therapy consists of glucocorticoids (oral or inhaled) and bronchodilators; however, these drugs may be contraindicated with certain concurrent diseases.[2–7] This case report describes a case of naturally occurring asthma in a cat with concurrent diabetes mellitus and compensated congestive heart failure (CHF) secondary to idiopathic hypertrophic cardiomyopathy.

A 5-year-old neutered male domestic shorthair cat was referred to the University of Missouri Veterinary Medical Teaching Hospital (VMTH) for the evaluation of coughing and episodes of respiratory distress. Two days prior to presentation, the cat had an episode of coughing, which was followed by an episode of increased respiratory effort. The patient had been diagnosed with diabetes mellitus 6 months prior to presentation and was being managed with glargine insulin (Lantus, Sanofi-Aventis; 4–5 units SC q12h). On physical examination the cat had a heart rate of 180 beats per minute and a rectal temperature of 37.8°C. It was tachypneic with a respiratory rate of 68 breaths per minute and normal effort. It had moderate dental tartar with gingivitis and patchy areas of alopecia.

A complete blood count revealed mild thrombocytopenia (85,000/µl; reference interval [RI] 300–800 $\times$ 10^3/µl) with platelet clumping. Serum biochemical abnormalities included mild hypercholesterolemia (343 mg/dl; RI 51–248 mg/dl) and increased alkaline phosphatase (62 U/l; RI 5–55 U/l). Blood glucose was normal (57 mg/dl; RI 52–153 mg/dl) approximately 4 h after insulin injection. Urinalysis revealed well-concentrated urine (urine specific gravity 1.090) with 3+ glucosuria, 3+ proteinuria confirmed with a positive sulfosalicyclic acid turbidity test (100 mg/dl) and rare white blood cells. Thoracic radiographs were performed without sedation or anesthesia, and significant findings included mild cardiomegaly with right caudal lobar pulmonary arterial and venous enlargement. A mild diffuse bronchial lung pattern was noted. To help rule out heartworm-associated respiratory disease, an antibody test for *Dirofilaria immitis* was submitted and the results were negative. An echocardiogram (ECG; GE Vivid 7) was performed and revealed severe global left ventricular hypertrophy, severe left atrial (LA) enlargement (LA diameter to aortic [Ao] diameter ratio [LA/Ao] = 2.35 [RI <1.5], LA long axis diameter [LA_{LAX}] = 2.23 cm [RI <1.6 cm]), mild-to-moderate mitral valve regurgitation and mild pericardial effusion, a common manifestation of CHF in cats.[8,9]

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Thoracic radiographic and echocardiographic findings were suggestive of concurrent left-sided CHF and lower airway disease. Although the patient was mildly tachypneic at presentation, it was not in respiratory distress and was considered stable for discharge from the hospital without the need for oxygen therapy. The cat was discharged with treatment for CHF with furosemide (2 mg/kg PO q12h), enalapril maleate (0.5 mg/kg PO q24h), and low-dose aspirin (0.6 mg/kg PO q72h) for thromboprophylaxis. Additionally, it was treated with fenbendazole (Panacur, Merck Animal Health; 50 mg/kg PO q24h for 14 days) and marbofloxacin (Zeniquin; Pfizer; 4 mg/kg PO q24h for 14 days) for treatment of potential pulmonary parasites and lower airway infection, respectively. In addition, treatment with glargine insulin (4 units SC q12h) was continued for the management of diabetes mellitus.

The cat returned to the VMTH 10 days later for re-evaluation. It had been doing well clinically, with no episodes of respiratory distress since starting the medications; however, its coughing persisted and it was mildly tachypneic with a respiratory rate of 56 breaths per minute. A total T4 concentration was performed and found to be normal (2.5 µg/dl; RI 0.8–4.0 µg/dl). A repeat ECG revealed near resolution of the pericardial effusion and reduced severity of left atrial enlargement (LA/Ao = 1.74, LA_{LAX} = 2.03 cm). Recommendations were to continue treatment with enalapril, aspirin, fenbendazole, marbofloxacin and glargine insulin as previously prescribed and continue furosemide at a decreased dose (1.6 mg/kg PO q12h).

The cat returned to the VMTH 1 month later for a re-check evaluation and blind bronchoalveolar lavage (BAL) procedure to further characterize the cause of its suspected lower airway disease based on continued coughing at home. Radiographs of the thorax were performed and revealed cardiomegaly with no evidence of CHF and a mild diffuse bronchial lung pattern. BAL fluid (BALF) was collected in a blind fashion as previously described.[1] Results revealed a total nucleated cell count of 1596 cells/µl and a 100 cell differential consistent with eosinophilic inflammation (50% macrophages, 38% eosinophils, 9% small lymphocytes, 3% neutrophils and rare mast cells). Previously established guidelines of <17% eosinophils and <7% neutrophils were applied as a cut-off for normal feline BALF.[10,11] Aerobic culture of the BALF was negative for bacterial growth. Based on the presence of eosinophilic airway inflammation in combination with a negative heartworm antibody test and appropriate course of dewormer, a diagnosis of feline asthma was made. Current standard therapy with a glucocorticoid and bronchodilator were considered to be contraindicated given the cat's concurrent heart disease and diabetes mellitus.[2–7] In an effort to avoid medications that could exacerbate the patient's concurrent diseases, ciclosporin (ciclosporin capsules United State Pharmacopeia [USP] modified, Teva Pharmaceuticals; 4 mg/kg PO q12h) was recommended. Furosemide, enalapril, low-dose aspirin and glargine insulin were continued as previously prescribed.

The patient returned to the VMTH 3 weeks after initiating ciclosporin for treatment of feline asthma. It reportedly had resolution of cough and tachypnea at home once starting ciclosporin and was tolerating all medications well with no overt adverse effects. A re-check blind BAL was performed and revealed a normal BALF cytology (78% alveolar macrophages, 12% eosinophils, 10% small lymphocytes) confirming resolution of eosinophilic airway inflammation with oral ciclosporin therapy. To minimize the cost and potential adverse effects of long-term ciclosporin therapy, recommendations were to initiate treatment with inhaled fluticasone proprionate (110 µg q12h) via pressured metered dose inhaler delivered with a spacer chamber and fitted face mask while tapering oral ciclosporin. Oral ciclosporin was chosen over an inhaled glucocorticoid agent as a first-line therapy to ensure that airway inflammation would be effectively suppressed quickly. Furosemide, enalapril, low-dose aspirin and glargine insulin were continued as previously prescribed.

The cat returned to the VMTH 2 months later (approximately 4 months after initial presentation) for re-evaluation. It was reportedly doing well clinically with no episodes of coughing or respiratory distress at home. The cat was receiving inhaled fluticasone proprionate as monotherapy for feline asthma for 3 weeks and continued to receive other medications (furosemide, enalapril, low-dose aspirin, glargine insulin), as previously recommended. A repeat blind BAL was performed and revealed normal BALF cytology (70% alveolar macrophages, 22% small lymphocytes, 5% eosinophils, 3% neutrophils) consistent with cytological remission of asthma with inhaled fluticasone proprionate therapy. A total nucleated cell count was not performed on the re-check blind BAL samples in this case. As a result, there is a limitation when interpreting these results, as an absolute cell count could not be obtained. The patient was discharged with recommendations to continue all medications as previously prescribed.

Ciclosporin has been shown to reduce airway eosinophilia and airway hyper-responsiveness in an experimental model of feline asthma.[12] To our knowledge, this is the first case of naturally occurring feline asthma successfully treated with ciclosporin monotherapy. Feline asthma is a type I hypersensitivity reaction to specific aeroallergens that is mediated by activation of predominantly T-helper 2 lymphocytes and subsequent cytokine production, which promotes an allergic inflammatory response.[13] Hallmark clinical features of asthma include eosinophilic airway inflammation and airway hyperresponsiveness, which can result in reversible bronchoconstriction.[13,14] Diagnosis of feline asthma can be

difficult and is based on the combination of compatible clinical signs, physical examination findings, thoracic radiograph findings and eosinophilic airway inflammation.[14] Cytologic evaluation of BALF is a key component of diagnosis, as other lower airway diseases (eg, chronic bronchitis) may result in similar clinical signs and radiographic abnormalities.[11,14] Management of feline asthma is focused on controlling airway inflammation, generally with glucocorticoids (oral or inhaled), and reducing bronchoconstriction.[13,14] There is recent evidence that many cats with asthma have resolution of clinical signs despite continued airway eosinophilia (ie, subclinical inflammation).[15] As a result, monitoring airway inflammation with re-check blind BAL procedures after instituting therapy is recommended, as controlling inflammation is extremely important in long-term management of feline asthma.[13,14]

Glucocorticoids are the mainstay of anti-inflammatory management in feline asthma.[13,14] Unfortunately, glucocorticoids have the potential for adverse effects and are considered relatively contraindicated in feline patients with diabetes mellitus and those with an increased risk of CHF. Glucocorticoids are proposed to unmask or worsen diabetes mellitus via insulin antagonism, stimulation of hepatic glucose production and inhibition of the GLUT4 glucose transporter in peripheral tissue.[2] The diabetogenic effect of glucocorticoids also contributes to the pathophysiology of corticosteroid-associated CHF through plasma expansion from hyperglycemia.[3,4] A recent retrospective study suggested that diabetes mellitus may be a risk factor for the development of CHF in cats.[16] Additionally, glucocorticoids may contribute to CHF through left ventricular concentric hypertrophy with diastolic dysfunction, increased vascular reactivity resulting in increased left ventricular preload and afterload, and volume expansion from mineralocorticoid excess.[4] Bronchodilators, such as beta-2 agonists and methylxanthines, are often used to alleviate the clinical signs of bronchospasm, but may also be relatively contraindicated in patients with heart disease given their cardiostimulatory and proarrhythmogenic effects.[5,7]

Ciclosporin, an immunomodulatory agent, is used commonly for the management of inflammatory and immune-mediated diseases in veterinary medicine. Ciclosporin inhibits T-lymphocyte activation via inhibition of calcineurin, resulting in downregulation of important proinflammatory cytokines, such as interleukin (IL)-2, IL-4, IL-5, interferon (IFN)-γ and tumor necrosis factor (TNF)-α.[17] *In vitro* evaluation of feline lymphocytes has shown that IL-2, IL-10, IFN- γ and TNF-α are decreased in the presence of ciclosporin.[18,19] In addition, ciclosporin is postulated to have many anti-inflammatory properties that are likely independent of T-lymphocyte inhibition, including blocking degranulation of mast cells and reducing IL-5-mediated mechanisms in eosinophil chemotaxis.[17] However, in experimentally induced asthmatic cats treatment with ciclosporin did not inhibit mast cell degranulation (as assessed via BALF histamine concentration) or lung resistance following antigen challenge.[20]

Successful treatment of feline atopic dermatitis, autoimmune skin disease, chronic stomatitis and pure red cell aplasia with oral ciclosporin has been described previously.[21–24] Another important indication for ciclosporin therapy in feline medicine is immunosuppression to prevent allograft rejection in renal transplant patients.[25] Although ciclosporin is an effective immunomodulatory agent, there is potential for adverse effects. The most commonly reported adverse events in cats receiving ciclosporin for treatment of allergic dermatitis were vomiting, diarrhea and weight loss.[26] Less common adverse effects include gingival hyperplasia, predisposition to infections and increased risk of developing malignant neoplasia.[26–29] In humans, nephro- and hepatotoxicity are reported, although these adverse events have rarely been reported in veterinary medicine.[30] Ciclosporin has been shown to result in pancreatic β-cell death in vitro, and both decreased and increased insulin sensitivity in humans. As a result, ciclosporin has the potential to result in alterations in glycemic control in cats.[31–33]

Conclusions

We report a case of naturally occurring feline asthma treated with oral ciclosporin, resulting in resolution of clinical signs and airway eosinophilia. The cat's clinical sign of coughing was attributed to lower airway disease such as asthma, as coughing is an exceedingly rare sign of CHF in cats.[34,35] Additionally, the cough was not responsive to initial diuretic therapy and only resolved after initiation of ciclosporin therapy. Other causes of lower airway disease and eosinophilic airway inflammation cannot be entirely ruled out, but were considered less likely given the lack of response to initial empirical therapy and negative *D immitis* antibody test. The cat did not have any overt adverse events or alterations in glycemic regulation associated with a relatively short course of oral ciclosporin administered at a standard immunosuppressive dose. It is also interesting to note regarding the potential, although rare, risk of nephrotoxicity associated with ciclosporin, that the cat maintained a normal blood urea nitrogen and creatinine while receiving furosemide and enalapril concurrently. Blood ciclosporin concentrations were not evaluated in this case, but would be useful in the future to better assess pharmacokinetics of ciclosporin in cats with asthma. Ciclosporin should be considered an alternative therapy for feline asthmatic patients with concurrent diseases that prohibit oral glucocorticoid administration. Clinicians should be aware of potential side effects of chronic ciclosporin administration and should consider tapering to the lowest effective dose and/or transitioning to inhaled glucocorticoids for long-term management.

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