SUCCESSFUL TREATMENT OF IDIOPATHIC SEBACEOUS ADENITIS IN A LIONHEAD RABBIT

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Abstract

A 15-month-old, ovariohysterectomized female Lionhead rabbit was presented with generalized chronic exfoliative dermatitis and patchy alopecia. General physical examination revealed no abnormalities apart from a body condition score of 4 of 9. Ectoparasitic infestation, dermatophytosis, *Malassezia* dermatitis, epitheliotropic lymphoma, thymoma-associated exfoliative dermatitis, and autoimmune hepatitis-associated exfoliative dermatitis were excluded on the basis of skin scrapings, fungal culture, cutaneous histopathology, thoracic radiography, and the results of hematologic and biochemical analyses. Histopathology of the skin showed orthokeratotic hyperkeratosis, absence of sebaceous glands and mural lymphocytic folliculitis, consistent with sebaceous adenitis. The extent and severity of the skin lesions were scored by the Rabbit Dermatitis Extent and Severity Index adapted from the recently published Canine Atopic Dermatitis Extent and Severity Index–03. Once-daily oral treatment with 5 mg/kg of ciclosporin A dissolved in an equal amount of a medium-chain triglyceride solution (Miglyol 812; Bufa, Uitgeest, The Netherlands) was initiated, but the response to this was poor. Therefore, while maintaining the oral treatment, topical treatment with phytosphingosine products was given. The rabbit's coat was clipped and a phytosphingosine 0.2% microemulsion spray (daily), a phytosphingosine 0.1% shampoo (weekly), and a phytosphingosine 1% spot-on treatment (weekly) were applied. Nine months later, there had been significant hair regrowth on previously hairless areas and the Rabbit Dermatitis Extent and Severity Index confirmed the marked improvement with a 91% reduction in the original score. Serum ciclosporin concentrations were undetectable throughout the treatment period.

Key words: ciclosporin; phytosphingosine; rabbit; sebaceous adenitis; treatment

Idiopathic sebaceous adenitis (ISA) is an inflammatory disease of the sebaceous glands, resulting in their destruction.[1] ISA is primarily diagnosed in dogs but has also been reported in rabbits, cats, a horse, and humans.[2-6] Currently, ISA is believed to be an immune-mediated disease, but the pathogenesis is not fully understood.[7] In rabbits, physical signs may include a focal to generalized, dry, brittle hair coat; scale; follicular casts; and alopecia. Affected animals are also predisposed to secondary bacterial pyoderma.[1,7] Compatible histologic findings include inflammation and a reduction in numbers or a total absence of sebaceous glands in combination with a mural lymphocytic folliculitis. These features are comparable with those observed with canine ISA.[8,9]

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It has been reported that the clinical disease differs in long- and short-coated dog breeds.[7] In the former, the lesions often appear as symmetric multifocal alopecia[10] associated with scaling and a dull and brittle hair coat.[11,12] Lesions start on the head, the pinnae, the dorsal neck, and the tail and can extend to the dorsal midline. In short-haired dogs, lesions are reported to be more arciform,[7] with coalescing areas of alopecia and fine, non-adherent scaling, predominately on the trunk.[2,13] Treatment has largely been restricted to antiseborrheic shampoos, emollient rinses, and humectants. The topical treatments have been useful for partial control of the scaling, but full recovery is rarely achieved and the treatment protocol is very labor intensive for the owner.[14,15] Recently, ciclosporin A (CsA) and triglycerides have been described as successful treatment regimens for this disease in the rabbit.[16]

CASE REPORT

A 15-month-old, ovariectomized female lionhead rabbit, weighing 1.8 kg, was referred to the Dermatology Service of The Hospital for Small Animals, The Royal (Dick) School of Veterinary Studies, The University of Edinburgh, with a 2-month history of a generalized dermatosis. The rabbit's diet consisted of commercial rabbit pellets, supplements, and a variety of vegetables. Vaccinations for myxomatosis (Nobivac Myxo; Intervet UK Ltd., Walton, UK) and viral hemorrhagic disease (Cylap; Fort Dodge Animal Health Ltd., Southampton, UK), as well as preventative treatment for *Encephalitozoon cuniculi* (Panacur Rabbit; Intervet UK Ltd., Bucks, UK), were up to date. There was another rabbit in the household, but neither it nor the owner had cutaneous lesions. The owner reported that the rabbit's general health was good. No treatment had been administered to the rabbit patient before referral.

On physical examination, the rabbit was bright and alert with a body condition score of 4 of 9, and apart from the cutaneous lesions, no abnormalities were detected. There was non-pruritic alopecia with multifocal, adherent white scales; hyperkeratotic crusts; and fronds (Figs. 1a and 1b). Follicular casts were most prominent on the dorsal cervical region and in areas of hyperkeratotic crusting. Lesions were generalized, affecting the head (periocular and occipital regions), the concave aspect of the pinnae, the neck, the body, and all 4 limbs. No lesions were detected in the oral cavity, on the planum nasale, or in the ear canals.

The extent and severity of the skin lesions were scored by adapting the recently published Canine Atopic Dermatitis Extent and Severity Index–03[17] to produce the Rabbit Dermatitis Extent and Severity Index (RDESI). In brief, 3 cardinal dermatologic signs of dermatoses (erythema, hyperkeratosis, and alopecia) were scored for severity (none, 0; mild, 1; moderate, 2-3; and severe, 4-5) at 41 different body areas (Table 1). This gave an extent and severity score of 235 out of a total possible 615.

Differential diagnoses for the rabbit included ectoparasitic infestation, dermatophytosis, *Malassezia* dermatitis, epitheliotropic lymphoma, ISA, thymoma-associated exfoliative dermatitis, and autoimmune hepatitis-associated exfoliative dermatitis.[8,16,18,19] Multiple skin scrapings, trichograms, and tape strippings were negative for ectoparasites, dermatophytes, and *Malassezia* spp. Samples collected for fungal culture were subsequently negative. Tape strippings made after removal of hyperkeratotic crusts showed degenerate neutrophils and phagocytosed cocci. A blood sample was collected for standard hematologic and biochemical analyses. The results of both tests were within the respective reference ranges (Table 2). Radiographic examinations of the dorsoventral and lateral thorax showed no abnormalities. Biopsy specimens from non-affected skin were obtained from the occipital area, dorsal thorax, and ventral abdomen under local anesthesia (0.5 mL of lidocaine, subcutaneously, 1% wt/vol lidocaine injection; B/Braun Melsungen, Melsungen, Germany) by use of disposable 6-mm biopsy punches (Stiefel Laboratories, High Wycombe, UK). The biopsy sites were closed with simple interrupted poliglecaprone 25 suture material (Monocryl 3-0 UPS; Ethicon, Livingston, UK). Samples were fixed in 10% buffered formol saline solution, processed to paraffin, and stained with hematoxylin-eosin and periodic acid-Schiff. On histopathologic examination of harvested skin lesions, there was, variably, an absence of sebaceous glands and/or sebaceous adenitis with marked follicular and superficial hyperkeratosis (Figs. 1g and 1h), which was consistent with a diagnosis of sebaceous adenitis. No evidence of dermatophyte infection was detected in tissue stained with periodic acid-Schiff.

In view of the severity of the physical signs and the cytological evidence of a secondary bacterial infection, therapy with enrofloxacin (Baytril 2.5% oral solution; Bayer Ltd., Newbury, UK) at a dosage of 20 mg/kg administered orally once every 24 hours was instituted after the initial ex-

FIGURE 1. (a) Hyperkeratotic crust affecting the lower left eyelid. (b) Hyperkeratotic crusts and fronds affecting the dorsal neck. Small white scales are also visible on the erythematous and alopecic skin. (c) The rabbit 12 weeks later during a whole body clip. Multifocal, circumscribed, hyperkeratotic crusts are visible. (d) Close view of the rabbit's dorsal neck and thorax from Figure 1c. (e) The rabbit 9 months after the treatment. (f) Close-up view of the dorsal thorax. The remaining adherent white scales and yellowish casts attached to the growing hair should be noted. (g) Photomicrograph of skin from the dorsal thorax. One should note the perifollicular lymphocytic folliculitis (hematoxylin-eosin stain, original magnification ×40). (h) Photomicrograph of skin from the dorsal thorax showing lymphocytic inflammation of a sebaceous gland (hematoxylin-eosin stain, original magnification ×400).

amination. However, there was no clinical improvement after 14 days of antibacterial treatment, and because a definitive diagnosis of ISA had been determined, treatment with CsA (Neoral; Novartis Pharmaceuticals Ltd., Surrey, UK) was instituted at a dosage of 5 mg/kg administered orally once every 24 hours dissolved in an equal amount of a triglyceride solution (Miglyol 812; Bufa, Uitgeest, The Netherlands) as reported in an earlier case.[16] Monitoring of biochemical parameters was recommended to the referring veterinary surgeon.

TABLE 1. Sample of a Rabbit Dermatitis Extent and Severity Index RDESI, adapted from the recently published Canine Dermatitis and Severity Index (CADESI)–03[17]

RDESI BODY AREAS				Erythema	Hyperkeratosis	Alopecia	TOTAL
	Left	Preauricular	1				
		Periocular	2				
	Right	Preauricular	3				
		Periocular	4				
	Muzzle		5				
	Chin		6				
Head	Dorsal		7				
Ear Pinna	Left	Convex	8				
		Concave	9				
	Right	Convex	10				
		Concave	11				
Neck	Dorsal		12				
	Ventral		13				
	Lateral	Left	14				
		Right	15				
Axilla	Left		16				
	Right		17				
Sternum			18				
Thorax	Dorsal		19				
	Lateral	Left	20				
		Right	21				
Inguinal	Left		22				
	Right		23				
Abdomen			24				
Lumbar	Dorsal		25				
Flank	Left		26				
	Right		27				
Forelimb	Left		28				
	Right		29				
Forefoot	Left	Palmar	30				
		Dorsal	31				
	Right	Palmar	32				
		Dorsal	33				
Hind Limb	Left		34				
	Right		35				
Hind Foot	Left	Plantar	36				
		Dorsal	37				
	Right	Plantar	38				
		Dorsal	39				
Perianal			40				
Perigenital			41				
grading: 0: NONE 1: MILD 2 or 3: MODERATE 4 or 5: SEVERE					**TOTAL Score** (615 maximum)		

After 6 weeks of therapy, there was a slight improvement in the skin condition, with a reduction in the RDESI score from 235 to 210. After 6 more weeks on the same treatment regimen, the RDESI had fallen by a total of 28.5% to 168 (Figs. 1c and 1d). A blood sample was collected to evaluate serum standard biochemical parameters and the CsA concentration (Table 2). All standard blood parameters were within the respective reference ranges, and the CsA assay, using tandem mass spectrometry, indicated that the serum concentration was less than 25 μg/L, the lower limit of the assay's sensitivity. During this follow-up visit, the rabbit's coat was clipped

TABLE 2. Hematologic and biochemical blood analyses

Parameters (Reference Range)	Day 1	Day 90	Day 270
Packed cell volume (33%-50%)	*	*	0.33
Red blood cells (5.1-7.9 × 10^{12}/L)	*	*	5.11
Hemoglobin (10-17.4 g/dL)	*	*	10.7
Reticulocytes (0.0-0.0 × 10^{12}/L)	*	*	0
White blood cells (3.94-8.192 × 10^{9}/L)	*	*	3
Neutrophils—segmented (0.75-3.78 × 10^{9}/L)	*	*	0.78
Lymphocytes (1.62-4.687 × 10^{9}/L)	*	*	2.13
Monocytes (0.07-0.46 × 10^{9}/L)	*	*	0.09
Eosinophils (0.01-2.69 × 10^{9}/L)	*	*	0
Platelets (250-650 × 10^{9}/L)	*	*	479
Bile acids (< 15.00 μmol/L)	4.3	3.7	5.9
Total protein (54-75 g/L)	58.3	60.8	61.8
Creatinine (44.2-229 μmol/L)	121	117	118
Urea (6.14-8.38 mmol/L)	7.2	6.7	8
Gamma-glutamyl transferase (0-7.0 IU/L)	7	6	6
Calcium (2.45-4.50 mmol/L)	3.52	3.92	4.38
Ciclosporin (μg/L†)	NA	<25	<25

Abbreviation: NA, not applicable.
*Values not determined.
†Reference range in rabbits not determined.

(Figs. 1c and 1d). Treatment with CsA and the oral triglyceride solution was continued as before, and in addition, phytosphingosine products designed for the treatment of seborrheic conditions in cats and dogs were included in the treatment protocol. The additional treatment products were a microemulsion spray (Douxo Seborrhea Micro-emulsion Spray; Sogeval Laboratories, Coppell, TX USA) that was applied daily and a phytosphingosine 0.1% shampoo (Douxo Seborrhea Shampoo) and phytosphingosine 1% spot-on treatment (Douxo Seborrhea Spot-on) that were both applied once weekly.

Nine months later, the rabbit was still receiving all medications. There had been significant hair regrowth on previously hairless areas (Figs. 1e and 1f). Most of the hyperkeratotic lesions had resolved, with only some healing lesions on the upper eyelids remaining, and there was only very mild generalized scaling. The RDESI confirmed the marked improvement with a further reduction in total score to 21, a 91.0% reduction from the original score. The results of the standard hematologic and biochemical tests were once again within the respective reference ranges, apart from a mild neutropenia (Table 2). Serum CsA concentrations were again undetectable. The owner was advised to maintain the treatment with oral CsA and triglycerides but to reduce the frequency with which the phytosphingosine products were used unless there was a relapse in the condition. Twenty-nine months later, the rabbit was still receiving all medications and all of the lesions had resolved; however, since that time, the case has been lost to follow-up.

DISCUSSION

The etiology of ISA is unknown. A genetically programmed destruction of the sebaceous glands has been hypothesized[12] on the grounds that, in certain dog breeds, it has an autosomal recessive mode of inheritance. An immune-mediated pathogenesis[20] is suggested by the presence of a T cell–mediated inflammatory reaction around the sebaceous gland duct and hair follicle.

ISA is characterized by varying degrees of exfoliation and alopecia. Pruritus is generally absent unless secondary microbial infection is present. The diagnosis of ISA is based on the cutaneous histologic changes and the elimination of other possible diagnoses.[8,16] The case reported here shares many of the clinical and histopathologic features (e.g., hyperkeratosis, loss of sebaceous glands, lymphocytic mural folliculitis, presence of apoptotic cells) of rabbit thymoma-associated exfoliative dermatitis[18] and autoimmune hepatitis-associated exfoliative dermatitis.[19] These were

excluded on the basis of thoracic radiography and the results of hematologic and biochemical analyses.

Dermatologic examination of a recently described case of ISA in another rabbit showed more severe scaling, erythema, and alopecia present on the head, dorsal cervical area, ventral thorax and abdomen, dorsum, and hind limbs.[16] Follicular casts were present, especially on the ear margins, and the rabbit showed a pain response when touched. This contrasts with the present case in which the lesions comprised multifocal alopecia associated with scaling, crusting, and a dull and brittle hair coat similar to those reported previously in dogs.[2,13]

A recent publication describes the successful treatment of ISA in a rabbit with oral CsA, multiple medium-chain synthetic neutral oil triglycerides, and a daily essential fatty acid supplement.[16] In the current case, the same combination of oral CsA and multiple medium-chain synthetic neutral oil triglycerides without the essential fatty acid supplement only achieved a minimal treatment response. However, the earlier case report concluded that the essential fatty acid supplement was unlikely to have contributed to the resolution of the ISA.[16] A recent comparison of treatment protocols for canine ISA found that topical treatment, both alone and in combination with CsA, appeared to reduce scaling more effectively than CsA alone.[15] This study also showed that the reduction in inflammation of the sebaceous glands was greater when oral CsA and topical therapy were combined.[15] These observations are supported by the response of the present case to the combination of oral CsA and topical phytosphingosine products, which resulted in an almost complete resolution of the clinical signs. The treatment regimen combining oral CsA and topical phytosphingosine products appears to be safe and effective. However, it is time-consuming and may have an impact on owner compliance, thereby limiting its use in practice situations.

Failure to identify serum concentrations of CsA above the lower limit of the reference range may be explained by individual variation in CsA metabolism. Such interindividual differences have been described in a canine study where trough serum CsA concentrations were measured 24 hours after medication administration in 16 dogs.[21] Detectable concentrations were present in only 14 samples, and the range of concentrations was wide (median concentration, 21.25 μg/L; range, 0.2-1076 μg/L).[21] In addition, a number of reports where CsA was used in dogs have concluded that the response of a condition is often independent of the actual plasma concentration.[21,22]

CsA is being increasingly used for the treatment of diseases of small animals.[23] CsA is licensed for veterinary use as a topical ophthalmic 0.2% ointment (Optimmune; Intervet/Schering-Plough, London, UK) for the treatment of keratoconjunctivitis sicca in dogs and as an oral 10, 25, 50, and 100 mg capsular preparation (Atopica; Novartis Animal Health, Basel, Switzerland) for the treatment of atopic dermatitis in dogs; in addition, it has recently been approved for the treatment of chronic allergic dermatitis in cats as a 100 mg/mL oral solution (Atopica for Cats; Novartis Animal Health).

Generic formulations of CsA for use in humans have recently been developed, and some of these are commercially available worldwide (http://www.equoral.net/files/regulatory.html) and may be significantly cheaper than the licensed preparations. Studies comparing the bioequivalence of Neoral and Equoral (Teva Pharmaceuticals, Praha, Czech Republic), a human generic (hgCsA) microemulsified formulation of CsA, and their pharmacokinetic conversion have shown that these drugs are bioequivalent and interchangeable in stable human patients.[24-26] The use of a generic formulation in clinical practice may increase the access to CsA in countries where the licensed product may be more expensive or not available. Recent observations indicate that Equoral oral solution has a similar efficacy to the licensed product and does not appear to be associated with a greater risk of adverse reactions in dogs.[27] However, randomized studies in greater numbers of animals are required before final conclusions are reached.

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