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Successful management of pemphigus foliaceus with mycophenolate mofetil as a steroid-sparing agent in a cat with corticosteroid-associated congestive heart failure

Giulia Striuli, Sophie Vandenabeele, Margot Gheeraert and Pascale Smets

Abstract

Case summary A 5-year-old British Shorthair cat was diagnosed with pemphigus foliaceus (PF) and was initially treated with methylprednisolone (0.7 mg/kg q12h), which possibly resulted in congestive heart failure (CHF). Treatment was switched to dexamethasone (0.09 mg/kg q24h) and mycophenolate mofetil (MMF) (10 mg/kg q12h) was added as a steroid-sparing agent. Although dexamethasone was slowly tapered off, MMF alone successfully maintained PF in remission. After 15 weeks of treatment, blood tests showed neutropenia and thrombocytopaenia. MMF dose reduction (10 mg/kg q24h) resulted in the normalisation of haematological parameters, although a mild flare of PF occurred. The reintroduction of dexamethasone (0.09 mg/kg twice weekly) rapidly restored disease control. MMF (10 mg/kg q24h) and dexamethasone (0.045 mg/kg twice weekly) were continued as maintenance therapy. After 36 weeks, the cat remained in clinical remission without further complications.

Relevance and novel information To the best of the authors' knowledge, this is the first case report to describe the use of MMF in a cat with PF. MMF was well tolerated and it was able to manage clinical signs even after the discontinuation of corticosteroids. Since mild and reversible haematological abnormalities were observed, careful monitoring during MMF administration is recommended. In this case, MMF dose reductions led to flares requiring a temporary reintroduction of corticosteroids to maintain disease control. MMF could be useful as an alternative treatment in cats affected by comorbidities where corticosteroid monotherapy would pose risks.

Keywords: Pemphigus foliaceus; mycophenolate mofetil; steroid-sparing agent; corticosteroid-associated congestive heart failure

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Introduction

Pemphigus foliaceus (PF) is the most common autoimmune skin disorder in cats. Immunoglobulins attack intercellular connections between keratinocytes, causing separation and acantholysis at the intragranular or subcorneal level. Most cases have no known underlying cause, although some may be drug-induced.[1,2]

Corticosteroids are the cornerstone of treatment for feline PF, mostly as monotherapy or with other immunosuppressive drugs.[1,2] Although cats are generally considered more resistant to corticosteroid-induced side effects than other species, some cases of congestive heart failure (CHF) after steroid administration have been reported.[3,4]

Small Animal Department, Faculty of Veterinary Medicine, Ghent University, Merelbeke, Belgium

Corresponding author:
Giulia Striuli DVM, Small Animal Department, Faculty of Veterinary Medicine, Ghent University, Salisburylaan 133, Merelbeke, 9820, Belgium
Email: Giulia.Striuli@ugent.be

Mycophenolate mofetil (MMF) is an inhibitor of inosine-5′-monophosphate dehydrogenase (IMPDH), an enzyme crucial for de novo purine synthesis. Once converted into its active metabolite mycophenolic acid (MPA), it prevents the formation of nucleotides necessary for DNA replication. This decreases proliferation of activated T and B lymphocytes and reduces autoantibody production.[5,6]

MMF has been used as a secondary immunosuppressant in veterinary medicine; however, research in cats is limited.[5–10] Emerging literature reports its use in feline immune-mediated diseases, with successful outcomes in refractory immune-mediated hemolytic anaemia (IMHA) and immune-mediated polyarthritis (IMPA), when combined with prednisolone.[11,12]

This report describes the use of oral MMF as a steroid-sparing agent for the management of PF in one cat with presumed corticosteroid-associated CHF.

Case description

A 5-year-old spayed female British Shorthair cat, weighing 5.5 kg, was presented for evaluation of a non-pruritic crusty dermatitis on the left pinna with a duration of 1 month. Previous treatment with methylprednisolone (0.4 mg/kg q24h for 1 week, Moderin; Zoetis) and one subcutaneous injection of cefovecin (8 mg/kg, Convenia; Zoetis), although suboptimal for antimicrobial stewardship, resolved the condition. However, 2 weeks later, the lesions reappeared on both pinnae and spread to the trunk and paw pads.

On first presentation to the authors' clinic, the general physical examination was unremarkable. A dermatological examination revealed alopecia, honey-coloured crusts and symmetric erythema on the pinnae (Figure 1a,b) and the flanks. The paw pads were scaly with crusts, predominantly at the periphery (Figure 1c). A cytological examination of impression smears from the skin underneath the crusts showed non-degenerate neutrophils and acantholytic cells in the absence of bacteria. A hair pluck revealed intact hair tips and anagen bulbs. General anaesthesia was achieved using dexmedetomidine (0.5 mg/ml, Dexdomitor; Zoetis), midazolam (5 mg/ml, Dormazolam; Dechra) and buprenorphine (0.3 mg/ml, Bupaq; VetViva) at standard dosages. Four 4 mm punch biopsy samples were obtained from the flank and paw pad regions. Histopathological examination revealed subcorneal pustules and serocellular crusts with neutrophils and acantholytic keratinocytes, consistent with PF. Periodic acid–Schiff (PAS) stains were negative for fungi and yeasts.

Treatment with methylprednisolone (0.7 mg/kg q12h, Moderin; Zoetis) was initiated. After 10 days, the cat was presented to the emergency department with dyspnoea and a 3-day history of inappetence, lethargy and increased respiratory rate. Clinical examination revealed tachypnoea, abdominal effort, amplified lung sounds dorsally, wheezes and crackles ventrally, and attenuated heart sounds. A complete blood count (CBC) and serum biochemistry profile (SBP) revealed normal parameters (Table 1).

A point-of-care ultrasound (POCUS) revealed B-lines bilaterally, indicating increased fluid within the lung interstitium or alveoli and mild pleural effusion. The heart showed left atrial enlargement and left ventricular thickening. Suspecting CHF, the cat was stabilised with oxygen supplementation and furosemide (Dimazon; MSD Animal Health) in three boli of 2 mg/kg IV every 30 mins, followed by continuous rate infusion of 0.7 mg/kg/h. Full echocardiography after stabilisation showed hypertrophic cardiomyopathy (HCM) phenotype stage C (Table 2). A blood sample for cardiac troponin I could not be analysed because of inadequate volume, while blood pressure measurements were normal. Differential diagnoses for the HCM phenotype were transient myocardial thickening (TMT) (corticosteroid-associated), primary HCM or myocarditis. Hyperthyroidism or acromegaly was less likely owing to the age and absence of clinical signs. Two days later, the cat was discharged with furosemide (2 mg/kg q12h, Libeo; Ceva) and clopidogrel (3.5 mg/kg q24h, Clopidogrel; Sandoz) for 7 days until the next revisit.

Suspecting methylprednisolone-associated TMT, treatment was switched to dexamethasone (Rapidexon; Dechra) to limit plasma expansion, and it was advised to reduce the dose to 0.09 mg/kg and the frequency to every other day. In addition, MMF (1 g/5 ml powder for oral suspension, CellCept; Roche) was started at 10 mg/kg q12h as a steroid-sparing agent.

Table 1 Haematological parameters at W0, W15, W18, W21, W24 and W36 of treatment with mycophenolate mofetil in a cat with pemphigus foliaceus, showing progressive normalisation of all values

Histological parameter	W0	W15	W18	W21	W24	W36	RI
WBC ($\times 10^9$/l)	7.74	3.24	3.55	4.12	4.12	4.28	2.87–17.02
NEU ($\times 10^9$/l)	6.3	1.13*	2.08*	2.22*	2.59	3.29	2.3–10.29
LYM ($\times 10^9$/l)	1.11	1.78	1.07	1.39	1.05	0.61*	0.92–6.88
PLT (K/µl)	161	85*	199	151	243	164	151–600

Only relevant data from blood examinations are reported
*Values deviating from the RIs (ADVIA 2120i; Siemens)
LYM = lymphocyte count; NEU = neutrophil count; PLT = blood platelet count; RI = reference interval; W = week; WBC = white blood cell count

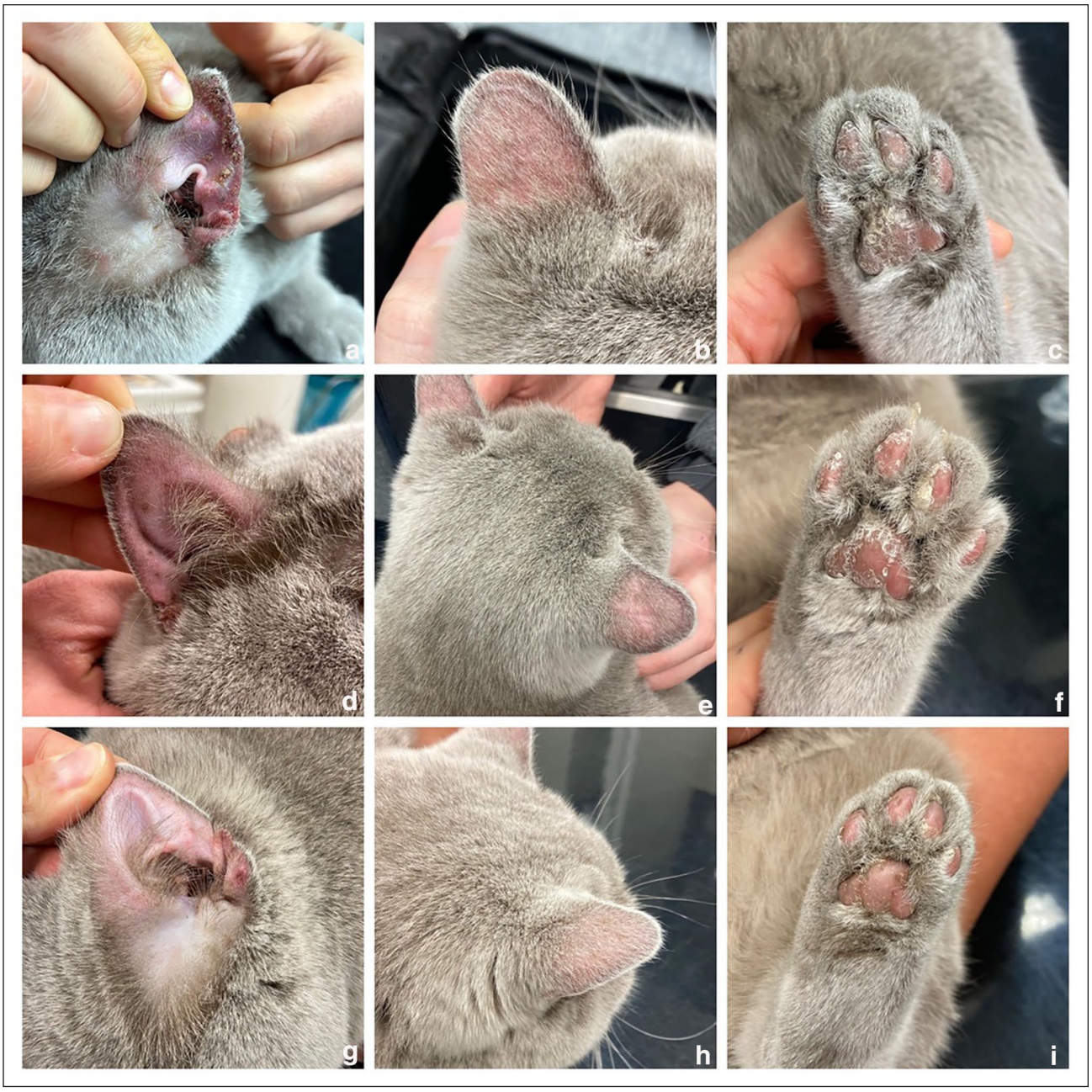

Figure 1 (a–c) Initial presentation of pemphigus foliaceus in a British Shorthair cat: (a) adherent honey-coloured crusts on the concave aspect of the pinna; (b) diffuse alopecia and focal crusts on the apical portion of the convex aspect of the pinna; (c) severe scaling and crusting of the digital and central paw pads. (d–f) Evolution of the clinical presentation after 1 month of treatment with mycophenolate mofetil (MMF) and glucocorticoids: (d) macular hyperpigmentation in previous areas of crust formation, now resolved; (e) initial hair regrowth of the convex pinnae, while crusts have disappeared; (f) partial improvement in scaling and crusting of the paw pads, mostly in the central areas. (g–i) Remission of clinical signs on both (g) concave and (h) convex pinnae and (i) paw pads after 4 months of treatment with maintained MMF and tapered corticosteroids.

One week later, the cat showed a 10% improvement in the severity of dermatological signs, mostly on the ears and flanks. Although the owner continued to administer dexamethasone once daily, pulmonary oedema resolved and the cardiomyopathy improved (Table 2), highly suggesting TMT. The current treatment for PF was maintained, while furosemide and clopidogrel were tapered over the next month and eventually discontinued.

One month later, lesion severity decreased by 25%, with noticeable hair regrowth on the pinnae and absence of crusts (Figure 1d,e). The paw pads showed the slowest improvement but significantly reduced scaling (Figure 1f). Control POCUS revealed positive progress

Table 2 Cardiac measurements obtained during sequential echocardiographic examinations in a cat with presumptive corticosteroid-associated congestive heart failure, showing initial left ventricular wall thickening and moderate left atrium enlargement at W0; institution of cardiac medications and slow withdrawal of dexamethasone led to normalisation of the left ventricular thickness with decreased left atrium enlargement at W1 and W5 and, finally, total normalisation of both left ventricular wall thickness and left atrium size at W18.

Cardiac measurements	W0	W1	W5	W18	RI
IVSd (mm)	6.53*	4.54	4.87	4.90	3.00–5.30
LVFWd (mm)	7.69*	5.02	4.72	4.90	3.00–5.30
La:Ao	2.10*	1.50*	1.70*	1.16	0.89–1.44
LAD (mm)	18.50*	18.08*	18.03*	14.55	8.70–15.40
FS (%)	10*	29	29	30	28–62

*Values deviating from the RIs (ADVIA 2120i; Siemens)
FS = fractional shortening of left atrium; IVSd = interventricular septum diastole; LA:Ao = left atrium to aorta ratio; LAD = left atrium diameter; LVFWd = left ventricular free wall diastole; W = week

after discontinuing the diuretic therapy (Table 2). Dexamethasone was gradually tapered and discontinued 4 months after initiating MMF, as PF had entered clinical remission (Figure 1g–i). By then, cardiac normalisation was also achieved (Table 2).

Although guidelines for MMF recommend baseline and periodic CBC and SBP analysis,[13] no tests were initially performed as a result of the owner's concerns about blood collection. After repeated discussions about monitoring, the owner permitted blood sampling at week (W) 15 of MMF treatment, which revealed neutropenia and thrombocytopaenia (Table 1). Tests for feline immunodeficiency virus (FIV) and feline leukaemia virus (FeLV) (WITNESS FeLV antigen/FIV antibody Rapid Test, Rapid Immuno Migration; Zoetis) were negative, and daily fever monitoring proved normal. Suspecting bone marrow suppression due to MMF, its frequency was reduced to once daily, with blood parameters monitored at 3-week intervals as recommended.[13]

Neutropenia improved throughout the first (W18) and second rechecks (W21) and normalised by the third recheck (W24) (Table 1). However, mild scaling reappeared on the pinnae, confirmed by cytological evidence of acantholytic keratinocytes. This incipient flare led to restart dexamethasone (Dexacortone; Dechra) at 0.09 mg/kg twice weekly for 3 weeks, followed by 0.05 mg/kg twice weekly as maintenance. At the fourth recheck (W36), the neutrophil count kept improving (Table 1), while mild lymphopenia was assumed to be related to corticosteroid use.

At 10 months after starting MMF, the cat remained lesion-free, with no further adverse effects reported related to the treatment.

Discussion

To the best of the authors' knowledge, this is the first case report to describe the use of MMF in a cat affected by PF.

Corticosteroids are commonly used for induction therapy in feline PF, with 90% of cats achieving disease control within 1 month.[1,2] Although cats are remarkably less susceptible to the side effects of corticosteroids, the cat developed CHF relatively quickly. This adverse event is probably the result of left ventricular hypertrophy and diastolic dysfunction combined with volume overload caused by some corticosteroids, more commonly methylprednisolone acetate. The effects of corticosteroids reflect enhanced vascular resistance, increased systemic blood pressure, sodium and water retention, and insulin resistance with associated extracellular hyperglycaemia, which may predispose cats to develop CHF.[4,14,15]

Adjustment of steroid therapy for the concurrent PF was deemed necessary, and dexamethasone was preferred over methylprednisolone acetate as its lack of mineralocorticoid activity minimises fluid retention, addressing one important cardiovascular risk associated with corticosteroids.[6,15] This choice was supported by a positive outcome, with regression of hypertrophic changes and sustained remission of CHF, even without cardiac medications. However, the reduction of steroid activity was modest when dexamethasone was initially given daily, and other factors may have contributed to the cardiac improvement.

To further mitigate the side effects of corticosteroids while maintaining therapeutic efficacy, the dose was reduced and a steroid-sparing agent was added. Azathioprine was excluded because of the high risk of bone marrow toxicity in cats, chlorambucil for its myelosuppressive effects and ciclosporin for requiring longer remission times.[6,13]

Although not reported before in feline PF, MMF was started as an adjunctive immunosuppressant. MMF is considered a low-risk, steroid-sparing therapeutic option for the treatment of canine PF,[5,6] while pharmacology and safety data of MMF in feline PF are lacking. Despite their deficiency in glucuronyl transferase activity,

healthy cats were proven able to rapidly eliminate MPA, although significant interindividual variability in MPA plasma levels could impact the safety and efficacy of MMF treatment.[7–10] In cats, the short-term side effects of MMF are generally mild, dose-dependent and gastrointestinal in nature,[7,8] while long-term use poses risks of infections, malignancies and potential hepatotoxicity or pancreatitis.[13,16]

The initial therapeutic dose was extrapolated from previous MMF feline studies in vitro and reports in vivo, reporting a good tolerance when 10 mg/kg q12h is given.[6–12,16] During clinical monitoring at regular 3-week intervals, the cat showed no obvious adverse events. Nevertheless, 2 months after starting MMF therapy, haematological changes were detected including, neutropenia and possibly thrombocytopaenia.

The differentials for neutropenia include infectious or inflammatory disease, but investigations (apart from FeLV/FIV tests) were not performed as the cat was systemically well. MMF has been reported to cause dose-dependent myelosuppression in humans[17] and, in this case, the evidence strongly suggests a drug-associated neutropenia. This conclusion is supported by the normal baseline haematology before starting MMF, the marked neutropenia during full-dose treatment and the gradual increase of neutrophils when the dose was halved. This relationship between MMF and neutropenia in cats is a novel finding and a dose-dependent, reversible manner is speculated.

Thrombocytopaenia was observed only at W15 of MMF treatment. In previous reports of MMF in cats, a decrease in platelet count was common but deemed artefactual, either due to platelet aggregation on blood smear analysis[9] or to loss or consumption, potentially from the gastrointestinal tract.[7] Thrombocytopaenia was therefore considered of limited significance in this case, as it was not reflected in clinical indications, bleeding or diarrhoea, and underestimation of platelet count is well recognised in cats due to aggregations.

Some limitations occurred in this study. First, blood tests within the first weeks of treatment could have clarified the onset of haematological abnormalities potentially related to MMF. Second, thrombocytopaenia observed at W15 was not confirmed with a blood smear, which could have supported artefactual thrombocytopaenia. Finally, no final full echocardiogram was performed as a result of stress during long restraint.

Conclusions

This paper reports the successful management of PF in a cat with MMF alone as well as an adjunct to corticosteroids. MMF was well tolerated, and adverse effects were limited to suspected drug-induced neutropenia and possible thrombocytopaenia, which were mild and reversible. Pending further data about the safety and efficacy of long-term dosing of MMF in cats, regular monitoring remains essential. In addition, veterinarians should be cautious of the potential risk of CHF in cats before initiating corticosteroids, particularly with methylprednisolone acetate.

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Ethical approval The work described in this manuscript involved the use of non-experimental (owned or unowned) animals. Established internationally recognised high standards ('best practice') of veterinary clinical care for the individual patient were always followed and/or this work involved the use of cadavers. Ethical approval from a committee was therefore not specifically required for publication in *JFMS Open Reports*. Although not required, where ethical approval was still obtained, it is stated in the manuscript.

Informed consent Informed consent (verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (experimental or non-experimental animals, including cadavers, tissues and samples) for all procedure(s) undertaken (prospective or retrospective studies). No animals or people are identifiable within this publication, and therefore additional informed consent for publication was not required.

ORCID iDs Giulia Striuli https://orcid.org/0009-0005-7755-4241
Margot Gheeraert https://orcid.org/0000-0001-9977-4660

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