

Short Communication

Canine atopic dermatitis reduces the risk of multicentric B cell lymphoma

A. Imai, D. Santoro

CANINE atopic dermatitis (AD) has been defined as 'a genetically predisposed inflammatory and pruritic allergic skin disease with characteristic clinical features associated with IgE antibodies most commonly directed to environmental allergens' (Halliwell 2006). Due to numerous similarities, several studies have demonstrated the usefulness of the canine animal model for human AD (Marsella and Girolomoni 2009, Olivry 2012).

In people, conflicting results have been published on the association between AD and the development of neoplasia; some studies suggest a protective effect of AD against the development of neoplasia due to a possible enhancement of the immune surveillance. Contrary, other studies have hypothesised that a chronic immune stimulation is at the base of the development of neoplastic diseases in people (Vena and others 1985, Hagstromer and others 2005, Wang and Diepgen 2005).

Recently, canine lymphomas have been established as a model for non-Hodgkin's lymphomas (NHLs) in people due to the striking similarities in clinical presentation, genomic instability, and cytological and histological features (Vail and others 2009, Marconato and others 2013). The most common NHL in dogs is multicentric B cell lymphoma (ML) (Teske 1994). Although a high incidence of AD and ML is present in dogs, no studies have been published on the possible association between these two disorders. Therefore, based on the similarities between canine and human AD and NHL, the goal of this study is to explore the association between canine AD and ML.

Medical records of dogs diagnosed with ML, characterised by rapid, non-painful development of generalised peripheral lymphadenopathy with evidence of malignant lymphocytes by histological examination were selected for this study. Systemic clinical signs (eg profound lethargy, weakness, fever, anorexia and dehydration) were also recorded. The main exposure of interest was canine AD, diagnoses based on compatible history, clinical signs and exclusion of other pruritic diseases as appropriate for each case (eg scabies, demodicosis, food allergy, flea allergy) (DeBoer and Hillier 2001). Dogs admitted to the author's institution during the same time period (2000–2010) not diagnosed with or without a historical diagnosis of ML were included as

controls, three dogs for each case-study dog were randomly selected (matched by year of admission) using the Research Randomizer Program (www.randomizer.com).

For each record the following information was retrieved and analysed: sex, breed, age of onset and at the time of diagnosis of both canine AD and ML, previous use of systemic anti-inflammatory drugs, and stage of ML. This latter was based on the World Health Organization staging system for canine lymphoma (Owen 1980), at the time of diagnosis. All the variables analysed were categorical in origin. Stepwise conditional logistic regression was used to estimate odds ratios with 95% confidence interval. Variables for sex, breed, age of onset and at the time of diagnosis of both canine AD and ML, and stage of ML were included to adjust for potential confounding factors. The variables' breed (Sousa and Marsella 2001, Santoro and others 2007; Jaeger and others 2009) and age were dichotomised (using the median as cut-off point) to facilitate the interpretation of the results. The Hosmer-Lemeshow test was used to assess the goodness of fit for the logistic regression model. For all analyses a P value <0.05 was considered statistically significant. Statistical analysis was done using MedCalc V.12.0 statistical software (MedCalc Software, Mariakerke, Belgium).

Medical records of 58,692 canine patients that were visited during the time period considered were evaluated. Of these, 258 dogs with a recorded diagnosis of ML fulfilled the inclusion criteria, 116 dogs were female (9 entire) and 142 were male (24 entire). Of the dogs, 185 were purebred and 83 were mixed-breed dogs. The average age at the time ML was diagnosed was 8 ± 3.4 years (range: 0–18 years). Six dogs had a previous diagnosis of AD (2.3 per cent). The average ($\pm$ sd) age of the dogs at the time AD was diagnosed was 4 ± 2.6 years (range: 3–9 years). The most common systemic anti-inflammatory drugs used included antihistamines (53/258), glucocorticoids (40/258), allergen-specific immunotherapy (20/258), ciclosporin (5/258), pentoxifylline and human α -interferon (1/258 each). The frequency distribution of ML and control dogs by the investigated risk factors is listed in Table 1. In the multivariate analysis canine AD was inversely associated with ML (odds ratio=0.28; 95% confidence interval=0.12 to 0.65; $P<0.05$, Table 1) indicating a decreased risk of developing ML in atopic dogs.

The results of the present study show that dogs with AD have a reduced risk of developing ML by a factor of 3.57 (1/0.28). These results are in agreement with previous reports in the human literature (Grulich and Vajdic 2005, Grulich and others 2005, Cozen and others 2007, Vajdic and others 2007). In people, case-control studies using atopy as predisposing risk factor, reported a reduction in the risk of developing NHL (Bernstein and Ross 1992, Doody and others 1992, Holly and Lele 1997, Holly and others 1999, Tavani and others 2000, Vineis and others 2000, Briggs and others 2002, Holly and Bracci 2003, Zhang and others 2004, Grulich and others 2005, Bracci and others 2006, Cozen and others 2007, Melbye and others 2007). On the contrary, a positive association between AD and cutaneous epitheliotropic T cell lymphoma has been shown in both people and dogs (Lamberg and Bunn 1979, Weinstock and Horm 1988, Bhang and others 2006, Santoro and others 2007, Fontaine and others 2009).

Many explanations have been suggested for the reduced risk of ML in atopic patients. Possible mechanisms involve the presence of high IgE levels in allergic patients. In fact, it has been hypothesised that specific and non-specific IgE can be directed against tumour cells (Jensen-Jarolim and others 2008). In particular, IgE antibodies have been associated with overexpressed tumour antigens as well as non-specifically attached to tumour cells establishing a powerful tumour-specific immune memory (Jensen-Jarolim and others 2008, Jensen-Jarolim and Pawelec

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TABLE 1: Multivariate analysis – Frequency distribution of atopic dermatitis and potential confounding factors (age, breed and sex), crude odds ratio (OR) and 95% confidence interval (CI) among 258 dogs with ML and 774 control dogs without ML

Variables	Control	ML	OR	95% CI (P<0.05)
Age				
0–6	413	122	1	NA
6<	361	136	1.28	0.96 to 1.69
Breeds				
Low*	465	163	1	NA
High†	309	95	0.88	0.66 to 1.17
Sex				
Female	394	116	1	NA
Male	380	142	1.27	0.96 to 1.68
AD				
NO	713	252	1	NA
YES	61	6	0.28‡	0.12 to 0.65

*Border collie, Chihuahua, Shetland sheepdog, Whippet, Airedale terrier, Akita, Alaskan malamute, American water spaniel, Australia terrier, Australian cattle dog, Australian shepherd, Beagle, Belgian malinois, Bernese mountain dog, Blue tick hound, Border collie, Bouvier des flandres, Brussels griffon, Catahoula hound, Chesapeake bay retriever, Chow chow, Clumber spaniel, Coonhound, Doberman pincher, Dachshund, Dalmatian, English sheepdog, Eskimo dog, Eskimo spitz, Fila brasileiro, German shorthair pointer, Great Dane, Great Pyrenees, Greyhound, Irish setter, Irish wolfhound, Italian greyhound, Keeshond, Lhasa apso, Mastiff, Mixed breed dog, Newfoundland, Papillion, Pekingese, Pembroke welsh corgi, Pit bull, Pointer, Pomeranian, Miniature poodle, Portuguese water dog, Pug, Rottweiler, Saint Bernard, Saluki, Samoyed, Schipperke, Miniature schnauzer, Setter Gordon, Sheltie, Shorthaired chihuahua, Shorthaired dachshund, Siberian husky, Swiss mountain dog, Toy havanese terrier, Treeing walker coonhound, Weimareiner, Whippet, Winchester, Wire fox terrier (Sousa and Marsella 2001, Santoro and others 2007, Jaeger and other 2009)

†American bull dog, American Staffordshire terrier, Basset hound, Bichon frise, Boston terrier, Bull terrier, Boxer, Brittany spaniel, Cairn terrier, Cavalier king Charles spaniel, Cocker spaniel, English bull dog, English setter, English springer spaniel, French bull dog, German shepherd, Golden retriever, Jack Russell terrier, Labrador retriever, Maltese, Rat terrier, Rhodesian ridgeback, Chinese shar pei, Scottish terrier, Shih tzu, Silky terrier, Staffordshire bull terrier, Tibetan terrier, Vizsla, West highland white terrier, York shire terrier (Sousa and Marsella 2001, Santoro and others 2007, Jaeger and other 2009)

‡Reference group; Low, low predisposed breeds for AD; High, high predisposed breeds for AD
AD, atopic dermatitis; ML, multicentric lymphoma; NA, non-analysable

2012). This may induce the activation of an effective anticancer immune response (Gould and others 1999, Wang and Diepgen 2005, Strik and others 2007, Jensen-Jarolim and others 2008, Jensen-Jarolim and Pawelec 2012). Such immune reaction might reduce the formation of lymphomagenic molecules (eg chromosomal translocation, oncogene mutation), resulting from somatic DNA-modifying events that occur in germinal B cells after activation, such as immunoglobulin class-switch recombination and somatic hypermutation (Skibola and others 2007, Pasqualucci and others 2008, Vajdic and others 2009). Since, most B cell NHLs are of germinal or postgerminal cell origin (Skibola and others 2007), a role for an allergy-associated decrease in such lymphomagenic molecules is a reasonable explanation (Vajdic and others 2009).

In conclusion, a negative association between AD and ML seems to be present in dogs. This study confirms the similarities between human and canine AD and NHL. However, due to the retrospective nature of this study and the impossibility to control environmental factors, further epidemiological studies are necessary. Ideally, a large-scale prospective controlled cohort study to observe if dogs with AD will develop ML later in life would be beneficial.

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