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Topical Application of 0.1% Tacrolimus Ointment for Treatment of Sinus Refractory Pododermatitis Secondary to Atopy in a Dog

Ha-Jung Kim, Jong-Hyun Yoo*, Chul Park and Hee-Myung Park[1]**

Departments of Veterinary Internal Medicine, College of Veterinary Medicine,
Konkuk University, Seoul 143-701, Korea
**BK21 program of Integrative network systems for veterinarians in basic science, industrial animals and preventive medicines, Konkuk University, Seoul 143-701, South Korea*
***Department of Medicine and Epidemiology, School of Veterinary Medicine, University of California, Davis, CA 95616, USA*

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Abstract : An 8-year-old, castrated male Shih-tzu was referred due to relapsing pododermatitis and generalized pruritus. On physical examination, right forepaw showed swelling and serosanguinous exudates from sinus tract on dorsal paw. There were no remarkable findings on complete blood count (CBC), serum chemistry, and radiologic examination. On cytological examination of exudates from sinus tract, phagocyted bacteria and numerous degenerative neutrophils were noted. Results of deep skin scraping and plucking hair examination were unremarkable. Skin biopsy was performed and ruled out other skin diseases. Histopathology showed epidermal hyperplasia and diffuse mononuclear cell inflammation in dermal layer. Moreover, pyogranulomatous inflammation was demonstrated in subcutaneous layer. This case was clinically diagnosed as pododermatitis secondary to atopic dermatitis (AD). Clinical signs of pododermatitis were gradually improved following topical application of tacrolimus 0.1% ointment. This case report describes that tacrolimus ointment can be applicable for the treatment of refractory pododermatitis.

Key words : dog, pododermatitis, tacrolimus.

Introduction

Pododermatitis is a common inflammatory skin disease of dogs (20). Its common causes in the dog include trauma, microbial disease, ectoparasitism, foreign-body reactions, hypersensitivities and immunological skin diseases (1,10,11,20). However, the cause of this disease is often unknown, and it is difficult to find correct etiology of it (16,20). Allergic reactions (hypersensitivities), especially atopic (AD) dermatitis can cause recurrent bacterial pododermatitis with generalized pruritus (11).

Tacrolimus ointment has been used currently for topical treatment of AD in dogs (2,8). The mechanism of action of tacrolimus in AD involves T cells, Langerhans cells, mast cells, basophils and keratocytes (6). Tacrolimus inhibits the T cell response to antigens and production of the cytokines responsible for T cell proliferation, i. e. interleukin (IL)-2. It also inhibits other T cells derived cytokines, such as IL-3, IL4, interferon gamma (IFN-γ), granulocyte/macrophage colony-stimulating factor and tumor necrosis factor alpha (TNF-α), that contribute to allergic inflammation (15). In addition, topical tacrolimus significantly inhibits T cell-mediated keratinocyte apoptosis that correlates with the clinical improvement of skin lesions (18).

This case report describes that refractory pododermatitis secondary to AD in a dog could improve clinical signs with 0.1% topical tacrolimus.

Case report

An 8-year-old, male Shih-tzu was presented with 8-month history of recurrent pododermatitis and generalized pruritus. A surgical resection for sinus tract of the right forepaw has been made by the referring veterinarian. However, the lesion was relapsed in spite of long-term aggressive antibiotic (Cefulen®, 30 mg/kg, PO, BID; Newgenpharm, Seoul, South Korea) and anti-inflammatory therapy (Rimadyl®, 2.2 mg/kg, PO, BID; Pfizer Animal Health, U.S.A). In addition, the patient have had history of chronic bilateral recurrent otitis and generalized recurrent pyoderma since he was 10 months old.

On physical examination, swelling and sinus tract with purulent discharge on interdigital area of right forepaw were found (Fig 1). There were also erythema and scales on the left forepaw. General skin condition of the patient was greasy and there were some papulopustular lesions on dorsum. Bilateral ear pinnae were also erythematouse and mildly swollen. His periocular regions were erythematous, and epiphora was shown on hyperemic bilateral eyes. The patient

[1]Corresponding author.
E-mail : parkhee@konkuk.ac.kr

Fig 1. Right forepaw of the dog with pododermatitis. Note serosanginous discharge from sinus tract (black arrow), scaling, erythematous and swollen skin lesions.

Table 1. Results of complete blood count in this case

Complete blood count	Day 0	Reference ranges
WBC (10^3/μl)	11.96	6.02-16.02
RBC (10^6/μl)	8.71	5.5-8.5
Hb (gm/dl)	17.1	12.0-18.0
MCV (fL)	66.2	60-77
MCHC (%)	31.6	32-36
MCH (pg)	20.9	19.5-24.5
PLT (10^3/μl)	362	200-500
PCV (%)	54.1	37-55

WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, MCV: mean corpuscular volume, MCHC: mean corpuscular hemoglobin concentration, MCH: mean corpuscular hemoglobin, PLT: platelet, PCV: packed cell volume.

exhibited pains and pruritus when palpated the right forepaw. Complete blood counts (CBC) and serum biochemistry profiles revealed no remarkable findings except for mildly elevated ALP (Table 1). Radiography of both paws was performed to rule out foreign bodies in interdigital lesion. But, there were no remarkable findings. Results of deep skin scrapings also revealed no remarkable findings. Cytological examination of exudates from sinus tract showed phagocyted cocci bacteria and degenerative neutrophils (Fig 2). Cocci bacteria were observed in otic cytology. Bacterial and fungal cultures of exudates on right dorsal paw were conducted and fungal culture was negative except for *Staphylococcus intermedius* isolation in bacterial culture. Biopsy samples were taken from the lesions of the right forepaw. Based on the results of fungal and bacterial cultures, cephalexin (Cefulen®, 30 mg/kg, PO, BID; Newgenpharm, Seoul, South Korea) was administered to treat secondary bacterial pododermatitis and otitis. Topical whirl pool therapy with 0.5% chlorhexidine (Chlocidin®, twice a week for each 15

Table 2. Results of serum chemistry in this case

Serum chemistry	Day 0	Reference ranges
BUN (mg/dl)	16.1	9.2-29.2
CRSC (mg/dl)	0.7	0.4-1.4
ALT (U/L)	31	17-78
AST (U/L)	17	17-44
ALP (U/L)	288	47-254
LDH (U/L)	25	20-109
CK (U/L)	51	49-166
GGT (mg/dl)	10	5-14
TBIL (mg/dl)	0.2	0.1-0.5
Tchol (mg/dl)	237	111-312
TG (mg/dl)	81	30-133
Amyl (U/L)	1281	269-2299
NH3 (μmol/L)	49	16-75
Glu (mg/dl)	87	75-128
TP (g/dl)	6.7	5.0-7.2
ALB (g/dl)	3.4	2.6-4.0
Ca (mg/dl)	11.9	9.3-12.1
P (mg/dl)	3.4	1.9-5.0
K (mmol/L)	4.3	3.8-5.0
Na (mmol/L)	144	141-152
Cl (mmol/L)	114	102-117

BUN: blood urea nitrogen, CRSC: creatinine, ALT: alanine transferase, AST: aspartate transferase, ALP: alkaline phosphatase, LDH: lactate dehydronase, CK: creatinine kinase, GGT: gamma glutamyl transpeptidase, TBIL: total bilirubin, Tchol: total cholesterol, TG: triglyceride, Amyl: amylase, NH3: nonionic ammonia, Glu: glucose, TP: total protein, ALB: albumin, Ca: calcium, P: phosphorus, K: potassium, Na: sodium, Cl: chloride.

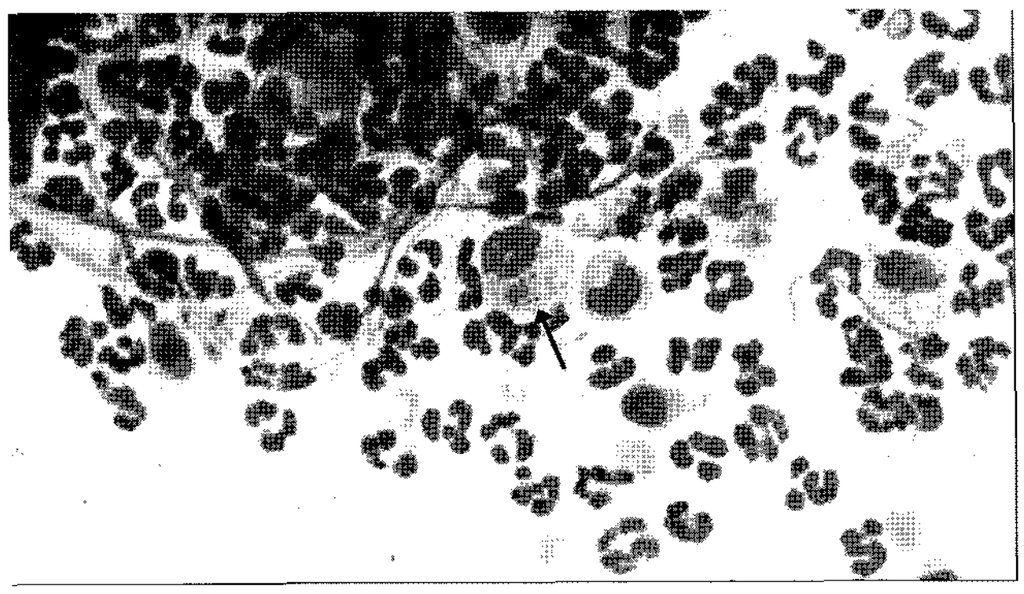

Fig 2. Cytology of exudates from sinus tract of dorsal right forepaw. Phagocyted cocci (black arrow) and predominant neutrophilic pyogranulomatous inflammation (Diff-Quik staining, ×1,000).

minutes, Ewha Pharmtek, Gimpo, South Korea) and was prescribed and carprofen (Rimadyl®, 2.2 mg/kg, PO, BID, Pfizer Animal Health, U.S.A) was administrated for swollen and painful paw. Topical shampoo (Sebolytic®, twice a week for

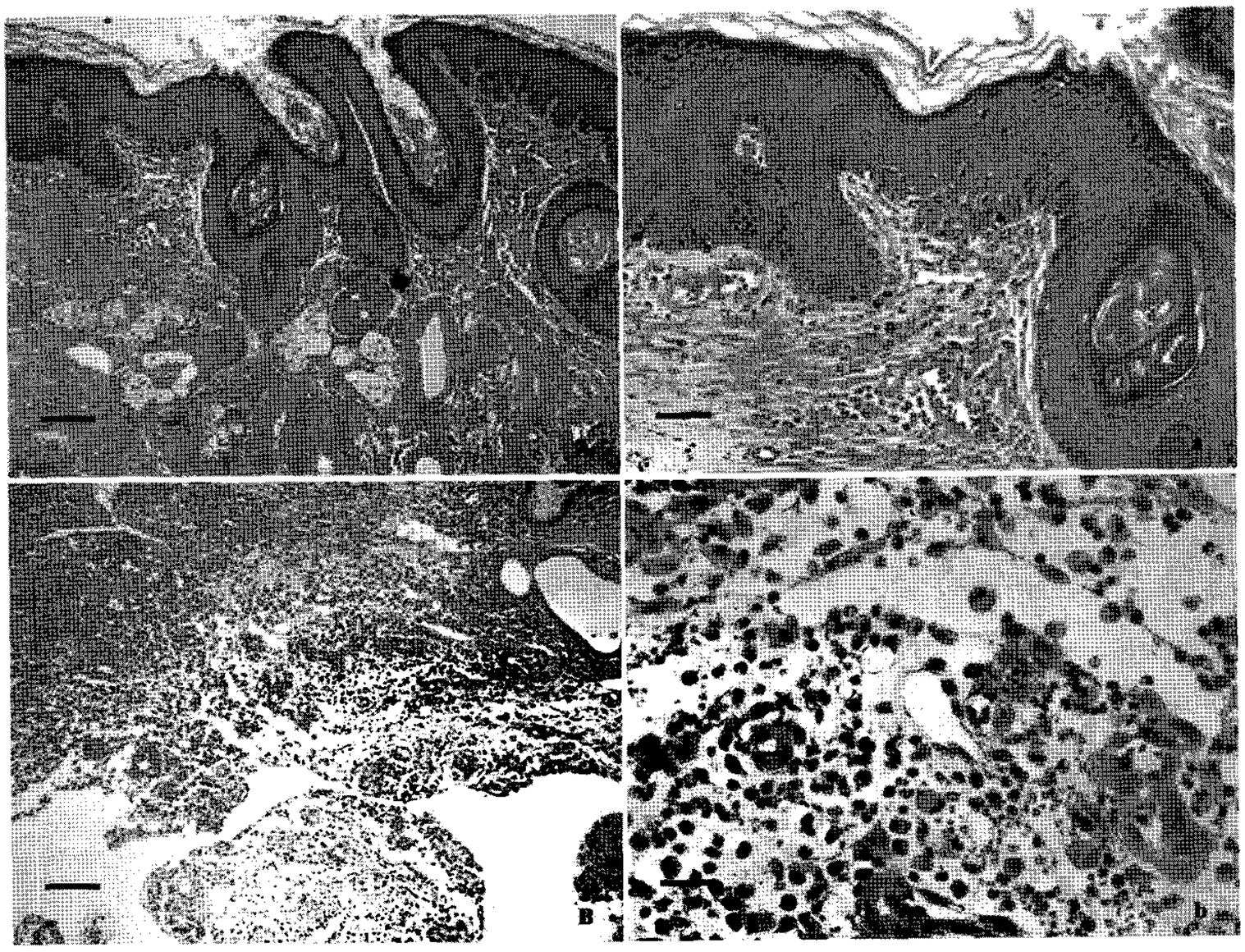

Fig 3. Histopathology of lesion on the right forepaw. Hematoxylin and eosin. (A) Low power photomicrograph shows marked follicular orthokeratotic hyperkeratosis, epidermal hyperplasia, and diffuse infiltration of inflammatory cells in dermal layer (×100). Bar = 140 μm. (a) Closer view of the (A). There are lymphocytic exocytosis and mononuclear cells infiltration in dermis (×200). Bar = 70 μm. (B) Diffuse pyogranulomatous inflammation in subcutaneous layer of the lesion (×100). Bar = 140 μm. (b) Closer view of the pyogranulomatous inflammation (×400). Bar = 35 μm.

each 15 minutes, Virbac Laboratories, Carros, France) was prescribed for greasy skin and pyoderma. Prescription hypoallergenic diet (ULTRA z/d®, Hill's, Pet Nutrition, Topeka, KS, U.S.A) was used to rule out food allergy. But, there was no response to hypoallergenic diet. Histopathological findings demonstrated orthokeratotic hyperplasia, perivascular dermatitis, and pyogranulomatous dermatitis (predominant neutrophilic inflammation) in dermis and subcutaneous layer (Fig 3), indicating chronic inflammatory deep pyoderma. Thus, the pedal lesion in this case was chronic inflammation; therefore there may be few specific findings on histopathological examination. But we ruled out plasmacytic-lymphocytic pododermatitis based on the results of histopathology.

Based on the results obtained here and Willemse criteria for AD (21), we tentatively diagnosed this patient as recurrent pododermatitis secondary to AD. The clinical signs of dog were partially improved 2 weeks after antibiotic therapy. Generalized pruritus, erythema, greasy skin and otitis were improved due to antibiotic and topical therapy. For this reason, we did not use glucocorticoids or antihistamines for pruritic skin. However, pododermatitis with sinus tract was relapsed after 4 weeks. Thus, we topically applied immune-suppressive tacrolimus ointment (0.1% Protopic®, once a day, Dong-A Pharma., South Korea) since refractory pododermatitis was not fully controlled only with antibiotic.

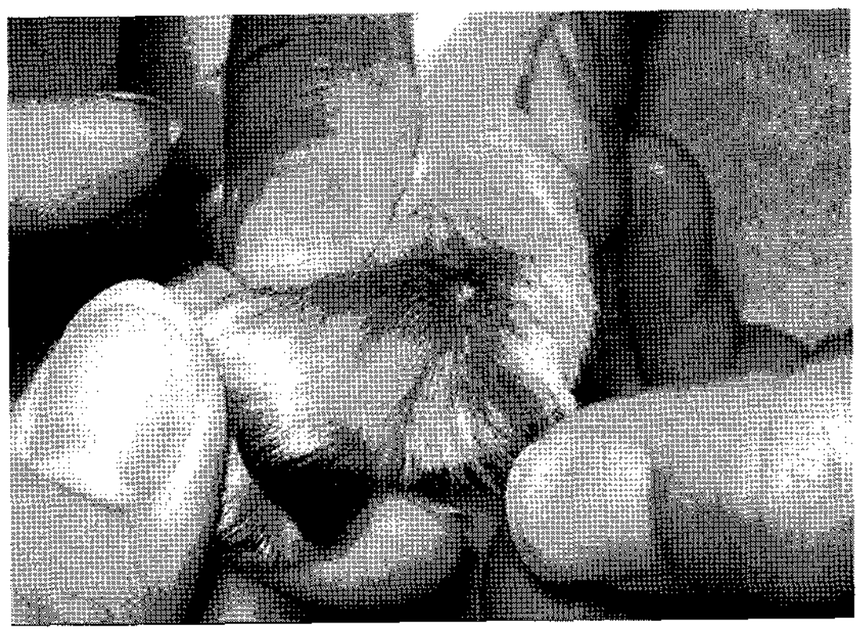

Fig 4. Photograph of the skin lesions 4 weeks after application of 0.1% tacrolimus ointment. Note disappearance of the sinus tract on right forepaw. Swelling and scaling, and erythematous lesion of the paw are improved.

The clinical signs were completely improved 4 weeks after application of tacrolimus (Fig 4). We conducted provocative test with original diet to rule out food allergy. However, the lesions were not relapsed when he resumed his original food regimen. Finally, we clinically diagnosed the dog as AD by his histories, clinical signs, and ruling out other pruritic skin diseases (ectoparasitic infestation). Superficial pyoderma and

otitis externa have been waxed and waned, but the lesion of paw was not relapsed until recently.

Discussion

This patient was given antibiotic therapy to remove secondary bacterial infection for 4 weeks. But, the clinical signs were relapsed in this case immediately after discontinuing therapy. Pododermatitis may respond poorly to antibacterial therapy if underlying cutaneous, metabolic or immunological diseases are not simultaneously addressed (5,14). Therefore, it is very important to verify the underlying cause of pododermatitis.

In this report, daily application of a commercially available 0.1% tacrolimus ointment for 4 weeks was shown to be effective for treatment of pododermatitis secondary to AD in a dog. Erythema and swelling of the paws were improved rapidly. The efficacy of tacrolimus for treatment of skin lesions of canine AD has reported in some studies (2,9). There were improvements from 40% to 75% in a clinically relevant reduction of lesional scores in those studies. The 0.1% tacrolimus ointment appeared to be equivalent in potency to that of potent topical glucocorticoid formulations (hydrocortisone butyrate or bethamethasone valerate) (2). However, unlike many corticosteroids, there are no skin atrophy, glaucoma, other local risks, and the systemic side effects such as hypothalamus/adrenal-axis suppression and growth retardation (5,16). Therefore, recent practice guidelines recommended the use of tacrolimus ointment for long term intermittent therapy of patients not adequately responsive to, or intolerant of, conventional therapy (22).

During the ointment application, there were no significant side effects in this study. According to a previous report (17), the most common adverse events were the sensation of skin burning and pruritus, especially among patients with severe or extensive disease in human. In veterinary studies, the side effects were not remarkable (2,8,9). Further long-term study is required to verify side effects in use of topical tacrolimus for canine AD.

In human, the applications of topical tacrolimus for various dermatoses have been tried. For example, AD, contact dermatitis, psoriasis, steroid-induced rosacea, pyoderma gangrenosum, leg ulcer, and hair growth are considered (7). Likewise, it can be applied in immunomodulatory therapy for various dermatoses in veterinary dermatology.

Although poorly defined, animals with pododermatitis related to immunological dysfunction also have been responsive in the use of anti-inflammatory or immunonodulating agent (12). The pododermatitis can be diagnosed by analysis of immunoglobulin, peripheral blood mononuclear cells assays, lymphocyte phenotyping studies, and histopathological examination (3,4). In this case, we ruled out lymphocytic-plasmacytic pododermatitis based on the results of histopathology and generalized pruritus which is consistent with AD. Therefore we did not perform those laboratory tests to rule out immunological dysfunction.

Even though oral glucocorticoids were conventional therapy for canine AD, for the reason of several side effects, cyclosporine and topical tacrolimus have become available in the last decade. Tacrolimus and cyclosporine share numerous mechanisms of action (19). The inhibition of cytokine gene transcription leads to secondary inactivation of the function of most immune cells involved in the allergic response, such as lymphocytes, dendritic cells, mast cells and eosinophils (13). Because the local lesion (right forepaw) was severely relapsed and tacrolimus is an expensive drug, thus we tried topical therapy with tacrolimus. However, it is less expensive than oral daily treatment with cyclosporine. In addition, the side effects of systemic cyclosporine therapy (vomiting, diarrhea) can be concerned by owner. Based on these considerations, application of tacrolimus ointment can be good choice in refractory localized skin lesions of canine AD.

In conclusion, this case report demonstrates that topical 0.1% tacrolimus ointment is effective treatment option for pododermatitis related to refractory localized skin lesions secondary to AD in the dogs.

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