

Investigation on the association between atopic dermatitis and the development of mycosis fungoides in dogs: a retrospective case-control study

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What is known about the topic of this paper

- In human medicine, a relationship between Mycosis Fungoides and a previous history of Atopic Dermatitis has been reported.
- No information is currently available in veterinary medicine.

What this paper adds to the field of veterinary dermatology

- Dogs with Atopic Dermatitis were found to be more likely to develop Mycosis Fungoides later in life.
 - Whether this is directly linked to Atopic Dermatitis or might be a consequence of immunomodulatory therapy or other factors is unknown.
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Abstract

In human medicine, the relationship between the immunodysregulation observed in atopic dermatitis (AD) and the development of mycosis fungoides (MF) has triggered considerable interest due to the increasing number of patients with MF who have a previous history of AD. The purpose of this retrospective case-control study was to investigate whether dogs diagnosed with MF were more likely to have AD. The records of 96 000 canine patients at the University of Florida were searched. Inclusion criteria were a clinical and histological diagnosis of MF. Dogs admitted to the University of Florida, Veterinary Medical Center during the same time period (1991–2004) without a diagnosis of MF were included as controls. Four controls for each study dog were randomly selected (matched by year of admission). Frequency of AD and other exposure variables were compared among case and control dogs by using conditional logistic regression. Records of 19 dogs with a diagnosis of MF were identified. Five of them (5/19, 26.3%) had previous diagnosis of AD. The odds of having MF was 12 times (OR = 12.54; 95% CI = 1.95–80.39; $P < 0.01$) higher in dogs with AD than in dogs without AD. In conclusion, this study suggests an association between AD and MF in dogs. Future studies

are necessary to confirm this finding and to investigate the pathogenic mechanisms involved in this association.

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Introduction

Cutaneous T-cell lymphomas (CTCLs) are a heterogeneous group of disorders of peripheral T lymphocytes.¹ The most frequent form of CTCL in humans and dogs is mycosis fungoides (MF). It is distinguished from other peripheral T-cell lymphomas that affect skin by the prominent epidermotropism of T-cell infiltrates.^{2–9} In the last decade in human medicine, there has been an increase of case reports of patients diagnosed with MF who had a previous history of atopic dermatitis (AD).^{10–15} This is of particular importance when considering the fact that the incidence of AD has dramatically increased in recent years in developed countries.¹⁶ The reason of increased number of anecdotal reports is not completely known. One possible explanation could be the increased incidence of AD or the increased expertise to diagnose MF. The clinical observation of this association has triggered a number of studies.^{17–23} Although the results of these studies are inconsistent, it is speculated that chronic skin diseases and persistent antigenic stimulation may lead to the stimulation of lymphocyte proliferation and, potentially, the development of MF.

In veterinary medicine, to the best of the authors' knowledge, there are no studies that have investigated such relationship. Because of the fact that AD is a common disease in dogs,¹⁶ it is important to evaluate whether these patients are at increased risk for developing MF later on in life. Thus, the purpose of this study was to evaluate whether there is an association between AD and MF in dogs.

Materials and methods

Study population

Medical records of dogs (96 000) seen from 1991 to 2004 at the University of Florida, Veterinary Medical Center (UF VMC) were retrospectively searched. Records of dogs diagnosed with MF were selected.

Study design

This study was designed as a case-control study. The frequency of the main exposure of interest (AD) and potential confounding factors was compared between case (MF) and control dogs.

Selection of cases

Mycosis fungoides cases were only included if information in the medical records showing suggestive clinical signs (e.g. pruritus,

Table 1. Details of 19 dogs diagnosed with mycosis fungoides and their concurrent skin diseases and therapies

N°	Sex	Age (years)*	Breed	Concurrent skin diseases and therapy
1	FS	2	Australian shepherd	None
2	FS	7	German shepherd	None
3	MC	10	West highland white terrier	None
4	FS	13	American Staffordshire terrier	None
5	FS	14	Mixed	None
6	FS	14	Mixed	None
7	M	10	Labrador	None
8	MC	11	German shepherd	AD, prednisone, amoxycillin-clavulanic acid, clindamycin
9	M	10	Labrador	AD, hydroxyzine, enrofloxacin, allergen-specific immunotherapy
10	M	8	German shepherd	AD, cephalexin, amoxycillin-clavulanic acid, allergen-specific immunotherapy
11	FS	12	Mixed	None
12	F	7	Mixed	None
13	FS	6	Mixed	None
14	M	2	Rottweiler	None
15	M	8	Gordon setter	AD, topical cyclosporin A (Optimmune®), diphenhydramine, cephalexin, amoxycillin-clavulanic acid
16	M	7	Shar-pei	AD, prednisone, cephalexin, enrofloxacin
17	FS	11	Eskimo spitz	None
18	F	10	Golden retriever	None
19	FS	8	Labrador	None

*Age of dogs at the time mycosis fungoides was diagnosed. AD, atopic dermatitis; F, female; FS, female spayed; M, male; MC, male castrated.

exfoliative erythroderma, plaques, and nodules) and characteristic histopathological findings was provided.^{3–5}

Selection of controls

Dogs admitted to the UF VMC during the same time period (1991–2004) and with a negative diagnosis of MF were considered for inclusion as controls. Four dogs for each case study dog²⁴ were randomly selected (matched by year of admission) using the Research Randomizer Program® (www.randomizer.com).

Diagnosis of atopic dermatitis

The main exposure of interest was AD. Information in the medical records of suggestive AD history, compatible clinical signs, and indication of exclusion of other pruritic diseases as appropriate for each case (such as, scabies, demodicosis, food allergy, flea allergy) was required for a diagnosis of AD. Additionally, positive allergy test [either intradermal test (IDT) and/or serology test] was required. At the UF VMC, an allergy test is considered positive when three or more positive reactions are detected. Moreover, a positive reaction on IDT is defined as 2+ or higher on subjective evaluation (saline being used as negative control and scored 0 and histamine being used as positive control and scored as 4+). At the UF VMC, serology samples are submitted to Heska® (Fort Collins, CO, USA). According to the company, a positive reaction is defined when the optical density (OD) is > 150 EA units (www.heska.com).

Data collection

For each record the following information was retrieved and analysed: sex, age of disease onset, breed, previous treatments [with special emphasis on cyclosporin A (CsA) and glucocorticoid therapy], and diagnosis of AD.

Statistical analysis

Conditional logistic regression²⁵ was used to model the odds of being a case dog (MF) as a function of exposure to AD. Variables for age, breed and sex were included as required variables in the model to adjust for potential confounding effects. Crude and adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were reported. Because this study included 19 case dogs only, the variable for age was dichotomized (by using the median as a cut-off point) to facilitate

the interpretation of the OR. Similarly, because the variable for breed included 39 breeds this variable was also dichotomized (high vs. low risk breeds). In this study, the OR was used as an epidemiologic measure of association between a factor (e.g. AD) and risk of lymphoma (MF). Thus, if a particular factor was not associated with risk of MF, the OR was 1. The greater the departure of the OR from 1 (either larger or smaller), the stronger the association (either positive or negative) was between the factor and the risk of MF. The upper and lower limits of a 95% CI indicate that one can be 95% confident in the assertion that the true OR falls within this interval. If the interval is broad, its precision is low. For all analyses a *P*-value < 0.05 was considered significant.

Results

Study population

Medical records of 19 dogs diagnosed with MF fulfilled the inclusion criteria. Eleven dogs were females (2 intact) and eight were males (6 intact) (Table 1). The average age of the dogs at the time MF was diagnosed was 8.95 years (range: 2–14 years). Fifteen dogs were purebred and four were mixed-breed dogs. Two dogs had a history of short-term therapy (< 3 months) with prednisone, and one dog had a history of topical CsA treatment for keratoconjunctivitis sicca. Five dogs were diagnosed with AD. Three of them were skin tested and had positive reactions on IDT and two of them were serologically tested. On average AD was diagnosed 4.4 years (range: 1–10 years) prior to diagnosis of MF. No other cutaneous diseases were reported.

Epidemiological analysis

The frequency distribution of case (MF) and control dogs by the investigated risk factors is shown in Table 2. In the univariable analysis, AD was significantly associated with the risk of developing MF (*P* < 0.01, Table 2). In the multivariable analysis, the odds of having MF were 12 times higher in dogs exposed to AD, compared to non-exposed dogs (OR = 12.54; 95% CI = 1.95–80.39; *P* < 0.01, Table 3).

Table 2. Univariable analysis – Frequency distribution of atopic dermatitis and potential confounding factors (age, breed and sex), crude odds ratio and 95% confidence interval among 19 dogs with mycosis fungoides and 76 control dogs without mycosis fungoides

Variables	MF cases	Controls	Crude OR	95% CI	P-value
AD					
No	14	74	1	*NA	NA
Yes	5	2	10	1.94–51.54	< 0.01
Age (years)					
1–7	6	41	1	NA	NA
≥ 8	13	35	2.36	0.84–6.58	0.1
Breed					
Low risk†	11	56	1	NA	NA
High risk‡	8	20	2.36	0.71–7.82	0.15
Sex					
Female	11	46	1	NA	NA
Male	8	30	1.1	0.41–2.99	0.83

MF, mycosis fungoides; AD, atopic dermatitis; OR, odds ratio; CI, confidence interval; NA, non-analysable.

*Reference group.

†Mixed breed, Australian Shepherd, American Staffordshire terrier, Rottweiler, Setter Gordon, Shar-pei, Eskimo spitz, Doberman, Newfoundland, Miniature pincher, Miniature schnauzer, Wire fox terrier, Whippet, Dachshund, Lhasa apso, Chihuahua, Pug, Airedale terrier, Belgian malinois, Poodle, Chow chow, Bichon frise, Pembroke welsh corgi, Yorkshire terrier, Fila brasileiro, German shorthair pointer, Border collie, Shetland sheepdog, Greyhound.

‡German Shepherd, West Highland White Terrier, Labrador, Golden retriever, Cocker spaniel, Shih tzu, Boxer, Basset hound, Boston terrier.

Although the 95% CI for the OR of age included 1, the odds of having MF increased among older dogs (Table 3).

Discussion

The results of this study suggest that dogs with MF were more likely to have been diagnosed with AD earlier in life. These results are in agreement with previous reports in the human literature in which patients with MF have frequently a clinical history of AD.^{10–12,14,15,26} Interestingly, in human medicine there is only one case-control study that showed a positive association between a familiar history of atopy (atopic eczema, allergic rhinitis and asthma) and development of MF.¹⁹ It is important to note that some studies in human medicine failed to report an association between atopy and MF,^{21–23} possibly, because in these studies atopy was defined as asthma, and hay fever rather than AD.^{21–23}

The mechanism for an association between AD and MF has not been elucidated. A possible association between these two diseases can be tentatively explained by similarities in lymphocyte phenotypes involved in AD and MF, an analogue cytokine background, and a potential role for IgE antibodies and persistent antigenic stimulation by bacteria in both disorders.^{1,27,28–47} It has been hypothesized that some of the immunological mechanisms involved in AD (e.g. over expression of IL-2, IL-4, IL-5, IL-10, and hyperplasia of dendritic cells) may modify the functionality of T cells, thus increasing the risk of lymphoma.¹⁴ IgE may possibly play a role in both diseases because patients with MF also have high serum IgE levels.^{10–13,48–50}

Table 3. Multivariable conditional logistic regression model for risk of mycosis fungoides in dogs. Analysis of atopic dermatitis and potential confounding factors (age, breed and sex), and adjusted odds ratio and 95% confidence interval

Variables	Adjusted OR	95% CI	P-value
AD			
No	1	*NA	NA
Yes	12.54	1.95–80.39	< 0.01
Age (years)			
1–7	1	NA	NA
≥ 8	2.19	0.74–6.49	0.15
Breed			
Low risk†	1	NA	NA
High risk‡	2.66	0.65–10.80	0.16
Sex			
Female	1	NA	NA
Male	0.47	0.13–1.67	0.24

AD, atopic dermatitis; OR, odds ratio; CI, confidence interval; NA, non-analysable.

*Reference group.

†Mixed breed, Australian Shepherd, American Staffordshire terrier, Rottweiler, Setter Gordon, Shar-pei, Eskimo spitz, Doberman, Newfoundland, Miniature pincher, Miniature schnauzer, Wire fox terrier, Whippet, Dachshund, Lhasa apso, Chihuahua, Pug, Airedale terrier, Belgian malinois, Poodle, Chow chow, Bichon frise, Pembroke welsh corgi, Yorkshire terrier, Fila brasileiro, German shorthair pointer, Border collie, Shetland sheepdog, Greyhound.

‡German Shepherd, West Highland White Terrier, Labrador, Golden retriever, Cocker spaniel, Shih tzu, Boxer, Basset hound, Boston terrier.

Interestingly, the bcl-2 gene, a gene encoding proteins that inhibit apoptosis, appears to play a role in both AD and MF as an over-expression has been reported in both diseases.^{51–53} Additionally, staphylococcal superantigens can exacerbate clinical disease of AD and MF.^{29,53} The ability of neoplastic lymphocytes to proliferate in response to bacterial toxins suggests that toxins may play an important role.⁵⁴ As bacteria have increased ability to colonize atopic skin,^{55–61} it is reasonable to speculate that persistent stimulation by bacterial antigens could contribute to the potential development of lymphoma in some patients with AD.

It is possible that chronic drug therapy rather than underlying AD plays a role in the development of MF. In the atopic dogs later on diagnosed with MF, treatments for AD included short-term therapy with prednisone ($n = 2$), antihistamine therapy ($n = 2$) and allergen-specific immunotherapy ($n = 2$). The possible implications of these therapies in the development of MF have not been investigated in veterinary medicine. In human medicine, case reports have linked antihistamines to the development of pseudolymphoma.^{62,63} Therefore, it is possible that multidrug therapy with agents known to exert immunomodulatory effects could increase the susceptibility to develop atypical lymphoid hyperplasia and malignant lymphoma, although in the cases reported in this study a temporal association was not noted.

It is possible that the large proportion of atopic dogs found in this study was the result of the fact that these patients had a long-standing relationship with the dermatology service and that their skin was more closely evalu-

ated and readily diagnosed with MF compared to other dogs that did not have a history of chronic skin disease. Because of the retrospective nature of this study and the small number of MF dogs, the results of this study are to be considered preliminary. A prospective case-control study with long-term follow-up of dogs with AD or another retrospective case-control study may be necessary to conclusively evaluate this association. In such prospective study, the AD group and the control group would have to be matched for exposure to drugs and breed.

To summarize, in this study, dogs with AD were found to be more likely to develop MF later in life. Whether this is directly linked to AD or might be a consequence of immunomodulatory therapy or other factors is unknown. A prospective long-term study with large number of patients would be ideal to better evaluate the association between these two diseases.

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Résumé En médecine humaine, la relation entre la dérégulation immunitaire observée dans la dermatite atopique (AD) et le développement d'un mycosis fungoides (MF) a suscité un intérêt considérable, à cause de l'augmentation du nombre de cas de MF pour lesquels une histoire de dermatite atopique existait. Le but de cette étude rétrospective était de déterminer si les chiens souffrant de MF étaient plus à risque d'être atopiques. Les données de 96000 chiens présentés à l'université de Floride ont été analysés. Les critères d'inclusion étaient un diagnostic clinique et histologique de MF. Les chiens admis à l'UF VMC pendant la même période (1991–2004) sans diagnostic de MF ont été inclus comme contrôles. Quatre contrôles pour chaque chien de l'étude ont été sélectionnés au hasard (choisis par année d'admission). La fréquence de l'AD et d'autres données épidémiologiques ont été comparées entre les cas et les contrôles en utilisant les techniques traditionnelles. 19 chiens à MF ont été identifiés. Cinq d'entre eux (5/19, 26,3%) souffraient auparavant d'AD. Le risque d'avoir un MF était 12 fois (OR = 12.54; 95% CI = 1.95 à 80.39; $P < 0.01$) plus élevé chez les chiens à AD que chez les chiens sans AD. En conclusion, cette étude suggère une association entre AD et MF chez le chien. Des études supplémentaires sont indiquées pour confirmer ces données et pour étudier les mécanismes pathogéniques responsables de cette association.

Resumen En medicina humana la relación entre la disregulación inmunológica observada en dermatitis atópica (AD) y la observada en micosis fungoides (MF) ha levantado un considerable interés debido al creciente número de pacientes con MF que previamente padecieron AD. El propósito de este estudio caso-control retrospectivo fue investigar si era más probable que los perros diagnosticados con MF hubieran tenido AD. Para ello se estudiaron los archivos de 96000 perros de la Universidad de Florida. Los criterios de inclusión fueron el diagnóstico clínico e histológico de MF. Perros admitidos a la Universidad de Florida durante el mismo período (1991–2004) sin un diagnóstico de MF se incluyeron como controles. Se escogieron al azar cuatro controles para cada perro del estudio (emparejados de acuerdo al año de admisión). La

frecuencia de AD y otras variables de exposición se compararon entre los perros del estudio y los control utilizando regresión lógica condicional. Se identificaron fichas clínicas de 19 perros con un diagnóstico de MF. Cinco de ellos (5/19, 26.3%) tuvieron una historia previa de AD. La probabilidad de tener MF fue 12 veces mayor (OR= 12.54; 95% CI=1.95 hasta 80.39; $P < 0.01$) en perros con AD que en perros sin AD. Así pues concluimos que este estudio sugiere una asociación entre AD y MF en perros. Más estudios serán necesarios para confirmar este hallazgo así como para investigar los mecanismos patogénicos implicados en dicha asociación.

Zusammenfassung In der Humanmedizin hat die Beziehung zwischen der Immundysregulierung, die bei atopischer Dermatitis (AD) beobachtet wird und die Entstehung von Mycosis fungoides (MF) aufgrund der zunehmenden Anzahl von MF Patienten, die eine vorhergehenden Anamnese von AD aufwiesen, ein beachtliches Interesse gefunden. Das Ziel dieser retrospektiven Case-Control-Studie war es, herauszufinden ob Hunde, die mit MF diagnostiziert worden waren, eine höhere Wahrscheinlichkeit aufwiesen, AD zu haben. Die Krankenakten von 96000 caninen Patienten an der Universität von Florida wurden durchforstet. Einschlusskriterien waren eine klinische und eine histologische Diagnose von MF. Hunde, die während derselben Zeitspanne (1991–2004) ohne eine Diagnose von MF an die UF VMC eingewiesen wurden, wurden als Kontrolltiere verwendet. Vier Kontrollen pro Hund in der Studie wurden zufällig ausgewählt (passend mit dem Jahr der Einweisung). Die Häufigkeit von AD und anderen äußerlichen Variablen wurden zwischen Fällen und Kontrolltieren mittels bedingter logistischer Regression verglichen. Die Krankenakten von 19 Hunden mit einer Diagnose von MF wurden identifiziert. Fünf davon (5/19, 26.3%) hatten eine vorhergegangene Diagnose von AD. Die Chancen ('Odds') MF zu haben waren 12 Mal höher (OR=12.54; 95% CI=1.95 bis 80.39; $P < 0.01$) bei den Hunden mit AD als bei den Hunden ohne AD. Zusammenfassend weist diese Studie auf einen Zusammenhang zwischen AD und MF bei Hunden hin. Zukünftige Studien sind notwendig um dieses Forschungsergebnis zu bestätigen und um die Pathomechanismen, auf die dieser Zusammenhang zurückzuführen ist, zu untersuchen.