

Increased numbers of peripheral blood CD34+ cells in dogs with canine atopic dermatitis

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Background – The bone marrow may be involved in human atopic diseases, as shown by the release of CD34+ cells into the peripheral blood.

Hypothesis/Objectives – The aim was to determine the numbers of CD34+ cells in atopic dogs.

Animals – The following three groups of dogs were studied: 27 dogs with nonfood-induced atopic dermatitis (NFICAD); 16 dogs with nonallergic inflammatory diseases; and 13 healthy control dogs.

Methods – Dogs with NFICAD were selected after fulfilment of Favrot's criteria and exclusion of other pruritic dermatoses, including flea infestation and adverse reaction to foods. The Canine Atopic Dermatitis Extent and Severity Index (CADESI)-03 and a Visual Analog Scale (VAS) score for pruritus were used to quantify clinical signs. A phycoerythrin-conjugated anticanine CD34 antibody was used to stain peripheral blood CD34+ cells, and these were enumerated using a flow cytometer. The CD34+ cell counts were compared between groups and tested (in the NFICAD group) for correlation with the severity of clinical signs.

Results – The numbers of peripheral CD34+ cells in dogs with NFICAD (median 1.7) were statistically higher than in dogs with other nonallergic inflammatory diseases (median 1.0; $P = 0.01$) and healthy control dogs (median 0.9; $P = 0.009$). In dogs with NFICAD, there was no correlation between CD34+ cell numbers and CADESI-03 scores or owner-assessed pruritus (VAS score).

Conclusions and clinical importance – The results of this study suggest the possible involvement of CD34+ cells in dogs with NFICAD. The role of CD34+ cells in the aetiopathogenesis of canine atopic dermatitis remains to be determined.

Introduction

Canine atopic dermatitis (AD) is a genetically predisposed inflammatory and pruritic skin disease defined by specific clinical features and often associated with immunoglobulin E (IgE) production directed against environmental allergens.¹ The pathophysiological aetiology of canine AD is complex and may involve altered skin barrier function and dysregulation of cytokine expression.²

Atopic disorders are generally thought to represent localized reaction patterns that are limited to specific organs (lung, skin and upper airway). Based on numerous clinical,^{3,4} neurophysiological⁵ and epidemiological findings,⁶ some authors have hypothesized that atopy could be a systemic disease.⁷ The 'atopic march', which is defined as the progression of clinical signs to involve multiple organs, supports this hypothesis.⁸ Support for a systemic basis for AD has been provided by studies of bone marrow transplantation, in which nonatopic recipients

have acquired both total and specific IgE responses following transplantation with bone marrow cells derived from atopic donors. Conversely, bone marrow transfer from nonatopic donors may cure AD in some recipients.⁹

A potential role for bone marrow as a mediator of atopic disease was first suggested by an experimental mouse model of allergic asthma.¹⁰ In these mice, an elevated count of bone marrow-derived eosinophil precursors was detected along with airway inflammation and was correlated with increased counts of mature eosinophils in blood and tissue.¹⁰ Bone marrow also constitutes the main reservoir of CD34+ haematopoietic progenitor cells, which are detectable in the peripheral blood by flow cytometry.¹¹ Using this technique, investigators have described increased numbers of CD34+ progenitor cells in patients suffering from atopic diseases.^{12–14} Together, these data suggest a fundamental role for bone marrow cells in the aetiopathogenesis of atopic inflammation.^{7,15,16}

Despite the routine use of a canine model for pre-clinical bone marrow transplantation studies¹⁷ and although haematopoietic cell transplantation has shown promising results in the treatment of some malignant

Accepted 24 September 2014

Sources of Funding: This study was self-funded.

Conflict of Interest: No conflicts of interest have been declared.

haematological conditions in dogs,^{18–21} the presence of CD34+ cells in the peripheral blood of dogs has not been confirmed previously. Consequently, the aim of the present study was to detect and quantify peripheral blood CD34+ cells in dogs with a diagnosis of AD, using flow cytometry.

Materials and methods

Group selection

This prospective study was carried out in the dermatology clinic of the veterinary teaching hospital of Oniris, Nantes-Atlantic National College of Veterinary Medicine, Food Science and Engineering (Nantes, France). The study protocol was reviewed and approved by the animal care and use committee of Oniris, and owner consent was obtained for each case.

Nonfood-induced atopic dermatitis (NFICAD) cases were selected by exclusion of other primary causes of pruritic dermatitis and the fulfilment of at least five criteria of Favrot.²² Inclusion required completion of a rigorous flea-control programme (use of an effective product applied monthly to all pets in the household), the absence of improvement after strict feeding of a hypoallergenic diet (novel protein or hydrolysed protein) for a minimum of 8 weeks and positive reactions to at least two aeroallergens injected intradermally. At the time of inclusion, dogs had received no glucocorticoids, ciclosporin or antihistamines within the previous month, nor any antimicrobial agents within the previous 9 days.

Two control groups were included, namely healthy dogs and dogs with nonallergic inflammatory diseases [other disease (OD) group]. Healthy control dogs had no history of prior cutaneous or systemic diseases. The OD group included dogs with nonallergic sources of inflammation, including autoimmune diseases, surgical procedures or infections.

Clinical evaluations

Clinical signs associated with NFICAD were evaluated and classified by the Canine Atopic Dermatitis Extent and Severity Index (CADESI)-03, and pruritus was scored by pet owners using a Visual Analog Scale (VAS), which ranked pruritus on a scale of 0–100.²³

Cell preparation

Peripheral blood (3 mL) was collected aseptically from the jugular vein into a 5 mL heparinized tube. Blood was diluted (1:1) in phosphate-buffered saline (PBS) and carefully poured over 3 mL of a separation solution (LSM 1077, PAA®; Sigma-Aldrich, Saint Quentin Fallavier, France). The separation process was then performed by centrifugation at 250g for 25 min (20°C).

The interface containing mononuclear cells was isolated and washed three times in ice-cold PBS supplemented with 10% fetal calf serum and centrifuged at 200g for 10 min. Supernatants were discarded and cells resuspended in 1 mL of PBS supplemented with 10% fetal calf serum. Cells were counted using a Malassez haemocytometer.

Flow cytometry

Mononuclear cells at a concentration of 10⁶ were stained with 1 µg of phycoerythrin-conjugated anticanine CD34 monoclonal antibody 1H6 (Becton Dickinson, Palo Alto, CA, USA) in PBS containing 5% canine serum. A phycoerythrin-conjugated murine IgG1 monoclonal antibody (Becton Dickinson) was used at the same concentration, as a control for nonspecific binding. Staining were performed at 4°C in the dark for 30 min. After extensive washing, 7-aminoactinomycin D (Sigma-Aldrich) was added, and cells were analysed using a FACs Aria flow cytometer (BD Biosciences, San Jose, CA, USA) equipped with DIVA software (BD Biosciences, San Jose, CA, USA). Doublet cells were excluded, and viable 7-aminoactinomycin D-stained cells were analysed for CD34 expression.

Statistics

The nonparametric unpaired tests of Kruskal–Wallis and Mann–Whitney were used to compare groups and sexes for the flow cytometric enumeration of CD34+ cells. Proportions were considered statistically significant with a *P*-value of <0.05.

Potential associations between CD34 cell counts and clinical scores (CADESI-03 and VAS scores) and age were investigated using the nonparametric Spearman's rank correlation test.

Results

Fifty-six dogs of various breed backgrounds were included in the study and are summarized in Table 1 (no statistical difference in age between groups). Causes of inflammation within the OD group were mainly postsurgical [bone fracture (×5), large skin plasty (×2), metritis and perineal hernia]; also, infectious diseases [bacterial pyoderma (×4) and kerion] and one febrile syndrome and one lupoid onychodystrophy.

As shown in Figure 1, the median percentages of CD34+ cells in the NFICAD, OD and healthy groups were

Table 1. Descriptive data

Group	Breed	Sex	Age (years)
H	Daschund (×2)	4 males	Minimum, 1.5; mean, 6.1; maximum, 14
	Cross-bred dog	9 females	
	Rottweiler		
	Jack Russell terrier		
	Yorkshire terrier		
	Great dane		
	Cocker spaniel		
	German shepherd		
	Miniature schnauzer		
	Miniature poodle		
	Cavalier King Charles spaniel		
	Bichon frisé		
NFICAD	West Highland white terrier (×4)	20 males	Minimum, 1.0; mean, 4.2; maximum, 9
	Bull terrier (×3)	7 females	
	Jack Russell terrier (×2)		
	Shih tzu (×2)		
	Bichon frisé (×2)		
	Boxer (×2)		
	German Shepherd (×2)		
	Labrador retriever		
	Golden retriever		
	German pointer		
	Dalmatian		
	Standard poodle		
	Basset Fauve de Bretagne		
	English bulldog		
	Cavalier King Charles spaniel		
	French bulldog		
OD	Cross-bred dog		11 males 4 females Minimum, 1.0; mean, 4.9; maximum, 11
	Beagle (×2)		
	Doberman pinscher		
	Pug		
	Yorkshire terrier		
	Borzoi		
	Boxer		
	Epagneul Breton		
	Cocker spaniel		
	Miniature schnauzer		
	Staffordshire bull terrier		

Abbreviations: H, healthy group; NFICAD, nonfood-induced canine atopic dermatitis; and OD, other diseases.

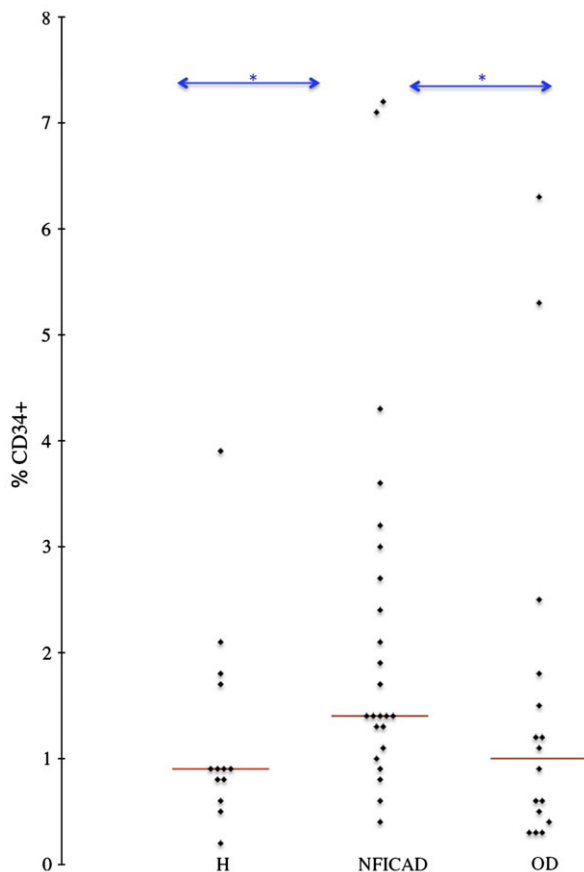


Figure 1. Enumeration of the percentage of CD34+ cells in peripheral blood in the three groups. Abbreviations: H, healthy; NFICAD, nonfood-induced canine atopic dermatitis; and OD, other diseases; the horizontal lines correspond to the median value. Statistical analysis (Mann-Whitney, *statistical difference at $P < 0.01$).

1.7 (0.4–28.3), 1.0 (0.3–5.3) and 0.9% (0.3–3.9%), respectively. Flow cytometric enumeration of CD34+ cells was statistically different between the three groups (Kruskal–Wallis test, $P = 0.007$). There were no differences observed between the healthy and the OD groups, while the NFICAD group had significantly higher counts than both the OD group (Mann–Whitney U-test, $P = 0.010$) and healthy control dogs ($P = 0.009$).

The correlation between CD34+ cell counts and CADESI scores in the NFICAD group was low, with a coefficient (r) of 0.14. Correlation coefficients did not improve when dogs were subcategorized to have mild or remitting disease (CADESI < 60 ; $r = -0.22$) or moderate-to-severe disease (CADESI ≥ 60 ; $r = 0.23$). The correlation between CD34+ cell counts and VAS scores was also low, with $r = 0.13$. Subcategorization of pruritus as mild (VAS score < 50) or moderate to severe (VAS score ≥ 50) had no effect on the correlation ($r = -0.13$ and $r = 0.34$, respectively). The correlation between age and CD34+ cell counts in the healthy and OD groups was also low ($r = -0.09$).

Discussion

To the best of our knowledge, this is the first study to demonstrate a significant increase in the number of

peripheral blood CD34+ cells in atopic dogs, compared with the number of CD34+ cells observed in dogs with inflammatory disorders unrelated to allergy. A study of atopic people has also described an increased number of CD34+ cells.²⁴ In that study, peripheral blood CD34+ cells were compared between three groups, including healthy control subjects and a group of patients hospitalized for infectious diseases. Although the infectious disease group had higher median CD34+ cell counts than healthy control subjects, only atopic patients showed a substantial number of CD34+ cells.²⁴

In a study of asthmatic people, the severity of clinical signs (measurement of forced expiratory volume) was significantly correlated with CD34+ cell counts, whereas in our study, the CADESI and VAS scores were not correlated with numbers of circulating CD34+ cells.¹⁴ This difference could be due to the fact that in allergic asthma the clinical sign measured (forced expiratory volume) is the result of only the local allergic inflammation, which is not the case in atopic dermatitis. In allergic skin disease, the clinical signs measured by CADESI result from a combination of local inflammation, abnormal skin barrier, self-trauma and secondary infections. This could account for the absence of correlation between CADESI and circulating CD34+ cells in NFICAD dogs in our study.

Alternatively, the observed CD34+ cell counts in canine AD could be related to the timing of allergenic challenge rather than to the severity of lesions or pruritus. In atopic humans, allergenic challenge results in increased CD34+ cell numbers before symptoms appear, as suggested by the fluctuation of eosinophil and basophil progenitors in the peripheral blood upon seasonal allergen exposure.⁷ In our study, an unknown delay between the allergenic challenge and the sampling for CD34 analysis may have impacted the results.

Finally, this lack of correlation could be due to an under-powered study if an insufficient number of dogs was tested.

The lesions of AD can vary greatly in severity and chronicity, complicating methods for monitoring a response to therapy. This is especially problematic when disease is mild or remitting.²⁵ Mastrandrea *et al.*²⁴ observed a progressive reduction of peripheral CD34+ cells, with no modification of allergen-specific IgE levels, in human patients treated with allergen-specific sublingual immunotherapy. Based on this, they proposed the enumeration of CD34+ cells as a good tool to score subclinical atopic dermatitis and to monitor treatment efficacy.²⁴ Future studies in atopic dogs should also assess the utility of this parameter as a tool for monitoring response to treatment.

The primary source of CD34+ cells in peripheral blood is the bone marrow; however, several mature cell populations, including mast cells, dendritic cells, eosinophils and lymphocytes,^{26–29} may also harbour the CD34 marker. Notably, in contrast to humans, a significant proportion of the canine CD34+ cell population is composed of lymphocytes, especially B cells.³⁰ Furthermore, the isolation of canine blood cells using gradient centrifugation does not separate mononuclear cells from polynuclear cells as efficiently as for human cells.³¹ Therefore, the enumeration of canine CD34+ cells could include

haematopoietic stem cells as well as mature inflammatory cells in numbers proportional to the severity of inflammation.

The numbers of peripheral blood CD34+ cells in canine AD could also represent a direct consequence of release of inflammatory mediators, as observed in some animal models.³² The mediators that induce specific release of CD34+ bone marrow cells during allergic inflammation are still unknown, but secretions from neighbouring cells, such as keratinocytes, are viable candidates. Epithelial cell-derived cytokines, such as thymic stromal lymphopoietin (TSLP), interleukin (IL)-25 and IL-33, have been shown to play important roles in the initiation and maintenance of allergic responses at epithelial surfaces of the skin, airway and gastrointestinal tract of humans.³³ Multiple lines of evidence, mainly from mouse experiments, suggest that TSLP acts on several haematopoietic cell types, such as dendritic cells, mast cells, natural killer cells, eosinophils and basophils, to induce allergic inflammation.^{34–36} The role of TSLP circulation in allergic patients is still a matter of debate because serum TSLP levels were not increased in adult patients with AD, whereas in children one study reported significantly increased serum TSLP levels compared with healthy control subjects.^{37,38} The epithelial cell-derived cytokines IL-25 and IL-33 play a supportive functional role in the maintenance of adaptive T-helper 2 memory cells induced by TSLP-activated dendritic cells, leading to the progression of chronic allergic disease and possibly to increased numbers of peripheral CD34+ cells.^{39–41} Additionally, the cytokines IL-31 and gastrin-releasing peptide may be involved in the mechanism of pruritus in AD^{42,43} and could also be involved in generation and migration of haematopoietic precursor cells.^{42,43} It may be speculated that these cytokines promote a constant production of CD34+ haematopoietic stem cells that are released into circulation, where they can differentiate into several lineages of inflammatory cells (e.g. eosinophils, mast cells) contributing to the chronicity of inflammatory diseases.³²

In conclusion, our study has demonstrated that the circulation of substantial numbers of CD34+ cells occurs in canine AD. Future studies should focus on testing a larger cohort of dogs to correlate the magnitude of this change with clinical severity, allergenic challenges and response to therapies. Studies to detect and characterize CD34+ cells in the inflammatory infiltrate of affected skin should also follow.

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Résumé

Contexte – La moelle osseuse peut être impliquée dans les maladies atopiques de l’homme comme en témoigne la libération de lymphocytes CD34+ dans la circulation périphérique.

Hypothèses/Objectifs – Le but était de déterminer le nombre de cellules CD34+ chez les chiens atopiques.

Sujets – Les trois groupes suivants ont été étudiés : 27 chiens atteints de dermatite atopique non liée à l’alimentation (NFICAD); 16 chiens atteints de maladies inflammatoires non allergiques; et 13 chiens sains contrôles.

Méthodes – Les chiens NFICAD ont été sélectionnés d’après les critères de Favrot et l’exclusion d’autres dermatoses prurigineuses comme la pulicose ou les réactions indésirables à l’alimentation. Un CADESI-03 (Canine Atopic Dermatitis Extent and Severity Index) et une échelle visuelle analogue (VAS) pour le prurit ont été utilisés afin de quantifier les signes cliniques. Un anticorps conjugué à la phycoerythrine anti-CD34 canin a été utilisé pour marquer les cellules CD34+ du sang périphérique, dénombrées ensuite par cytométrie de flux. Le comptage des cellules CD34+ a été comparé entre les groupes et corrélé (dans le groupe NFICAD) avec la sévérité des signes cliniques.

Résultats – Les nombres de cellules CD34+ périphériques chez les chiens avec NFICAD (médiane 1.7) étaient statistiquement plus élevés que les chiens avec d’autres maladies inflammatoires non allergiques (médiane 1.0; $P = 0.01$) et les chiens contrôles (médiane 0.9; $P = 0.009$). Chez les chiens NFICAD, il n’y avait pas de corrélation entre le nombre de cellules CD34+ et les scores CADESI-03 ou les scores VAS.

Conclusions et importance clinique – Les résultats de cette étude suggèrent que l’implication possible des cellules CD34+ chez les chiens avec NFICAD. Le rôle des cellules CD34+ dans l’étiopathogénie de la dermatite atopique reste à déterminer.

Resumen

Introducción – la médula ósea por estar implicada en las enfermedades atópicas humanas, tal y como lo demuestra la liberación de linfocitos CD34 positivos en la sangre periférica

Hipótesis/Objetivos – el propósito fue determinar el número de linfocitos CD34 positivos en perros atópicos.

Animales – se estudiaron los siguientes grupos de perros: 27 perros con dermatitis atópica no inducida por alimentos (NFICAD); 16 perros con enfermedades inflamatorias no alérgicas; y trece perros control sanos

Métodos – los perros con dermatitis atópica no inducida por alimentos fueron seleccionados tras corroborar los criterios de Favrot y la exclusión de otras dermatosis pruriginosas, incluyendo infestación por pulgas, y reacción adversa a alimentos. El índice de extensión y severidad de la dermatitis atópica canina CADESI-03 y una escala visual análoga (VAS) se utilizaban para evaluar el prurito y para cuantificar los signos clínicos. Un anticuerpo anti-CD34 canino conjugado con ficoeritrina se utilizó para teñir las células de sangre periférica CD34 positivas, y éstas se evaluaron utilizando citometría de flujo. Los recuentos de células CD34 positivas se compararon entre grupos y se probaron (en el grupo NFICAD) para la correlación con la severidad de los signos clínicos

Resultados – el número de células CD34 positivas periféricas en perros con dermatitis atópica no inducida por alimentos (media 1,7) fue estadísticamente mayor que en perros con otras enfermedades inflamatorias no alérgicas (media 1,0; $P = 0,01$) y perros control sanos (media 0,9; $P = 0,009$). En perros con dermatitis alérgica no inducida por alimentos no hubo correlación entre los valores de células CD34 positivas y los valores de CADESI-03 o el prurito evaluado por los propietarios (valor VAS).

Conclusiones e importancia clínica – los resultados de este estudio sugieren que las células CD34 positivas están implicadas en casos de dermatitis atópica canina no inducida por alimentos en perros. El papel de estas células en la patogenia de la dermatitis atópica aún está por determinar.

Zusammenfassung

Hintergrund – Das Knochenmark könnte bei der atopischen Dermatitis des Menschen eine Rolle spielen, was durch den Ausstrom von CD34+ Lymphozyten ins periphere Blut gezeigt werden konnte.

Hypothese/Ziele – Das Ziel war es, die Anzahl der CD34+ Zellen bei atopischen Hunden zu bestimmen.

Tiere – Die folgenden drei Gruppen von Hunden wurden untersucht: 27 Hunde mit nicht durch Futter induzierter atopischer Dermatitis (NFICAD); 16 Hunde mit nichtallergischer entzündlicher Erkrankung; und 13 gesunde Kontrollhunde.

Methoden – Hunde mit NFICAD wurden nach Erfüllung der Favrot Kriterien und nach Ausschluss anderer juckender Hauterkrankungen, inklusive Flohbefall und Futtermittelallergien, ausgewählt. Der Canine Atopic Dermatitis Extent and Severity Index (CADESI)-03 und eine Visuelle Analogskala (VAS) für den Juckreiz wurden verwendet, um die klinischen Symptome zu quantifizieren. Ein mit Phycoerythrin-konjugierter anti-caniner CD34 Antikörper wurde verwendet, um periphere CD34+ Zellen im Blut anzufärben und diese mittels Flowzytometrie zu zählen. Die CD34+ Zellzahlen in den verschiedenen Gruppen wurden verglichen und in Bezug auf eine Korrelation mit dem Schweregrad der Symptomatik (in der NFICAD Gruppe) untersucht.

Ergebnisse – Die Anzahl der peripheren CD34+ Zellen bei Hunden mit NFICAD (Median 1,7) war statistisch höher als bei Hunden mit anderen nichtallergischen entzündlichen Erkrankungen (Median 1,0; $P=0,01$) und bei den gesunden Kontrollhunden (Median 0,9; $P=0,009$). Bei Hunden mit NFICAD bestand keine Korrelation zwischen CD34+ Zellzahlen und CADESI-03 Werten oder dem durch die BesitzerInnen beurteilten Juckreiz (VAS score).

Schlussfolgerungen und klinische – Bedeutung – Die Ergebnisse dieser Studie weisen auf eine mögliche Beteiligung von CD34+ Zellen bei Hunden mit NFICAD hin. Die Rolle der CD34+ Zellen in der Ätiopathogenese der caninen atopischen Dermatitis ist noch abzuklären.

要約

背景 – CD34+リンパ球の末梢血への放出によって示されるように、骨髄はヒトのアトピー性皮膚炎に関与している可能性がある。

仮説/目的 – 目的はアトピー犬におけるCD34+細胞の数を測定すること。

供与動物 – 以下の3つのグループのイヌで調査を行った、27頭の非食物誘発性アトピー性皮膚炎(NFICAD)、16頭の非アレルギー性炎症性疾患、13頭の健康コントロール犬。

方法 – NFICADのイヌは、Favrotの基準を満たし、ノミ感染症と食事に対する有害反応を含む他の掻痒性皮膚症を除外して選出した。Canine Atopic Dermatitis Extent and Severity Index (CADESI)-03および痒みに対するビジュアルアナログスケール (VAS) スコアは臨床症状を定量化するために用いた。フィコエリトリン-標識抗イヌCD34抗体を末梢血CD34+細胞の染色に使用し、それらはフローサイトメーターを用いて計測した。CD34+細胞数はグループ間で比較し、臨床サインの重症度との相関を(NFICADグループとで)分析した。

結果 – NFICADのイヌにおける末梢CD34+細胞数(平均1.7)は他の非アレルギー性炎症性疾患のイヌ(平均1.0; $P=0.01$)および健康なコントロール犬(平均0.9; $P=0.009$)より統計的に多かった。NFICADのイヌでは、CD34+細胞数とCADESI-03スコアあるいは飼い主が評価したそう痒(VASスコア)の間に相関はみられなかった。

結論および臨床的な重要性 – この研究の結果はNFICADのイヌにおけるCD34+細胞の関与の可能性を支持している。イヌアトピー性皮膚炎の病因論におけるCD34+細胞の役割は究明されていない。

摘要

背景 – 人异位性皮膚炎可能涉及骨髓, 表现为CD34+淋巴细胞向外周血中释放

假设/目的 – 目的为确定异位性皮膚炎患犬中CD34+的数量。

动物 – 将患犬分为三组研究: 27只没有食物过敏因素的异位性皮膚炎患犬(NFICAD); 16只非过敏的炎性疾病患犬; 13只健康犬作为对照。

方法 – 被选中的NFICAD患犬符合Favrot's标准, 并排除其他搔痒症, 包括跳蚤叮咬过敏和食物副反应。犬异位性皮膚炎程度及严重性指数(CADESI)-03和视觉模拟评分法(VAS)的搔痒分数, 用于量化临床症状。藻红蛋白共轭抗犬CD34+抗体结合外周血中CD34+细胞, 用流式细胞仪计数。对比各组CD34+细胞数量, 并评估其与临床症状严重性的相关性(NFICAD组)。

结果 – NFICAD患犬外周血中CD34+细胞的数量(中值为1.7)明显高于非过敏的炎性疾病患犬(中值为1.0; $p=0.01$)及健康对照组(中值0.9; $p=0.009$)。NFICAD患犬中, CD34+细胞数量与CADESI-03分数, 或 主人的搔痒评分(VAS分数)无关。

总结与临床意义 – 研究结果显示NFICAD患犬可能涉及CD34+细胞。CD34+细胞在犬异位性皮膚炎病因病理学作用尚不明确。