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Feline Atopic Skin Syndrome: an Introduction to Recently Proposed Terminology and How to Work Up the Case

Michael Gunawan[1,*], Andhika Hardani Putra[2], Tiara Widyaputri[1]

[1]Fakultas Kedokteran Hewan, Universitas Brawijaya
[2]Peterinary Medical Centre, Kelapa Gading, North Jakarta, Indonesia
*Correspondence : michgun68@gmail.com
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Abstract

Atopic disease remains as an enigmatic hypersensitivity disorder in feline patients. Studies of cutaneous atopic syndrome in cats have reported several reaction patterns in cats, presenting as a diagnostic challenge, and a recent literature review has proposed a new set of terminologies for such diagnoses. This paper aims to report a case workup of feline atopic skin syndrome in a patient presented with severe pruritus and reaction patterns of self-inducd alopecia and facial excoriation. Feline food allergy and flea allergic dermatitis were ruled out by a 6-week elimination diet and use of fluralaner respectively. Clinical symptoms were successfully managed with the use of oral glucocorticoid (GC) and systemic and topical antimicrobial, the use of all of which for 8 weeks was deemed successful based on the degree of clinical relief provided. It is concluded that feline atopic skin syndrome is a clinical diagnosis and pharmacological interventions, including drugs to treat skin inflammation and secondary infection, are warranted.

Keywords: Atopic syndrome, feline atopic skin syndrome, clinical diagnosis

Abstrak

Sindrom atopik pada kucing masih belum dipahami dengan baik hingga kini. Berbagai studi mengindikasikan adanya beberapa pola reaksi klinis yang dapat muncul pada kucing dengan diagnosa serupa. Hal ini menjadi tantangan bagi dokter hewan dalam penguhan diagnosa, dan studi literatur terbaru mengajukan beberapa terminologi baru yang digunakan untuk mendiagnosa sindrom atopic pada kucing. Studi kasus ini dibuat untuk menjelaskan peneguhan diagnosa serta manajemen pengobatan kasus *feline atopic skin syndrome* pada seekor kucing dengan gejala klinis berupa pruritus berat dan pola reaksi klinis berupa *self-induced alopecia* dan ekskoriasi wajah. Diagnosa banding *feline food allergy* dan *flea allergy dermatitis* dieliminasi, masing-masing melalui diet eliminasi selama 6 minggu dan administrasi fluralaner. Gejala klinis diatasi dengan administrasi glukokortikoid oral dan antimikroba sistemik dan topical. Oleh karena itu, dapat disimpulkan bahwa diagnosa *feline atopic skin syndrome* bersifat klinis daripada laboratoris dan pengobatan dilakukan untuk meredakan keradangan kulit dan eliminasi infeksi sekunder.

Kata kunci: Sindrom atopik, *feline atopic skin syndrome,* klinis

INTRODUCTION

Atopy, a Greek-derived term with meaning of "out of place" or "strange" disease, is coined to refer to the propensity of immune system to exaggeratedly upregulate immunoglobulin E (IgE) when exposed to antigenic proteins. The understanding of atopy has improved tremendously since its introduction by Coca and Cooke in 1923 to describe clinical resemblances of two different diseases, namely allergic rhinitis and asthma, in humans (Coca & Cooke, 1923). Many studies pointed out the similarities in the pathogenesis and disease phenotype of atopic dermatitis (AD) in both humans and dogs that may involve genetic factors, such as impaired skin barrier and involvement of Th_2 cells and IgE expression. However, cats with such disorder may exhibit various clinical signs, and more studies are needed to implicate genetic involvement in the development of the disease. Therefore, the use of "atopic dermatitis" has been concurred to be improper to be used to diagnose cats with suspected skin allergy (Halliwell, Pucheu-Haston, *et al.*, 2021).

Feline atopic syndrome (FAS) is a recently proposed umbrella term to describe atopic disorders in cats that affect the skin, gastrointestinal and respiratory system. Feline atopic skin syndrome (FASS) is another novel term coined to explain inflammatory and pruritic skin disorder in cats that may manifest in a limited spectrum of clinical reaction patterns: milliary dermatitis (MD), head and neck pruritus (HNP), eosinophilic granuloma complex (EGC), and self-induced alopecia (SIA) (Halliwell, Pucheu-Haston, *et al.*, 2021; Santoro *et al.*, 2021). This diversity in clinical reactions signifies a complex nature of the disorder. Furthermore, there have not been many discoveries that serve as advancements in the study of FAS. For example, as opposed to its canine counterpart, genetic predisposition in the pathogenesis of atopic syndrome in feline is undetermined, rendering "outside-inside theory" in FAS disputable (Combarros *et al.*, 2020; Olivry, 2011; Szczepanik *et al.*, 2018; Zaniboni *et al.*, 2016). Therefore, in this report, we described the diagnosis management of an FASS case in a patient to help improve better understanding of this feline-specific disorder.

METHODOLOGY

The diagnostic criteria used in this paper follow the updates on FASS or feline food allergy (FFA) diagnosis proposed by Santoro et al (2021). Although no set of criteria has been determined to distinguish between FASS and FFA, two different sets of diagnostic criteria have been made for allergic dermatitis where FFA has and has not been ruled out, respectively (**Table 2**). Nonetheless, FASS, FFA, and even non-atopic dermatitis like flea allergic dermatitis (FAD) are diagnoses of exclusions, based on complete history of the disease and clinical features of the lesions.

Due to the inherent dependency of FAS diagnosis on client-derived information, there is a need to have a valid, reliable owner-assessed metrology instrument that can signify the severity of the disease, especially when discussing the degree of pruritus. Since cats may covertly display the extent of itchiness they are experiencing, a dual-visual analog scale, as opposed to the single visual analog scale that has been developed for dogs, is warranted. The authors use a feline-specific pruritus scale (VAScat) that has been developed and recently validated by Colombo and colleagues (2022) (**Figure 1**).

Skin and ear swab cytology were performed to: (1) rule out possibility of *Otodectes cynotis* infection, and (2) determine the microscopic features of the skin and ear lesions. All cytologic specimens were subjected to semiquantitative assay, with the classification obtained from the work by Budach and Mueller (2012) (**Table 1**).

CASE PRESENTATION

A 1-year-old intact male British shorthair was first presented for a severe pruritus, with 7/10 pruritus level evaluated with VAScat. The cat also had a focal excoriation on the caudolateral side of both ear pinnae, and diffuse erosion expanding from axilla to antebrachium of left forelimb one week after glucocorticoid was withdrawn without the attending clinician's advice. Skin and ear swab cytology revealed proliferation of cocci (3+) with possible biofilm formation and yeast (2+), respectively. Cytology of the excoriated skin indicated significant presence of degenerate neutrophils (4+), erythrocytes (4+), accompanied with occasional macrophages (1+). One month prior to the currently discussed presentation, the attending clinician made three differential diagnoses: FASS, FFA, and FAD. Administration of spot-on ectoparasiticide, fluralaner (Bravecto®, Merck Animal Health, 40 mg/kg), and enrolment to elimination diet (Hypoallergenic cat diet, Royal Canin®) were completed, every 3 months and for a period of 6 weeks, respectively. Inflammatory skin symptoms were managed with oral dexamethasone sodium phosphate solution (DSP, 0.2 mg/kg q24h, for 10 days). Based on the previous visitation, FAD was ruled out due to minimum improvement despite a strict ectoparasite control. FASS was ruled in with high probability of hypersensitivity to environmental

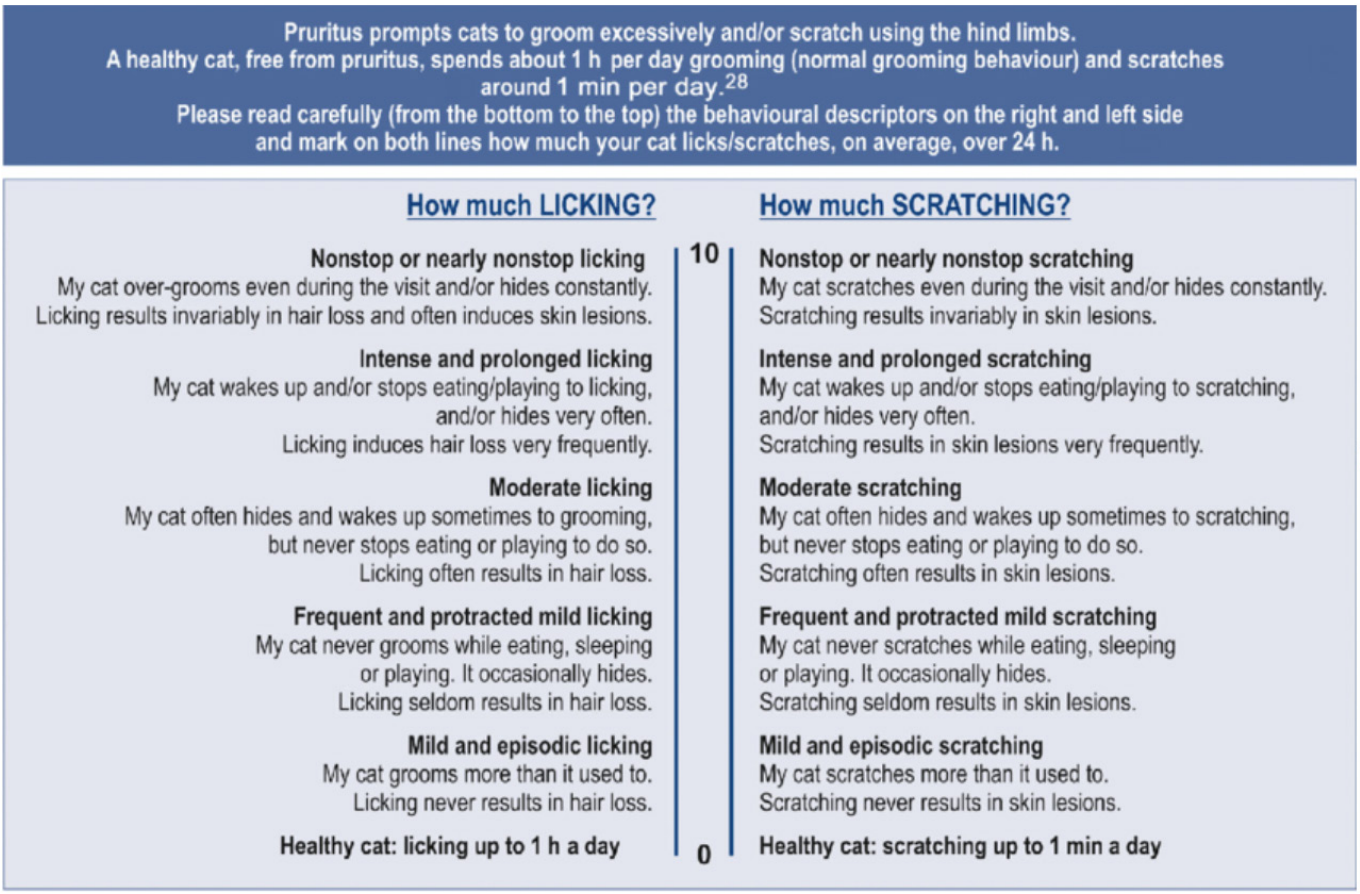


Figure 1. Feline-specific owner-assessed VAScat (Colombo et al, 2022)

Table 1. Cytology semiquantitative criteria (Budach and Mueller, 2012)

Classification	Description
0	No bacteria/yeast/inflammatory cells (B/Y/IC)
1+	Occasional B/Y/IC is present, but slide should be scanned carefully for detection
2+	B/Y/IC presents in low number, but detectable immediately without difficulties
3+	B/Y/IC presents in larger number and readily detectable
4+	Massive amounts of B/Y/IC present and readily detectable

allergens, although the possibility of coexistence with FFA could not be ruled out due to the possibility of unreported protein allergen contamination in the used food. Neither intradermal testing (IDT) nor allergen-specific IgE test (ASIT) was performed following client's wish not to treat the cat with allergen-specific immunotherapy.

Besides the skin lesions on the current presentation, the cat was also presented with characteristics consistent with mild dehydration (slightly delayed skin turgor and capillary refill time). The cat was also hyperthermic. Despite the report of these findings by the clinician, the client insisted on continuing therapy for FASS management. Lactated Ringer's solution was administered subcutaneously with replacement dose. At-home treatment was prescribed with oral DSP solution, oral amoxicillin-clavulanate suspension (Clavamox®, Zoetis, 62.5 mg), topical antiseptic (4% chlorhexidine gluconate, q12h), hydrocortisone aceponate (0.584 mg/ml, Cortavance®, Virbac), and otic antifungal, antimicrobial, anti-inflammatory solution (Surolan®, Elanco).

Ten days later, the cat was readmitted to the clinic for re-evaluation. Partial response to the treatment with VAScat of 5/10 (2-level reduction from last visit) and sign of good wound healing, indicated by regeneration of skin tissue in all visible lesions, was noted. However, marked decline in overall physical condition was noted, with a 0.4 kg weight loss, sign of labored breathing (tachypnea and increased involvement of abdominal muscles), distended abdomen with pain response on palpation, and

Table 2. Diagnostic criteria of allergic dermatitis in cats

Non-flea hypersensitivity dermatitis (NFHD)	NFHD if FAD has been excluded
Presence of at least two body sites affected	Presence of pruritus at onset
Presence of at least two of the four clinical patterns (SIAH, EGC, HNP, MD)	Presence of at least two of the four clinical patterns
Presence of symmetrical alopecia	Presence of at least two sites affected
Presence of any lesion on the lips	Presence of MD as a dominant pattern
Presence of erosions or ulcerations on the chin or neck	Presence of eosinophilic dermatitis or symmetrical alopecia or erosions/ulcerations of the head, face, lips, ears, or neck
Absence of lesions on the rump	Presence of non-symmetrical alopecia on the rump, tail, or hindlimbs
Absence of non-symmetrical alopecia on the rump or tail	Presence of symmetrical alopecia on the abdomen
	Absence of erosions/ulcerations on the forelimbs
Absence of nodules or tumors	Absence of lesions on the sternum or axilla
	Absence of nodules or tumors
Fulfillment of 5/8 criteria gives a sensitivity of 75% and a specificity of 76% for NFHD diagnosis	Fulfillment of 6/10 criteria gives a sensitivity of 90% and a specificity of 83% for NFHD diagnosis

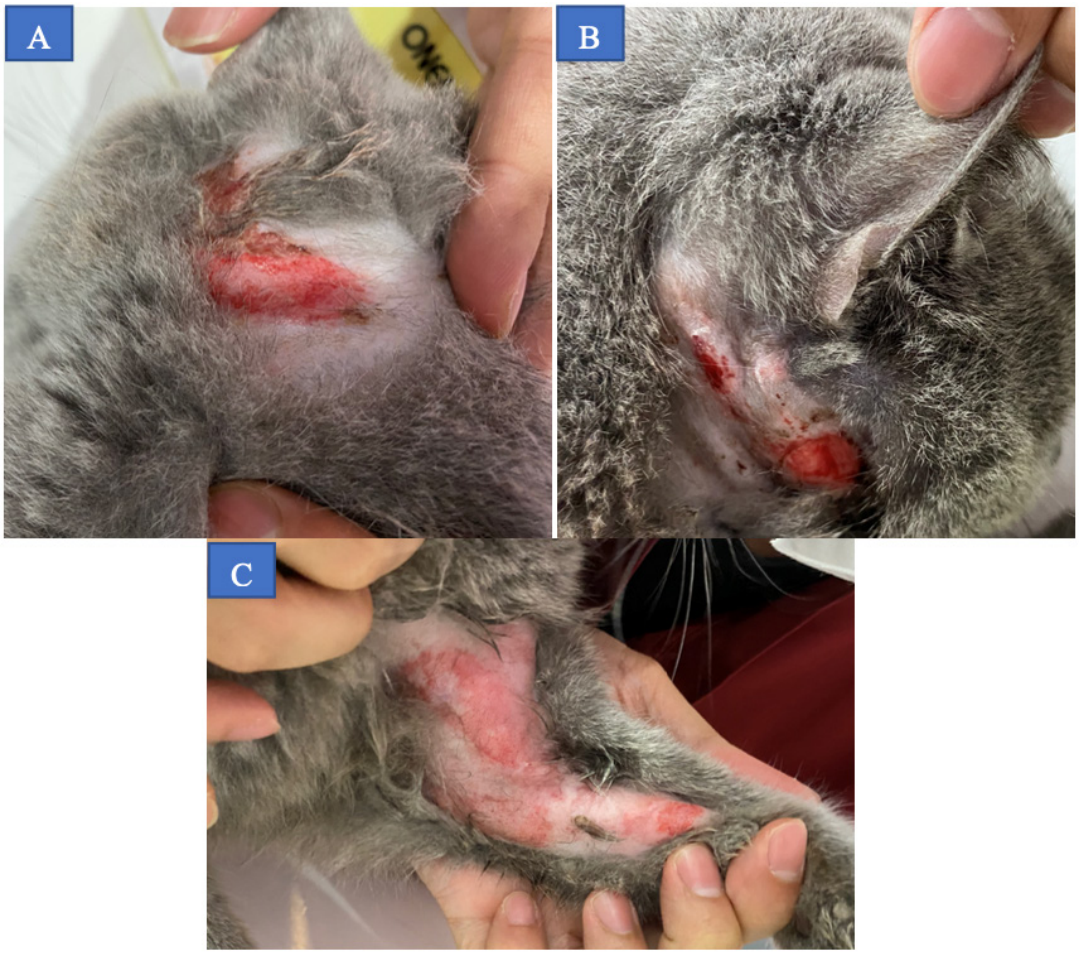
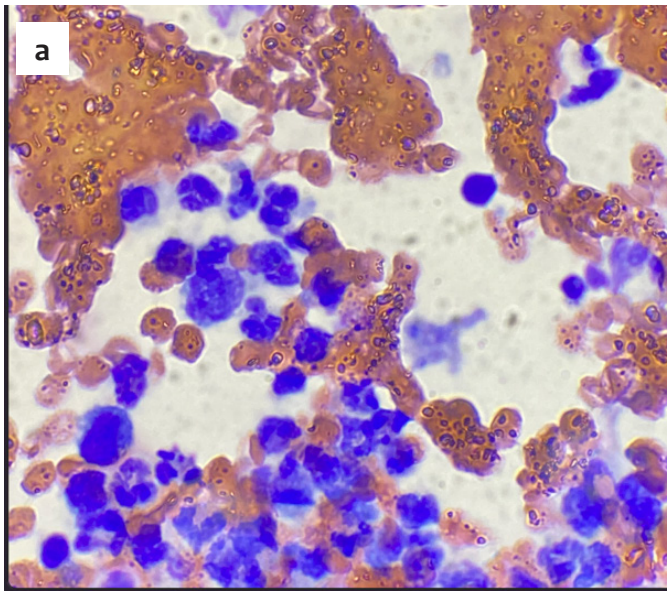


Figure 2. Skin lesions on the cat. Focal (a) and multifocal (b) excoriation on caudolateral aspect of left and right ear pinna, respectively, indicated head and neck pruritus (HNP) reaction pattern. Multifocal to diffuse erosion and diffuse alopecia of the left forelimb indicated a self-induced alopecia (SIA) clinical reaction pattern.



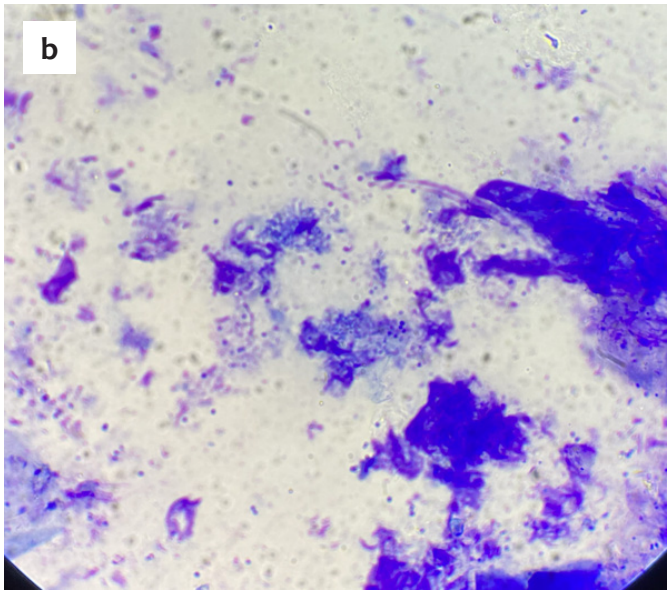


Figure 3. Direct smear cytology of the excoriated skin. Marked proliferation of neutrophils (with degenerated nuclei) (4+), erythrocyte (4+), followed with some macrophages (1+) (a). Other fields of view revealed marked proliferation of cocci (3+) with possible biofilm formation (b).

moderate dehydration. Auscultation of the heart was unremarkable. However, lung auscultation revealed crackling sound on both sides of the thorax. It is concluded that the cat might have other underlying systemic anomalies the client may be unaware of. Use of dermatologic drugs was halted. Despite intensive care in the clinic, the cat died from other causes unrelated to FASS.

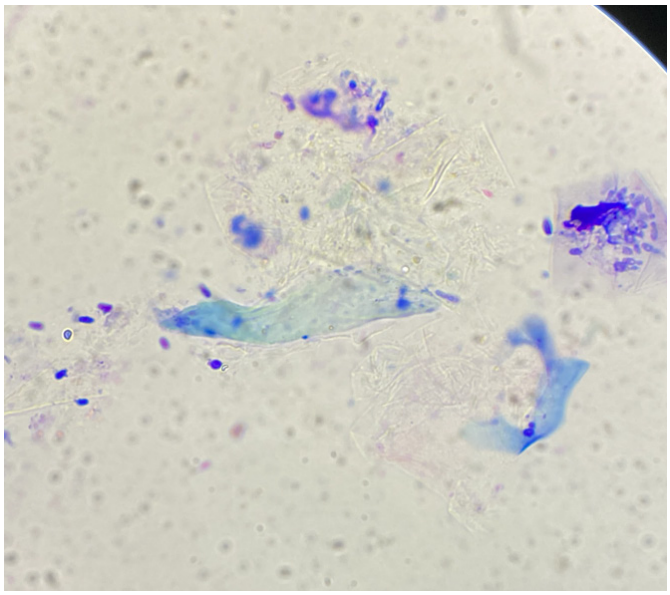


Figure 4. Ear cytology revealed *Malassezia* otitis external.

DISCUSSION

Feline atopic syndrome (FAS), feline atopic skin syndrome (FASS), and feline food allergy (FFA) are proposed nomenclatures that were introduced recently by Halliwell et al (2021) to refer to aberrant immune reactions to some allergenic proteins. Non-flea, non-food dermatitis and feline atopic-like dermatitis were archaically used to describe FASS (Gedon & Mueller, 2018; Marsella, 2021; Santoro *et al.*, 2021). FAS encompasses allergic dermatitis, food allergy, and asthma, all of which involves type-I hypersensitivity, although non IgE-mediated hypersensitivity has been reported in FAS cases, termed as intrinsic FAS. These terms are proposed considering known clinical reaction pattern differences between cats and dogs. For instance, there are 4 recognized cutaneous patterns in cats: MD, HNP, SIA, and EGC, whereas canine atopic dermatitis (CAD) has lesion distribution that is limited to skin regions such as face, ventrum, inguinal area, and distal extremities (Hensel *et al.*, 2015). Although FASS is frequently associated with environmental allergens, it can be elicited by or coexist with food allergy. Furthermore, the clinical reaction may be induced by or may overlap with concurrent flea allergy, a hypersensitivity disorder outside of atopic syndrome due to its postulated complex immunopathogenesis (Halliwell, Banovic, *et al.*, 2021; Halliwell, Pucheu-Haston, *et al.*, 2021).

In our case, this cat has been diagnosed with FASS based on suitable medical history and presence of clinical reaction patterns. FAD was ruled out with the use of fluralaner, the only isoxazoline with

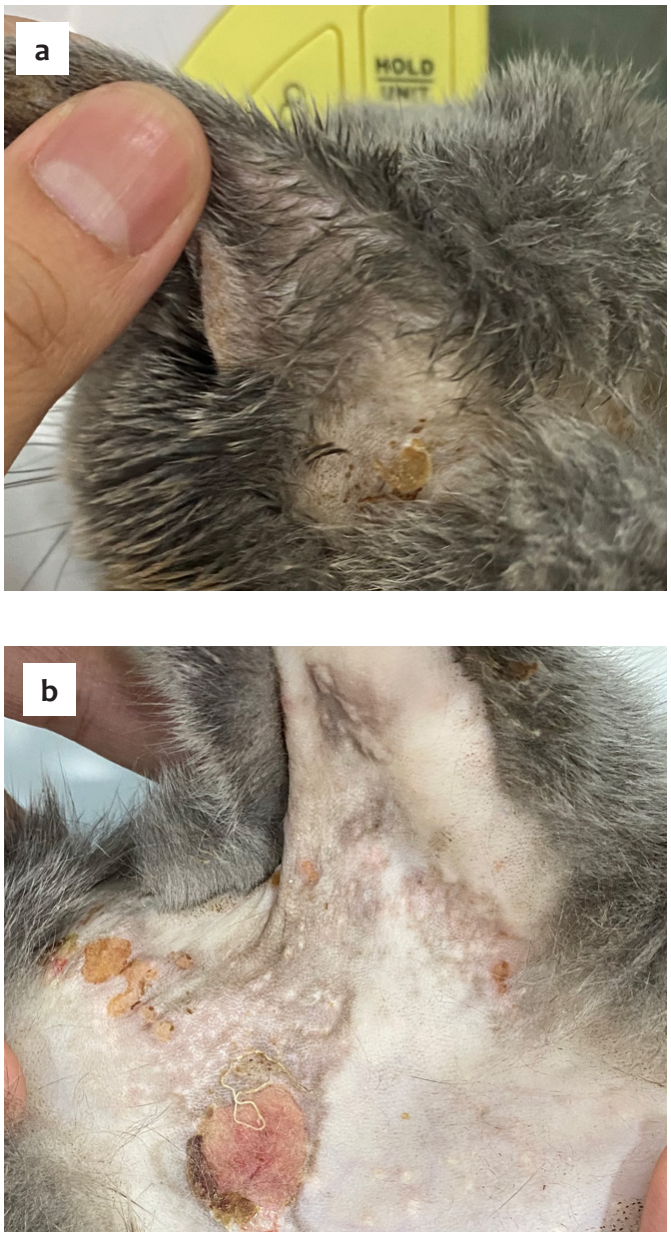


Figure 5. Skin lesion 10 days post treatment. Lesions on the caudolateral aspect of the left ear pinna (a) and left forelimb (b) showed significant improvement; evidence of skin reepithelialization and decrease in skin erythema are noted.

extended plasma half-life, thereby providing longer protection against ectoparasites (Zhou *et al.*, 2021). This cat showed no significant clinical improvement despite strict adherence to hypoallergenic elimination diet. Due to the possibility of the presence of cross contamination with proteins that are not listed on the ingredients, anallergenic diet might be more superior to hypoallergenic diet to completely rule out FFA (Olivry & Mueller, 2018; Ricci *et al.*, 2013). 'Anallergenic' diet with extensively hydrolyzed protein molecules is recommended to further diminish the antigenicity. Nevertheless, one study reported that even hydrolyzed-protein commercial pet food may have varying molecular weights of detected protein and presence of ancillary proteins (*eg,* plant proteins) that may be antigenic. Less than 1 kDa of protein molecule is required to fit the criteria of "true anallergenic diet", making it challenging to obtain such food (Lesponne *et al.*, 2018). Novel diet is another promising alternative to hypoallergenic diet. Novelty of a protein is characterized by its *de novo* molecular pattern that has not previously been encountered *in vivo* by an animal with a suspected food allergy (van Putten *et al.*, 2006). Nonetheless, there remains a likelihood that the cat in this case might have concurrent food allergy with environmentally derived atopic skin syndrome.

Flaring out of the skin due to inflammation necessitates the use of broad-spectrum anti-inflammatory drugs. This cat was presented with two of four classic reaction patterns: head and neck pruritus (HNP) and self-induced alopecia (SIA). Skin inflammation in FASS upregulates many pro-inflammatory cytokines, particularly the pruritogenic IL-4, IL-13, and IL-31, resulting in varying degree of lesions found in this cat from hypotrichosis-to-alopecia to more invasive lesions, erosions, and excoriations (Gedon & Mueller, 2018; Halliwell, Banovic, *et al.*, 2021; Peng & Novak, 2015). Glucocorticoid (GC) is the drug of choice to manage acute skin inflammation of severe intensity. DSP was the GC of choice in this case, administered orally. Despite its off-label use and different bioequivalence compared to oral dexamethasone concentrate (Toledo *et al.*, 2015), DSP has been proven to give satisfactory clinical remission when administered at 0.2 mg/kg/day. Administration of solution also increases drug palatability, hence client compliance. A study in cats has proven the efficacy of DSP, although there was marked variability in post-administration serum concentration between individuals. Adverse drug reactions associated with administration of DSP are also deduced to be mild and self-limiting in nature, indicating good safety (McClintock *et al.*, 2021). This might be related with the postulated hypothesis that cats have lesser *in vivo* GC receptors compared to dogs (Lowe *et al.*, 2008). Notwithstanding the proposed idea of its good safety margin, long-term GC administration may induce broad spectrum of systemic adverse reactions like hyperglycemia, secondary hyperadrenocorticism and its subsequent atrophy of adrenal glands, and compromised immune response, warranting careful monitoring throughout the course of therapy (Narang & Singh Preet, 2019). Besides systemic GC, topical GC (0.574 mg/ml hydrocortisone aceponate,

Cortavance®) was also administered. It is indicated that the use of both topical and systemic GC is warranted in case of severe flare out (Mueller *et al.*, 2021; Olivry & Banovic, 2019).

Secondary skin infection is a disorder that is commonly found in atopic patients. This skin dysbiosis is comparable between human and canine AD and atopic skin syndrome in cats (Gedon & Mueller, 2018; Hensel *et al.*, 2015; Santoro *et al.*, 2021). Treatment of superficial pyoderma in case of CAD should be based on bacterial culture and susceptibility test or at least skin cytology and the extensiveness of the infection (*ie.* topical antibiotics are preferred in less extensive pyoderma). Compared to dogs, there is less option for first-line antibiotics to treat pyoderma in cats (Hillier *et al.*, 2014). Amoxicillin-clavulanate is the most used antibiotic of choice in FASS with secondary superficial pyoderma (Mueller *et al.*, 2021). This restricted selection is related to low bioavailability and less metabolism activity for prodrug conversion of other oral antibiotics (Brown *et al.*, 1990; Kietzmann *et al.*, 1992; Papich & Lindeman, 2018). In this case, combination of topical and systemic antimicrobials is based on the judgment of the attending clinician. Due to the wide distribution of pyoderma in this cat, use of both agents helps to accelerate the resolution of the infection. Use of topical antiseptic, chlorhexidine, may aid in elimination of surface-dwelling pathogens while systemic antibiotic helps in elimination of deep-dwelling pathogens. *Malassezia* otitis in this cat also warranted the use of miconazole nitrate as a topical antifungal agent. Nonetheless, in this day and age where antimicrobial resistance is becoming a more threatening issue, microbial culture and susceptibility testing are always preferred whenever possible and if there is little to no improvements, despite appropriate therapy regimen has been employed.

CONCLUSIONS

1. FAS and FASS are new nomenclatures that need to be familiarized with to diagnose cats with skin-related atopic syndrome.
2. Considering that hypersensitivity dermatitis, especially FASS and FFA of feline atopic syndrome, is a diagnosis of exclusion, it is a due diligence to perform a thorough inspection of both medical history and clinical features of the patient.
3. Treatment regimen is designed to ameliorate the degree of skin inflammation and eliminate the presence of secondary infection. Therefore, GC and antibiotics, both systemically and topically, were used to manage this case.

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