

Combination of prednisolone and mycophenolate mofetil for the treatment of a cat with immune-mediated panniculitis: A case report

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Abstract

A 3-year-old domestic shorthair cat presented with severe diffuse skin lacerations and cutaneous nodules with purulent discharge. Primary immune-mediated panniculitis was diagnosed. After surgical excision of the lesions, immunosuppressive therapy with prednisolone and mycophenolate mofetil was initiated. The cutaneous lesions resolved, and no recurrence was observed over a 2-year follow-up period.

Keywords: cat, immune-mediated, mycophenolate mofetil, panniculitis

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Introduction

Panniculitis is a multifactorial inflammatory condition of subcutaneous fat, which presents as deep subcutaneous cystic nodules (Miller *et al.*, 2013). There are several etiologies for panniculitis in cats, including infection, pancreatic disease, and hormonal diseases (Malik *et al.*, 1994; Fabbrini *et al.*, 2005; Miller *et al.* 2013; Cox and Udenberg, 2020; Steffl *et al.*, 2020). Once these causes are excluded, immune-mediated panniculitis is diagnosed and managed using various immunosuppressants (Miller *et al.*, 2013).

Mycophenolate mofetil (MMF) is an immunosuppressant that is a prodrug of the active moiety mycophenolic acid (MPA) (Tamura *et al.*, 2020). MPA is a noncompetitive, selective, and reversible inhibitor of inosine 5'-monophosphate dehydrogenase (IMPDH) (Klotsman *et al.*, 2019). Inhibition of IMPDH, a regulator of the intracellular guanine nucleotide pool, leads to arrest of T- and B-lymphocyte proliferation (Klotsman *et al.*, 2019). This, in turn, prevents lymphocyte proliferation, antibody production, cellular adhesion, and T- and B-lymphocyte migration (Tamura *et al.*, 2020). Due to its rapid action, commercially available generic formulations, and documented efficacy (Klotsman *et al.*, 2019). In human medicine, MMF is used for organ transplants and various immune-mediated diseases (Tamura *et al.*, 2020). However, information and reports on its use in cats are limited (Slovak *et al.*, 2017; 2018; 2019; Kopke and Galloway, 2020; Tamura *et al.*, 2020). Herein, we detail the successful treatment and management of feline immune-mediated panniculitis with prednisolone and MMF over 2 years of monitoring.

Case description

A 3-year-old spayed female domestic shorthair cat (body weight: 5.2 kg) was presented to our hospital for investigation and treatment of severe diffuse skin lacerations and nodules with associated purulent discharge. The cat had been in the owner's possession since it was a kitten and was fed a proprietary diet. There were no other pets in the house. An initial vaccination course had been given at 1 year of age, but the cat had not received any booster vaccinations. Monthly endoparasite and ectoparasite prophylaxis was given routinely. The dermal lesions were first noticed 2 days after a 2-week stay at a pet hotel and spa.

The dermal lesions on the dorsum started as hair loss and copious scurf with no signs of pruritus. Empirical antibiotics (Cefovecin 8 mg/kg SC) were prescribed by a local hospital; however, the skin lesions continued to progress, ultimately becoming lacerated and exuding purulent discharge. During a 10-day of hospitalization period, the skin lesions, being open, were managed with disinfection, and the patient received oral antibiotics (amoxicillin clavulanate 13.75 mg/kg BID, metronidazole 15 mg/kg BID, enrofloxacin 5 mg/kg SID), a gastroprotective agent (famotidine 0.5 mg/kg BID), and topical gentamicin ointment. Among the four skin lesions, two lesions improved; however, the other two showed no improvement. Thus, the patient was referred to our hospital.

At referral, the cat had four open wounds on the dorsum, two of which exposed the underlying muscle (Fig. 1). Cytology of a discharge swab revealed numerous ruptured neutrophils. No infectious agents were identified. Fine-needle aspirates from skin nodules contained abundant neutrophils and macrophages. Aerobic bacterial and fungal cultures on sheep blood agar and Sabouraud agar showed no growth after 5 days.



Figure 1 Four lesions on the dorsum at first presentation.

The patient was hospitalized to manage the skin lesions using dressings with 0.05% chlorhexidine and gentamicin ointment. Oral medications included metronidazole (15 mg/kg, BID), cephalexin (20 mg/kg, BID), tramadol (2 mg/kg, BID), and famotidine (1 mg/kg, BID). On day 2 of hospitalization, the cat was anesthetized for surgical repair of the skin defects. The wound edges were scarified, and the surrounding skin was closed using 3-0 nylon. The patient was discharged the same day and continued the same oral regimen.

One week after discharge, new skin nodules were identified on the abdomen. A 6-mm punch biopsy was obtained from one of the new nodules. Histopathology was consistent with necrotizing panniculitis, showing disruption of subcutaneous adipose tissue by foamy macrophages admixed with neutrophils, lymphocytes, and plasma cells. Scattered fibrin and occasional foci of necrotic adipose tissue were also observed (Fig. 2). No infectious organisms were detected on routine or acid-fast stains. Aerobic, anaerobic, and fungal cultures were negative. Results of adrenocorticotrophic hormone (ACTH) stimulation and low-dose dexamethasone suppression testing (Table 1) did not suggest hyperadrenocorticism as a cause of skin fragility. Abdominal ultrasonography was unremarkable. Given the lack of evidence for pancreatitis, hormonal disease, or infections, immunosuppressive therapy with prednisolone (4 mg/kg/day) and cyclosporine (6 mg/kg PO SID) was initiated for treatment of suspected immune-mediated panniculitis. Cyclosporine was discontinued 36 days later due to anorexia. Oral prednisolone (4 mg/kg/day) was continued.

Because the skin lesions were old, the wounds did not heal completely. Thus, two further surgical corrections were performed. After the second surgery, near-infrared rays were applied to the skin lesions for 30 min BID for 1 month.

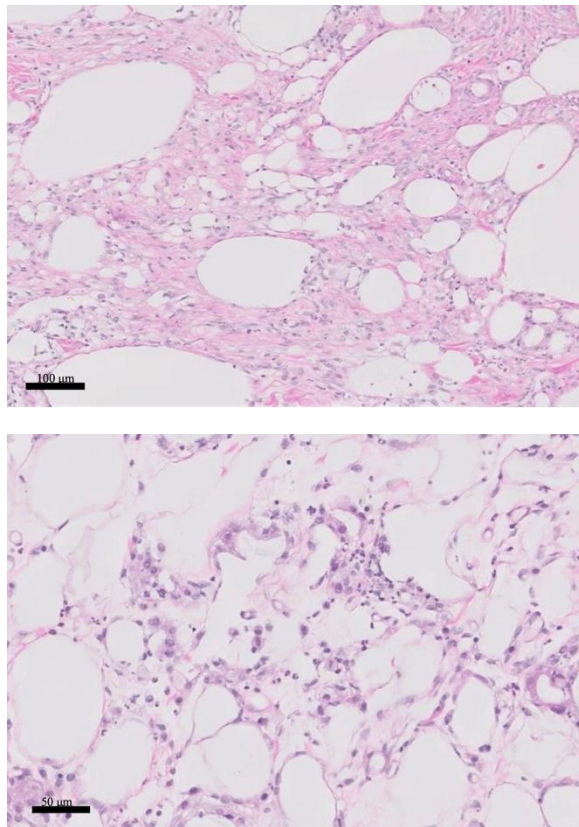


Figure 2 Histopathological images of the biopsy sample. There are severe necrotizing and ulcerative dermatitis and cellulitis, with granulomatous and suppurative steatonecrosis.

Three months after the third surgery, the ventral and dorsal surgical sites were completely healed and filled with granulation tissue and prednisolone therapy was gradually tapered (Fig. 3). One month later, when the prednisolone dose had been reduced to

0.3 mg/kg PO SID, the panniculitis recurred on the skin of the medial aspect of the right hindlimb (Fig. 4). The dose of prednisolone was then increased to 4 mg/kg/day, which helped control lesion progression. However, side effects of chronic steroid use, including polydipsia, polyuria, and thin skin, were observed. MMF (CellCept, 10 mg/kg, PO, BID) was therefore added as a second immunosuppressant. The lesion resolved within 2 weeks of the addition of MMF, and tapering of prednisolone by 20%–25% every 2–3 weeks was continued. When the prednisolone dose was 0.2 mg/kg PO EOD, the hematocrit decreased from 41% to 29.6%, concurrent with decreased appetite and body weight. Since physical examination and diagnostic imaging tests were normal, the clinical signs were interpreted as a possible MMF side effect. The MMF dose was tapered by 20% every 3 weeks, which rapidly increased the hematocrit and improved the anorexia. However, as the dose of MMF decreased, the number of neutrophils also decreased. When the dose of MMF was reduced to 1.5 mg/kg SID, the patient developed severe neutropenia ($0.84 \times 10^9/L$), which resolved several days after the dose was increased back to 10 mg/kg PO BID. During the 2-year follow-up period, treatment with 0.2 mg/kg/day of prednisolone and 16–18 mg/kg/day of MMF was maintained. The cat's dermatological lesions were well managed with no other clinical signs, hematological abnormalities, or side effects reported.

Table 1 The results of the ACTH stimulation test and the low dose dexamethasone suppression test of the patient.

ACTH stimulation test		
Basal cortisol		Post-ACTH cortisol
1.8 µg/dL		7.4 µg/dL
Low dose dexamethasone suppression test		
Sample 1 (0 h)	Sample 2 (4 h)	Sample 3 (8 h)
5 µg/dL	5.1 µg/dL	2.5 µg/dL

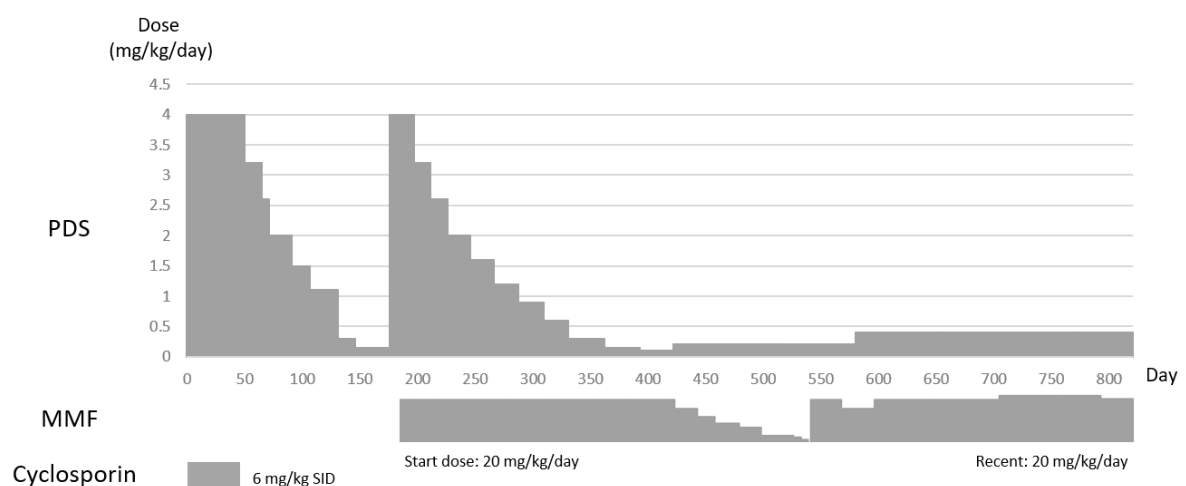


Figure 3 Graph showing immunosuppressant doses over time.



Figure 4 Panniculitis recurred on the medial aspect of the right hind limb.

Discussion

Panniculitis encompasses diverse etiologies that result in inflammation of subcutaneous fat (Miller *et al.*, 2013). In cats, most lesions of panniculitis are solitary with rare reports of cases with multiple or disseminated lesions (Miller *et al.*, 2013). When multiple lesions are present, cats often show signs such as fever, depression, weight loss, and abdominal pain (Malik *et al.*, 1994; Fabbrini *et al.*, 2005; Cox and Udenberg, 2020). The present case showed disrupted subcutaneous adipose tissue with foamy macrophages and a small number of neutrophils, lymphocytes, and plasma cells. Scattered fibrin and occasional necrotic adipose cells were also observed. The patient was thus diagnosed with panniculitis.

Panniculitis can be classified as either primary or secondary (Miller *et al.*, 2013). Secondary panniculitis has underlying causes such as infection, pancreatic diseases, endocrine diseases such as hyperadrenocorticism and fatty irritant subcutaneous injection (Miller *et al.*, 2013). Secondary panniculitis was excluded based on patient history, ultrasonography, and hormonal test results (Miller *et al.*, 2013). In contrast, primary panniculitis is an immune-mediated idiopathic disease based on the exclusion of secondary panniculitis (Miller *et al.*, 2013). Primary panniculitis can be controlled using immunosuppressive systemic glucocorticoids (Miller *et al.*, 2013). The patient in this case responded well to high-dose PDS. However, since the symptoms of panniculitis recurred when the PDS dose was tapered, MMF was included as a second immunosuppressant with good efficacy.

MMF has been recommended as an additional immunosuppressant agent for several canine immune-mediated diseases; however, information on its use in cats is limited (Slovak *et al.*, 2017; 2018; 2019; Klotsman *et al.* 2019; Kopke and Galloway, 2020; Tamura *et al.*, 2020). Recent studies have shown the efficacy and safety of MMF use in cats (Slovak *et al.*, 2017; 2018; 2019; Kopke and Galloway, 2020; Tamura *et al.*, 2020). Side effects of MMF in cats include gastrointestinal symptoms, lethargy, and myelosuppression (Slovak *et al.*, 2018; Kopke and Galloway, 2020). The side effects of MMF observed in our patient were anorexia, anemia, and neutropenia at different doses. In general, MMF can cause bone marrow suppression at high doses (Klotsman *et al.* 2019); however, our patient developed neutropenia when the MMF dose was decreased, which then improved when the dose was increased. This may be due to adjusted bone marrow function at high doses of MMF.

One study reported that the use of MMF in cats can induce hepatopathy and pancreatitis; therefore, we administered preemptive hepatoprotectant agents, and no abnormal liver enzyme values were observed.

During the 2-year monitoring period, the patient's symptoms were well-managed with low-dose PDS and high-dose MMF, with no severe complications. Thus, we conclude that PDS and MMF immunosuppressive therapy can be effective for long-term treatment of immune-mediated panniculitis in cats.

In conclusion, multifocal panniculitis in cats is uncommon and has diverse causes. When panniculitis is suspected, clinicians should perform diagnostic tests to exclude infections, pancreatic disease, and endocrine disorders. After excluding secondary, immune-mediated panniculitis can be diagnosed and

managed with immunosuppressants. Prednisolone and cyclosporine are appropriate first line options in cats; however, long term use may cause adverse effects or be ineffective. In such cases, MMF is a suitable alternative. When MMF is used in cats, periodic monitoring, including complete blood count and serum chemistry, is required to detect adverse effects such as hepatic failure or bone marrow suppression.

Author Contributions

All authors contributed to the diagnosis and had direct patient contact. MH Jeon and JH Kim served as the primary and assisting clinicians, respectively, and drafted the manuscript. YS Kwon performed the surgery, and SG Bae supervised.

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