NOTE *Internal Medicine*

A Case of Hyperplastic Dermatosis of the West Highland White Terrier Controlled by Recombinant Canine Interferon-γ Therapy

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ABSTRACT. A 3.5-year-old, male West Highland White Terrier was diagnosed as having hyperplastic dermatosis by clinical and histopathological findings. Controlling of *Malassezia* overgrowth by antifungal drugs provided a temporal improvement of the skin lesions, but the disease was deteriorated within the next 2 months despite the negative demonstration of the yeasts. Induction of recombinant canine interferon-γ (rCaIFN-γ) therapy resulted in almost complete cure of the skin lesions within 2 months after the initiation of the therapy. No adverse effects were detected during the therapy. Our results suggested that the rCaIFN-γ therapy is potential to be a novel therapeutic option for controlling the breed-specific hyperplastic skin disease.

KEY WORDS: canine, hyperplastic dermatosis, interferon-gamma.

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Hyperplastic dermatosis of the West Highland White Terrier, also known as epidermal dysplasia or armadillo Westie syndrome, is an uncommon, severe and chronic hyperplastic skin disease resembling seborrheic dermatitis or primary seborrhea [1, 7, 8]. Based on the restriction of the disease to West Highland White Terrier, coupled with the evidence of familial involvement, this disease has been considered to have a mode of inheritance [1, 7, 8]. It has been recognized that *Malassezia* overgrowth is associated with the onset or aggravation of the disease in many cases [1, 7, 8]. A recent paper reported two young West Highland White Terrier siblings, in which clinical signs were potentially induced by underlying type-I hypersensitivity to environmental allergen or *Malassezia* yeasts [3]. These findings led us to speculate that this disease is a breed specific hyperproliferative reaction pattern induced by various inflammatory stimuli or infectious agents such as *Malassezia* yeasts [1]. Prognosis of this disease is usually guarded, although control of *Malassezia* overgrowth would provide temporal improvement of clinical signs [1, 7,]. In this study, we describe a canine case of hyperplastic dermatosis of the West Highland White Terrier, whose skin disease was successfully controlled by a recently described immunomodulating therapy of canine allergic dermatitis, recombinant canine interferon-γ (rCaIFN-γ) therapy [2].

A 3.5-year-old, male West Highland White Terrier weighing 8.4 kg, bred indoor, was examined by a referring veterinarian for 8-month history of severe greasy coat and flaking on the entire surface of the body. The dog had episodes of mild otitis externa and seborrheic changes of the skin from 3-month of age, and the lesions were gradually worsened with advancing age. The dog had no signs of respiratory or gastrointestinal diseases around the time of the skin disease. Treatment by oral prednisolone (0.6 mg/kg q24h) and antibiotics (amoxicillin or enrofloxacin, doses unknown), bathing with sulfur-salicylic acid shampoo, feeding with commercially-available lamb&rice diet (manufacturer unknown) and ear cleansing for 4 months had provided temporal improvement of the skin lesions. However, discontinuation of oral prednisolone and antibiotics caused aggravation of the skin lesions within the next 2 months. After 1-month treatment by oral prednisolone (0.3 mg/kg q24h) and enrofloxacin, the lesions had no apparent improvement, and the case was referred to Veterinary Hospital of Tokyo University of Agriculture and Technology (VHTUAT).

Physical examination at VHTUAT on January 2002 revealed a healthy dog except for skin lesions. The dog exhibited generalized hair loss and highly pruritic, erythematous skin lesions covered with large amounts of keratosebaceous debris on the entire surface of the body. Marked hyperpigmentation and lichenification were observed on the ventral aspects of neck, thorax and abdomen, axilla, groin, extremities and tail (Fig. 1). Bilateral ceruminous otitis externa was also recognized. Severe excoriation as a result of self trauma was also observed on the trunk. Careful skin scrapings of the skin lesions were negative for mites or fungi. Impression smears of the keratosebaceous debris on the surface of thorax using tape stripping revealed numerous cocci but no *Malassezia* yeasts. A complete blood count (CBC) analysis and serum chemistry panels yielded unremarkable results.

Treatment by oral cephalexin (30 mg/kg q12h), topical emollients and ear cleansing did not provide any improvement of the lesions. Intradermal tests (IDT) was performed under the sedation by medetomidine hydrochloride (Domitor, Turku, Finland), and revealed positive reaction to Japanese cedar (Hitachi Chemicals, Ibaraki, Japan), but negative for Grass mix (equal parts mixture of orchard, meadow fescue, perennial rye, timothy, Kentucky blue and velvet, Greer

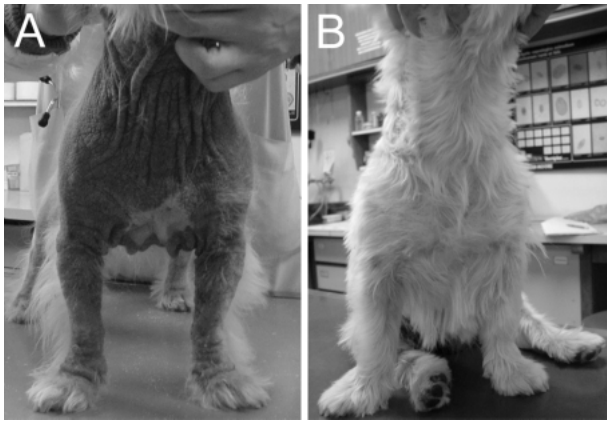

Fig. 1. (A) Clinical findings of the canine case before treatment by rCaIFN-γ. Marked alopecia, lichenification and hyperpigmentation were observed on the neck, ventral thorax and radial forelimbs. (B) Clinical findings in the same dog 2 months after initiating the treatment. No apparent skin lesions were demonstrated on the neck, trunk and extremities.

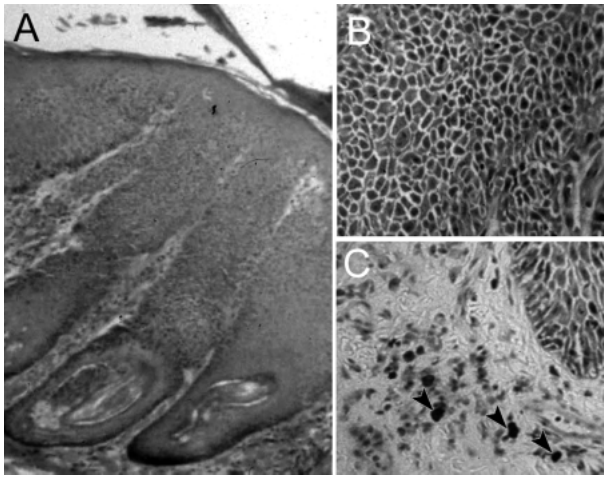

Fig. 2. (A) Skin biopsy of the canine case showing marked acanthosis with hyperplasia of follicular infundibular epithelium (hematoxylin and eosin (H&E) × 100). (B) Higher magnification of skin biopsy in Fig. 2A showing diffuse spongiosis and loss of epidermal polarity (H&E × 400). (C) Toluidine blue staining confirmed some perivascular infiltration of mononuclear cells to be mast cells (arrowheads, Toluidine blue × 400).

Laboratories, Lenoir, NC), mugwort common (Greer Laboratories), house dust mite mix (GS mite mix, Greer Laboratories), molds (*Aspergillus* and *Cladosporium*, Greer Laboratories), flea or cat epithelia (Greer Laboratories) [5, 6]. Serologic allergy tests to detect canine IgE (Hitachi Chemicals, Ibaraki, Japan) revealed low titer of circulating IgE exclusively to timothy.

A skin biopsy was taken from thoracic skin and was fixed in 10% neutral formalin. Hematoxylin and eosin staining of the skin sections revealed marked hyperkeratosis, acanthosis of the epidermis with diffuse spongiosis, excessive keratinocyte mitosis, loss of epidermal polarity, irregular hyperplastic changes of follicular infundibular epithelium and a moderate, perivascular infiltrate of mononuclear cells in the superficial dermis (Fig. 2). The dermal infiltrate was comprised of lymphocytes and mast cells; the latter was confirmed by metachromasia of the cytoplasms by toluidine blue staining (Fig. 2). No mites or fungi were detected anywhere on the skin section. The histopathological findings of the skin lesion in the present case were considered to be compatible with that of hyperplastic dermatosis of the West Highland White Terrier, rather than that of severe allergic dermatitis [1, 8].

At the third presentation to VHTUAT on February 2002, presence of *Malassezia* yeasts was demonstrated by cytological examination of the debris on the thoracic skin. The dog was treated with topical ketoconazole cream (Janssen, Piscataway, NJ) and twice-weekly shampoos with antiseptic and moisturizing agents. Following a 3-month course of treatment, the lesions were markedly improved. At presentation in the middle of April, there was regrowth of hair and resolution of scaling and lichenification, whereas erythema and pruritus were still observed. However, erythema, scaling and pruritus were deteriorated within the next 2 months despite the negative demonstration of the yeast organisms from the skin surfaces. As a therapeutic trial to control the hypersensitivity reactions, the dog was treated by subcutaneous injections of rCaIFN-γ (Toray Company, Tokyo, Japan) [4] at a dose of 10,000 U/kg three times weekly for 2 weeks (days 1, 2, 3, 9, 10 and 11) [2]. At 21 days after initiation of the therapy, pruritus and erythema were markedly decreased, whereas scaling was still observed. The rCaIFN-γ therapy was continued by reducing the frequency of the injection from once in every 7–14 days, depending on patient's response to the maintenance therapy. The skin of the dog was almost normal at 2 months after initiation of the therapy (Fig. 1), except for the existence of mild pruritus only on the face and forelimbs, and did not show apparent relapse of the disease in the next one month. No adverse effects including clinical, hematological and serum biochemical abnormalities were detected during the therapy.

In the present case, the skin disease was started from 2-year of age. However, it shoud not be excluded, that this disease had a mode of inheritance as the mild scaling dermatitis as well as otitis externa, which can be seen as the early lesions in cases of hyperplastic dermatosis, were observed at 3-month after birth. Controlling *Malassezia* overgrowth with topical antifungal cream provided marked improvement of the skin condition, whereas deterioration of the disease was seen on June despite the negative detection of the yeast organisms. These findings taken together suggest that *Malassezia* overgrowth might be at least an aggravating factor of the skin disease in the present case.

rCaIFN-γ therapy has recently been described as a novel, safe and effective therapeutic option for treatment of canine atopic dermatitis [2]. The mechanisms of action of this therapy for canine atopic dermatitis are currently not confirmed, but suggested to be related to the suppression of IgE produc-

tion through the modulation of the Th1/Th2-cytokine imbalance towards Th1 dominance from Th2 dominance [2]. In this study, we applied the rCaIFN-g therapy for the first time for controlling the clinical signs of hyperplastic dermatosis of the West Highland White Terriers. From the positive response to rCaIFN-γ therapy, it is speculated that the hypersensitivity associated with cytokine imbalance is one of the aggravating factor of the skin disease in the present dog, although the involvement of factors other than cytokine inbalances in the pathogenesis of this disease should not be excluded. The allergen causative for the skin disease could not be identified in the present dog. The dog showed negative IDT to environmental allergen except for Japanese cedar. However, hypersensitivity to Japanese cedar was unlikely to be a cause of the skin lesions, as the lesions showed no aggravation during the season of scattering of Japanese cedar pollen (from February to April). Hypersensitivity to timothy was also suspicious in the present case since the low titer of circulating IgE to timothy was inconsistent to the negative findings of IDT; the latter is currently believed as the most reliable method to detect allergen-specific IgE in a highly specific manner [8]. Nevertheless, the present study suggests that the rCaIFN-γ therapy is potential to be a therapeutic option for controlling the breed-specific disorder, even though the causative stimuli of the disease are unidentifiable or unavoidable.

In conclusion, although a short-term clinical course in only one dog was evaluated in this study, our results raise a speculation that hypersensitivity associated with cytokine imbalances is one of the aggravating factors, at least in a part of dogs affected with the disease. Further studies with a long-term evaluation in a larger group of dogs will provide novel insights not only into the therapeutic effectiveness of the therapy but also into undefined pathogenesis in the breed-specific hyperplastic skin disease.

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