The Correlation between Localization of Skin Changes and Risk Factors Associated with Atopic Dermatitis

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Abstract. *The aim of this study was to investigate the frequency of localization of skin changes in dogs with atopic dermatitis (AD) with regard to some risk factors for development of atopic dermatitis in dogs (age, sex, breed, living conditions, seasonality, washing/bathing, Malassezia infections and intradermal testing results). Among 50 dogs with clinical signs compatible with atopic dermatitis, pruritus was observed in 37 (74%), and alopecia in 19 (38%) of dogs ($P < 0.05$). Pruritus was commonly noted in purebred dogs compared with crossbreed dogs ($P < 0.05$). Malassezia yeasts were noted in 25 (50%) dogs by cytological examination, most commonly from ear samples ($P < 0.05$); there was no correlation between the cytology presence of yeast and positive IDT to M. pachydermatis allergen or pruritus. The skin changes were located on legs/paws (n = 23; 46%) abdomen/chest/axillae (n = 12; 24%), back/sacral area/tail (n = 12; 24%), head (n = 11; 22%), inguinal/genital area (n = 11; 22%) and hips/groin (n = 9; 18%); otitis was noted in 13 (26%) dogs. Most dogs had changes on the skin of legs/paws ($P < 0.05$). Female dogs and dogs over 3 years of age were predisposed to otitis, while male dogs, dogs up to 3 years of age, dogs kept indoor as well as dogs with a positive intradermal test to house dust and the house dust mite allergen group were predisposed to skin changes on legs/paws ($P < 0.05$). In frequently washed/bathed dogs, skin changes on leg/paws were more commonly noted, while in rarely washed/bathed dogs, skin changes were more common on abdomen/chest/axillae ($P < 0.05$). Also, the correlation was found between the seasonality onset of AD signs and the localization of skin changes.*

Introduction

Atopic dermatitis (AD) is one of the most common dermatoses in dogs (Favrot, 2009). It is defined as a genetic predisposed inflammatory and pruritic disease with characteristic clinical features associated with IgE, mostly, against environmental allergens (Halliwell, 2006).

Clinical signs in dogs with AD were described in the last century. From the first description to date, clinical signs differ significantly in the prevalence of the features such as age, sex, breed, localization and description skin visible changes, as well as extent and pruritus distribution (Griffin and DeBoer, 2001; Bruet et al., 2012). Depending on included allergens, clinical signs of AD can be seasonal (e.g., hypersensitivity to pollen) and non-seasonal (e.g., hypersensitivity to house dust mite) (Zur et al., 2002; Brar et al., 2017). Also, there is a possibility that breed predisposition and clinical signs may vary depending on geographical regions (Jaeger et al., 2010.). Pruritus without lesions is a common primary clinical sign in CAD (Olivry, 2012; Griffin and DeBoer, 2001), or if lesions are present, then they are in the form of erythema (Griffin and DeBoer, 2001; Favrot, 2009; Olivry, 2012). In the acute form, skin lesions are characterized by intensive pruritus with excoriations and/or salivary staining (Nagata, 2000). However, AD is often diagnosed as a chronic form characterized by alopecia, hyperpigmentation and lichenification, particularly at predilection areas (Nagata, 2000; Griffin and DeBoer, 2001). Pruritus and consequently lesions usually involve face, ears, limbs, abdomen, axilla, groin and perineum (Nagata, 2000; Griffin and DeBoer, 2001; Favrot, 2009). Any one or any combination of those areas can be affected (Nagata, 2000; Griffin and DeBoer, 2001; Olivry, 2012). In some cases, mild pruritus can be unrecognized by the owner, but indirect proofs of pruritus such as excoriation or saliva-dyed hair may be present (Griffin and DeBoer, 2001; Favrot, 2009). Bacterial and *Malassezia* infections are common complications (Zur et al., 2002), and low percentage (about 5%) of dogs may show chronic otitis externa as the main clinical sign (Nagata, 2000).

The diagnosis of CAD is difficult, and requires patience, time and effort, so it is a time-consuming and complicated process (Hensel et al., 2015; Gedon and Mueller, 2018; Harvey et al., 2019). Since no clinical signs or manifestations are pathognomonic, a definitive diagnosis is not possible based on an interview with the owner and a clinical examination (DeBoer and Hillier, 2001). Dogs can exhibit different clinical signs. Many of them may be caused by other skin conditions, and body areas and intensity of affection may be different (Hensel et al., 2015; Gedon and Mueller, 2018; Harvey et al., 2019).

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The differential diagnosis of AD is based on age onset, breed and clinical signs. Ectoparasites and flea bite hypersensitivity must be ruled out by ectoparasite control, as well as sarcoptes mange and food allergy. Up to date, there is no single test that can distinguish atopic from non-atopic dogs (DeBoer, and Hillier, 2001; Gedon and Mueller, 2018).

The aim of this study was to show frequency of localization (distribution) of skin changes in dogs with AD, and to determine if there is any correlation of risk factors for development of AD (age, sex, breed, living conditions, seasonality, washing/bathing, *Malassezia* infections and intradermal testing results) on their localization.

Material and methods

In this study, 50 dogs (26 female and 24 male dogs) with a history and clinical signs compatible with AD were included. The average age was 4.2 years (20 dogs up to 3 years and 30 dogs over 3 years of age). Forty dogs were purebred and 10 dogs were crossbreed. A detailed history was followed by clinical and dermatological examination of the dogs. Intensity of pruritus was evaluated by the owners (Rybncek et al., 2008) and grouped as no pruritus, mild, moderate and severe pruritus. Also, the owners assessed the dog's activity (scratching, chewing, licking or rubbing) as normal, mild, moderate and severe (Bruet et al., 2012). All information obtained from the owners was recorded. Skin changes at any site on the body were documented as absent or present (Graham et al., 2019). For data analysis, the distribution of skin changes was systematized in seven areas: ears (presence of otitis); legs and/or paws; hips and/or groins; abdomen and/or chest and/or axillae; back and/or sacral area and/or tail; and inguinal and/or genital area.

For AD diagnosis, criteria according to Prelaud (Prelaud et al., 1998) and positive intradermal tests were used. Food allergy, ectoparasites and other pruritic diseases were ruled out. For the detection of *Malassezia* yeasts, samples from ear external canals and skin with changes were collected from all dogs using sterile cotton swabs. Gram's stained slide smears were used for microscopic examination. Five random fields were examined under an oil immersion objective (x1000 high power field). Yeast cells were characterized according to their morphology compatible to *Malassezia* yeast. Absence of yeast cells per field was considered negative, while one and more cells per field were considered positive (Nascente et al., 2015).

An intradermal test (IDT) was performed by 15 allergens according to manufacturer's instructions (Greer, Lenoir, USA). For data analysis, allergens were grouped into six groups: 1) house dust and house dust mites; 2) grass and weeds (plantain/sorrel mix, 7 grass mix, and ragweed); 3) tree pollens (pine mix and 7-east tree mix); 4) fungi (*Trichophyton mentagrophytes*, *Malassezia pachydermatis* and mould mix); 5) insects (*Culicoides*, house fly and flea antigen); 6) epithelia and feathers (cat epithelia and feather mix). The influence of age, sex, seasonality onset of signs, living conditions, washing/bathing, *Malassezia* infections and IDT results to lesion distribution in dogs with AD were examined.

Statistical analysis. χ^2 and Fisher's exact test were used for comparison of examined parameters and localization of skin changes. A probability value of $\leqslant 0.05$ was considered statistically significant.

Results

According to the data obtained from histories, the highest percentage of dogs lived indoors (86%), had AD signs in spring and summer (52%), and washed/bathed 1–4 times per a month (58%).

The owners noticed pruritus in 74% of dogs. The intensity of pruritus was evaluated as follows: mild in 2 dogs, moderate in 14 dogs, severe in 14 dogs. The owners could not determine intensity of pruritus in 7 dogs. According to the owners, 13 dogs showed no signs of pruritus. The activity of these dogs (scratching, chewing, licking or rubbing) was assessed by the owners as moderate in 8 dogs. For 5 dogs, the owners could not determine intensity of activity. Skin lesions and/or pruritus were observed in this group of dogs as indirect signs of pruritus. In the examined dogs, pruritus was a more common sign than alopecia (38% of dogs) ($P < 0.05$). Pruritus was more commonly noted in purebred than in crossbreed dogs ($P < 0.05$), while no significant difference was noted for occurrence of alopecia regarding all compared parameters. Pruritus compared with alopecia was more common in both sexes and age groups, in pure breed dogs, as well as in dogs with the spring and summer onset of signs ($P < 0.05$).

Malassezia yeasts were detected in 25 dogs by cytology (in ears in 19 dogs, skin in 4 dogs, ears and skin in 2 dogs). Yeast was more commonly detected in ears ($P < 0.05$). Among 19 dogs with positive cytological examination in ears, 8 dogs had otitis externa. Seven dogs with a positive cytological test and 10 dogs with a negative cytological test had a positive IDT to *M. pacydermatis* antigen. There was no correlation between the cytology presence of yeasts and a positive IDT to *M. pachydermatis* allergen or pruritus.

Skin changes were present in the form of erythema/urticaria, hyperpigmentation, rash, macules/papules, crusts, lichenification, seborrhea, oedema and alopecia. Not all areas were affected simultaneously in the same dogs. The greatest number of dogs had leg and/or paw skin changes ($P < 0.05$), while otitis externa was noted in 13 dogs (Fig. 1). Pruritus and skin changes were commonly noted in dogs with a positive IDT to house dust and house dust mite, the grass and weed pollen allergen group and the tree pollen allergen group.

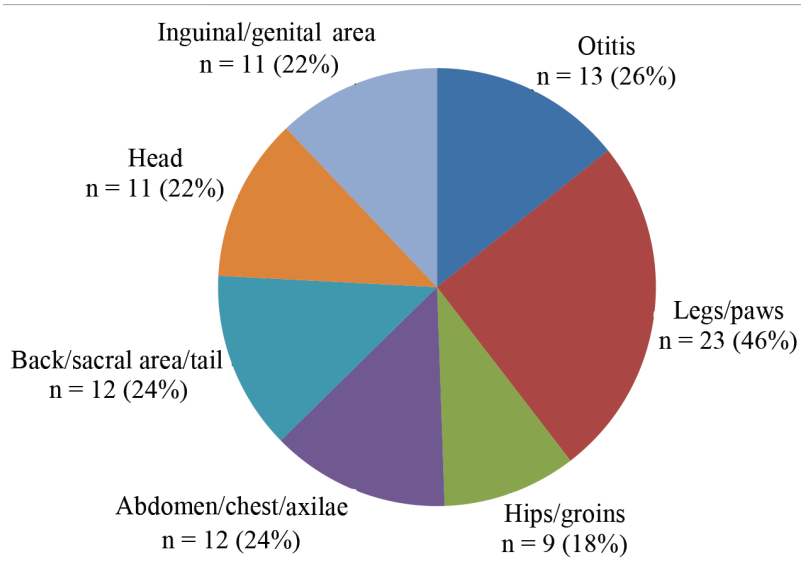

Fig. 1. Distribution of skin changes in 50 dogs with atopic dermatitis

Otitis externa was commonly observed in female dogs and dogs over 3 years of age ($P < 0.05$). In female dogs as well as in dogs over 3 years of age and in purebred dogs, more changes were noted on legs/paws than on hips/groins, abdomen/chest/axillae, head and inguinal/genital area ($P < 0.05$). On the other hand, the skin changes on legs/paws were more common than otitis in male dogs and dogs up to 3 years of age ($P < 0.05$) (Table 1).

Significant statistical differences ($P \leqslant 0.05$) were found for compared parameters as follows (Table 2 and Fig. 2):

Dogs living indoor commonly had leg/paw skin changes. Frequently washed/bathed dogs had a greater number of leg/paw skin changes regarding other body areas (except inguinal/genital area). Generally, the largest number of rarely washed/bathed dogs had skin changes on abdomen/chest/axillae. On the other hand, in this group of dogs, skin changes localized on abdomen/chest/axillae were frequently observed than on hips/groins.

In dogs with the spring and summer onset of AD signs, changes on leg/paw skin were noted more often than otitis and hip/groin skin changes, while in dogs with the non-seasonal onset of AD signs, skin changes on legs/paws were more frequently noted than on the inguinal/genital area. In dogs with the spring and summer onset of AD signs, changes on hip/groin skin were rarely noted compared with the back/sacral area/tail and the inguinal/genital area.

Otitis was frequently observed among dogs with an IDT positive to the tree pollen allergen group than among dogs with an IDT positive to the epithelia and feather allergen group. In dogs with an IDT positive to house dust and house dust mite allergen group, changes were more frequently localized on legs/paws than on abdomen/chest/axillae skin. Among dogs with an IDT positive to the fungi allergen group, skin changes on legs/paws were most often observed compared with all other examined body areas, except otitis.

Table 1. Distribution of skin changes regarding breed, sex and age of dogs

Distribution of changes (number of dogs with skin changes)	Number of dogs with skin change					
	Breed		Sex		Age	
	Cross breed	Pure breed	Male	Female	Up 3 years	Over 3 years
Otitis (n = 13)	1	12	3	10	2	11
Legs/paws (n = 23)	4	19	9	14	8	15
Hips/groins (n = 9)	1	8	4	5	3	6
Abdomen/chest/axillae (n = 12)	2	10	4	8	6	6
Back/sacral area/tail (n = 12)	1	11	7	5	4	8
Head (n = 11)	3	8	6	5	6	5
Inguinal/genital area (n = 11)	3	8	4	7	4	7

Table 2. Distribution of skin changes regarding living conditions, washing/bathing and seasonality of AD onset in dogs

History parameters (number of dogs)		Number of dogs with skin change						
		Otitis n = 13	Legs/paws n = 23	Hips/groins n = 9	Abdomen / chest/axillae n = 12	Back/sacral area/ tail n = 12	Head n = 11	Inguinal/genital area n = 11
Living conditions	Indoor (n = 43)	11	21	8	9	9	9	10
	Outdoor (n = 5)	1	1	0	2	2	1	1
	Box (n = 2)	1	1	1	1	1	1	0
Washing/ bathing	1–4 times per a month (n = 29)	6	14	6	3	6	6	7
	1–5 times per a year (n = 18)	5	7	2	8	5	4	3
	Unknown (n = 3)	2	2	1	1	1	1	1
Seasonality	Spring-summer (n = 26)	5	13	2	7	8	7	8
	Autumn/winter (n = 9)	3	4	3	2	4	1	2
	Non-seasonally (n = 15)	5	6	4	3	2	3	1

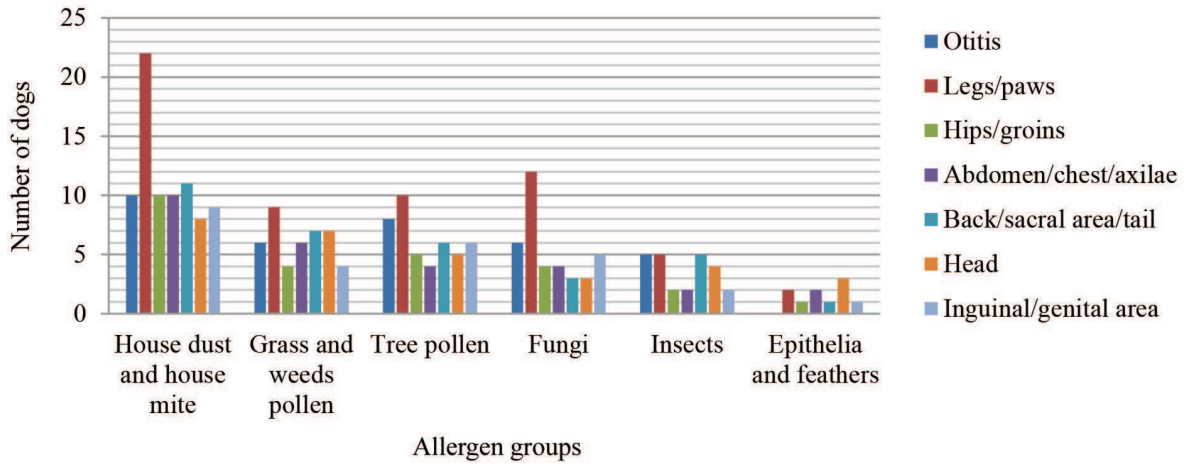

Fig. 2. Distribution of changes regarding IDT results

Discussion

Atopic dermatitis in dogs is a lifelong disease with variable clinical presentation (Nuttal et al., 2013; Hensel et al., 2015). It is a chronic clinical syndrome with a complex pathogenesis (Marsella, 2012). There are no pathognomonic clinical signs, and a definitive diagnosis cannot be made based on history and clinical examination (DeBoer and Hillier, 2001). The diagnosis of CAD is based on the fulfilment of clinical criteria, excluding other possible cases with similar clinical signs, skin scraping and cytology, and allergy testing should be performed to identify potential allergen causes that can be avoided or treated with allergen-specific immunotherapy (Hensel et al., 2015). Therefore, every case should be treated individually (Nuttal et al., 2013), and it must be kept in mind that dogs that do not fulfil diagnostic criteria may actually be atopic (Khoshnegah and Pakzad, 2009). In addition to pruritus, as the most common signs of CAD, particularly on face, ears, paws, extremities and/or ventrum (Griffin and DeBoer, 2001; Hillier, 2002), secondary skin lesions often occur at the pruritus site as a consequence of self-trauma, secondary infections and chronic inflammations (Griffin and DeBoer, 2001; Favrot, 2009; Hensel et al., 2015). The individual threshold for pruritus and a threshold for AD development of each patient play a very important role in development of clinical signs of disease (Marsella and Sousa, 2001); and the skin reaction pattern as well as the distribution of skin lesions vary according to breed, individual and clinical course (Nagata, 2000). Furthermore, dogs

living outdoors can be less carefully followed for allergic signs than indoor dogs; therefore, the signs may not be easy to determine (Hakanen et al., 2018).

Depending on the allergens involved, pruritus and clinical signs may initially be seasonal and non-seasonal (Zur et al., 2002; Favrot, 2009; Brar et al., 2017). On the other hand, some dogs may develop seasonal and non-seasonal pruritus, or pruritus present year-round that may worsen during particular seasons (Hillier, 2002). According to our data, the highest percentage (52%) of dogs had the spring-summer onset of signs (Table 2), which is in consistence with data suggesting the seasonal character of CAD (Griffin and DeBoer, 2001; Zur et al., 2002; Favrot et al., 2009). Although pruritus is the main clinical sign of CAD, it must be kept in mind that mild forms of pruritus may be unrecognized by the owner (Griffin and DeBoer, 2001; Favrot, 2009), and the mild disease form or the form associated with minimal pruritus may be unreported (Griffin and DeBoer, 2001). According to literature data, pruritus is present in 69% (Jang et al., 2013) to 100% (Brar et al., 2017) dogs with AD. In this study, pruritus was noted by the owners in 74% dogs. It should be mentioned that it was more commonly observed in purebred dogs. Activities related to pruritus such as scratching, chewing, licking or rubbing (Bruet et al., 2012) were not recognized by the owners as a sign of pruritus, which they considered as normal dog behaviour. The owners rated this activity as moderate in 8 dogs; and in 5 dogs, they could not determine the intensity of these activities. In dogs without evidence of pruritus by the owners, skin changes and/or alopecia due to pruritus have been noted (Favrot, 2009; Jaeger et al., 2010). Alopecia as one of the most common signs of AD, especially in chronic cases (Nagata, 2000; Brar et al., 2017), was noted in 38% of dogs in our study. This is in accordance with literature data stating the presence of alopecia in dogs with AD from 34% (Sung and Huang, 2009) to 78.26% (Jyothi at al., 2013). We also noted pruritus more commonly than alopecia in both sexes and age groups, as well as in purebred dogs and dogs with the spring and summer onset of AD signs.

In animals with overgrowth of *Malassezia* yeast, or in individuals that are predisposed to allergic sensitization, the consequent inflammatory response can cause clinical signs such as dermatitis and pruritus (Bond et al., 2020). Infections caused by this yeast are common in dogs with atopic dermatitis. In the present study, *Malassezia* yeasts were noted in 25 (50%) dogs by cytology examination. This is in accordance with previous studies (Zur et al., 2002; Jang et al., 2013). In our study, there was no correlation between the cytology presence of yeasts and a positive IDT to *M. pachydermatis* allergen or pruritus. This is in contrast to previous findings where atopic dogs with *Malassezia* dermatitis more frequently had a positive IDT response then without *Malassezia* dermatitis or otitis (Farver et al., 2005). In our study, among 19 dogs with cytological evidence of *Malassezia* in ears but not on the skin, 5 dogs had a positive IDT to *M. pachydermatis* allergen; there was no significant difference in a positive IDT to *M. pachydermatis* allergen between dogs with and without cytological presence of the yeast in the ears. In previous research (Farver et al., 2005), all dogs with *Malassezia* otitis but without dermatitis (MD-MO+) reacted with a positive reaction. On the other hand, in research by Layne et al. (2016), there was no significant difference in the concentrations of *Malassezia*-specific IgE between dogs with recurrent *Malassezia* otitis and dogs with healthy ears, suggesting that hypersensitivity is not always involved in such infections. So, proteins from *Malassezia* yeasts can act as allergens in dogs predisposed to the development of atopic dermatitis (Bond et al., 2020).

Any one or any combination of the body areas can be affected (Griffin and DeBoer, 2001). Lesions are most commonly present on face, and flexural and friction areas; most commonly affected areas are face (particularly periocular and periorbital skin), inside aspect of the pinnae, dorsal and ventral interdigital areas, flexural aspects of joints and extremities (cubital, tarsal, carpal and metatarsal flexures), axillae, abdomen, groin, perineum and ventral tail); and otitis externa is commonly present (Olivry, 2012). Although, most publications suggest legs and paws as the most commonly affected areas, there are some studies where lesions are more commonly noted on the ventral part of the body (ventral abdomen and chest, inguinal area, axillae, ventral neck) than on paws (Zur et al., 2012). In this study, we noted the presence of skin changes on one or a combination of areas as follows: legs/paws (n = 23; 46%), abdomen/chest/axillae (n = 12; 24%), back/sacral area/tail (n = 12; 24%), head (n = 11; 22%), inguinal/genital area (n = 11; 22%) and hips/groin (n = 9; 18%), and otitis was noted in 13 (26%) of dogs (Fig. 1). The distributions of lesions are in accordance with literature data (Khoshnegah and Pakzad, 2009; Jaeger et al., 2010; Brar et al., 2017; Graham et al., 2019).

Our data show that the highest percentage (58%) of dogs with AD were washed/bathed 1–4 times per month; skin changes on legs/paws were more common than on any other body area (except inguinal/genital area). While in the group of rarely washed/bathed dogs (1–5 times per year), changes were most commonly noted on the skin of the abdomen/chest/axillae. Comparing frequently and rarely washed/bathed dogs, we found that skin changes on the abdomen/chest/axillae were more common in frequently washed/bathed dogs (Table 2). Although, washing/bathing helps remove allergens from the coat (Marsella, 2012), according to Meury et al. (2011), washing/bathing of dogs once or more per week is strongly correlated with development of CAD, because washing the dogs is an element of normal

treatment of allergic dogs. Also, it is possible that frequent washing/bathing removes sebum affecting the epidermal lipid layer, thus compromising the function of the skin barrier (Meury et al., 2011).

In research by Chanthic et al. (2008), it was concluded that most of the skin reactions to each allergen group had no significant association with a skin lesion location. However, they found a correlation between a positive IDT to the pollen group and skin lesions on the perineum and the tail area. On the other hand, they noted that dogs with a positive IDT to house dust and the house dust mite group more likely had skin lesions of the feet, but there is no statistical significance (Chanthic et al., 2008). According to our data, pruritus and skin changes were frequently noted in dogs with a positive IDT to house dust and the house dust mite group, the grass and weed pollen group and the tree pollen group of tested allergens. Furthermore, skin changes on legs/paws were more frequently observed in dogs with a positive IDT to the groups of tested allergens as follows: house dust and house dust mite, tree pollen as well as fungi (Fig. 2). Additionally, dogs included in this study in the highest percentage (86%) were kept indoors. In these dogs, the most common localization of skin changes was in the area of the legs/paws (Table 2). This could be explained by the presence of house dust mite indoors, because the ventral parts of the body were more often affected in dogs kept indoors (Wilhem et al., 2011), and prolonged exposure to this allergen may trigger or worsen clinical signs of CAD (Favrot, 2009). According to Marsella et al. (2006), the epicutaneous route of allergen exposure may play an important role in CAD, for the purposes of both the sensitization and the perpetuation of CAD (Pucheu-Haston et al., 2008). Consequently, skin barrier dysfunctions may lead to increased allergen penetration and an increased risk for allergic sensitization (Marsella, 2012). In addition, Marsella et al. (2006) consider that an allergen exposure route does not determine the distribution of lesions, but continuous epicutaneous exposure to allergens probably may play the most important role.

We noted that skin of legs/paws was affected in the highest percentage (46%) of dogs. This is in accordance with other research. The skin of legs and paws was more commonly affected, and the percentage ranges from 21.9% (Chanthick et al., 2008) to 72% (Khoshnegah and Pakzad, 2009). Possible explanations may be direct percutaneous allergen resorption or high density of cutaneous mast cells on paws (Jaeger et al., 2010). Mast cells directly participate in CAD pathogenesis and their number can vary depending on the body area (Jaeger et al., 2010). Besides, according to Auxilia and Hill (2000), their number is highest in the medial and lateral pinna and in the ventral interdigital skin of the hind and fore feet. Auxilia and Hill (2000) suggest that cutaneous mast cell distribution may be involved in the frequent occurrence of ear and foot pruritus, but also suggest that differences in mast cell counts, epidermal thickness or hair follicle density do not adequately explain the predilection sites of CAD.

Atopic dermatitis is one of the primary causes of the development of otitis externa in dogs (Saridomichelakis et al., 2007), and if the otitis externa occurs for the first time in middle or older age of dogs, allergy cannot be ruled out as the primary cause (Paterson, 2016). We recorded otitis externa in 26% of dogs. That is in accordance with literature data that otitis externa has been reported in a wide range from 28% (Chanthick et al., 2008) to 79% (Sung and Huang, 2009). A possible contributing factor to its development in dogs with AD is the increased number of cutaneous mast cells in the lateral and medial pinna (Auxilia and Hill, 2000; Jaeger et al., 2010). We noted sex and age predisposition to develop otitis externa in dogs with AD; female dogs and dogs over 3 years of age were predisposed. Although the highest number of dogs with otitis externa was recorded in purebred dogs, we did not find significant differences regarding crossbreed dogs (Table 1). Contrary to our data, Zur et al. (2002) did not find sex and age predisposition to otitis externa in dogs with AD, but they noted that crossbreed dogs had the lowest risk for otitis externa development. On the other hand, in the research by Saridomichelakis et al. (2007), the higher prevalence of otitis externa associated with AD was in female dogs with a history of pruritic skin diseases. In a study conducted on dogs with AD, a significant correlation was found between a positive IDT to cultivated plant pollen and otitis externa (Zur et al., 2002). The correlation of a positive IDT and otitis externa was also found in our study. Otitis externa was more common in dogs with a positive IDT to the tree pollen allergen group than in dogs with a positive IDT to the epithelia and feather allergen group. Similar to our results, in research by Zur et al. (2012), dogs with otitis externa were less allergic to feathers, but had more positive IDT reactions to house dust and house dust mite allergens than to other tested groups of allergens.

Conclusion

Based on the data from this study, we can conclude that dogs with atopic dermatitis were prone to leg/paw skin changes, and pruritus was the most dominant sign. The skin changes on legs/paws were more common in female dogs, dogs over 3 years of age and dogs with a positive IDT to house dust and the house dust mite allergen group. The correlation was also found between localization of skin changes and frequencies of washing/bathing of dogs, as well as the seasonality onset of signs of AD. There was no correlation between the cytology presence of yeasts and a positive IDT to *M. pachydermatis* allergen or pruritus.

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