Pilosebaceous Dysplasia (Abnormal Orientation of Pilosebaceous Units): A Histopathological Finding Indicative of Yeast Dermatitis in Dogs

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Abstract: The objective of this study was to characterize the histological appearance, prevalence, and association of pilosebaceous dysplasia (PD) in dogs with yeast dermatitis. A retrospective, light-microscopic study of H&E-stained skin-biopsy specimens from 670 dogs with non-neoplastic dermatoses and 28 normal dogs was performed. Chi-square and rank-sum analyses were used to compare the prevalence and abundance of PD in dogs with yeast dermatitis, normal dogs, and dogs with non-yeast dermatoses. PD was observed in 76 of 98 (78%; 95% confidence interval (CI) 68%, 85%) of dogs with yeast dermatitis and in 14 of 572 (2.4%; CI 1.4%, 4.2%) dogs with non-yeast dermatoses. PD was not observed in any normal dogs (CI 0%, 15%).

The prevalence (presence, yes/no) of PD was significantly greater in dogs with yeast dermatitis (chi-square = 424.49; degrees of freedom = 2; p<0.0001) than in dogs with non-yeast dermatoses and in normal dogs. Also, among the dogs with PD present, the percentage of affected units in each dog was greater (p=0.0002) in dogs with yeast dermatitis (minimum 12%; median 75%; maximum 100% affected units/dog) than in dogs with non-yeast dermatoses (minimum 3%; median 30%; maximum 100%). There was no significant difference (p>0.05) between the prevalence of PD in dogs with non-yeast dermatoses and in normal dogs. These findings suggest that the finding of PD in skin-biopsy specimens of dogs is significantly associated with yeast dermatitis and could be considered when making this histological diagnosis.

Key words: dog, Malassezia, pilosebaceous dysplasia, skin, yeast dermatitis

要約: 今回の研究目的は、犬の酵母による皮膚炎における毛嚢脂腺の異形成の病理組織学的所見、出現率そして関連性についてである。670頭の犬の非腫瘍性皮膚症および28頭の健常犬からのHE染色した皮膚生検試料について、光学顕微鏡学的に行った回顧的な研究である。犬の酵母による皮膚炎、正常皮膚、非酵母性皮膚病における毛嚢脂腺の異形成の発生率および存在率を比較するために、カイ二乗および順位検定を行った。犬の酵母による皮膚炎における毛嚢脂腺の異形成は、98頭中76頭（78%；95%の信頼水準で、68 ～ 85%の信頼区間）で、非酵母性皮膚病では14頭中572頭（2.4%；95%の信頼水準で、1.4 ～ 4.2%の信頼区間）であった。毛嚢脂腺の異形成は、正常犬では認められなかった（95%の信頼水準で、0 ～ 15%の信頼区間）であった。毛嚢脂腺の異形成の発生率（存在する／しない）は、非酵母性皮膚病および正常犬に比べて、酵母による皮膚炎において
Introduction

Dysplastic disorders of the hair follicles or sebaceous glands of dogs have previously been described. Follicular dysplasia syndromes are documented in numerous dog breeds\(^2,5,7\). Sebaceous gland dysplasia has recently been described in a small number of dogs\(^2,5,7\). Fibroadenexal dysplasia is a well-recognized cause of cutaneous nodules in dogs\(^2,5\).

The histopathological features of yeast (\textit{Malassezia}) dermatitis in dogs are well-known\(^2–5\). One of the authors of the current paper (DWS) has long believed that a previously unreported form of pilosebaceous dysplasia (PD) is also indicative of \textit{Malassezia} dermatitis in dogs. An anecdotal observation in a recent textbook suggests that the histopathologic finding of “hyperplastic sebaceous glands in disarray” is associated with \textit{Malassezia} dermatitis in dogs\(^4\). Our purpose in this study was to document the prevalence of PD in skin-biopsy specimens from dogs with various inflammatory dermatoses. We were particularly interested to learn whether there was a statistically significant association between the prevalence of PD and yeast (presumably \textit{Malassezia}) dermatitis. Our secondary question was whether the percentage of units with PD among dogs with any PD differed between dogs with and without yeast dermatitis.

Materials and Methods

A retrospective light-microscopic study of skin-biopsy specimens of 670 dogs with non-neoplastic dermatoses was performed (Table 1). All specimens had been submitted to the Diagnostic Pathology Service at Cornell University College of Veterinary Medicine (Ithaca, New York, USA). One author (DWS) initially selected 702 dog skin-biopsy specimens in chronological order with no preferential selection of any specific disease. The specimens were from various breeds of dogs and were obtained between 1988 and 2000. Diagnoses for the non-neoplastic diseases had been made using previously established clinical and histological criteria\(^2\). All patients were managed by the members of the Dermatology Service at Cornell University. Dogs with yeast dermatitis had typical clinical signs, positive cytology, compatible skin-biopsy findings, and resolution of clinical signs with topical (lime sulfur or acetic acid leave-on rinses) and/or systemic (ketoconazole) anti-yeast therapy. Cultures for yeast were not performed.

Of the 702 specimens selected, 670 were included in this study. The remaining 32 specimens were excluded because they were either the wrong species (2 cats, 1 alpaca) or they were additional specimens from the same dog. In the instances where multiple specimens from the same dog were discovered the specimen with the lowest case number was chosen to avoid selection bias. Of the 670 specimens, 602 (90%) had been taken from the truncal region.

Skin-biopsy specimens from the dorsolateral thorax of 28 normal dogs were also included in the study. All of these specimens were obtained by the Diagnostic Pathology Service during necropsy of dogs with no gross skin lesions or history of skin disease.

All specimens were previously formalin-fixed, paraffin-embedded, sectioned at 4 µm, and stained with hematoxylin and eosin (H&E). One author (DWS) selected one section per sample and marked it appropriately to ensure all evaluators examined the same section. The following criteria were used in selection of the sections: (1) there was adequate depth of the dermis so that evaluators could examine pilosebaceous units if they were present; (2) it contained the most pilosebaceous units; (3) it was the best H&E-
stained sample available (least sampling and processing artifact).

Two authors (DCF and JPK) were blinded to the diagnosis of each sample prior to examination. All specimens were independently examined by two of the authors (DCF and JPK) for the presence of pilosebaceous dysplasia (PD). During evaluation the evaluators examined only the pilosebaceous units and made no attempt to evaluate the remainder of the section or determine a histopathologic diagnosis. If PD was seen in a section, the percentage of dysplastic pilosebaceous units was recorded.

Fig. 1. Normal skin. A = Note the size of sebaceous glands (arrow) and location relative to hair follicle. H&E stain 200×. B = Note the size of sebaceous glands (arrow) and location relative to hair follicle. H&E stain 200×.

Fig. 2. Yeast dermatitis. A = Sebaceous glands are hyperplastic and directed laterally (arrow) and dorsally (asterisk). H&E stain 200×. B = Sebaceous glands are hyperplastic and directed dorsally (arrows). H&E stain 200×.
### Table 1. Prevalence of pilosebaceous dysplasia in 698 dogs with non-neoplastic dermatoses or normal skin

| Diagnosis                                                | Total # of specimens | # of specimens with PD* | % of specimens with PD | 95% CI for the % of specimens with PD |
|----------------------------------------------------------|----------------------|-------------------------|------------------------|----------------------------------------|
| Acanthosis nigricans                                      | 2                    | 0                       | 0                      | 0, 80                                  |
| With yeast dermatitis                                     | 1                    | 1                       | 100                    | 5, 100                                 |
| Acral lick dermatitis                                     | 10                   | 0                       | 0                      | 0, 34                                  |
| With bacterial folliculitis                               | 1                    | 0                       | 0                      | 0, 95                                  |
| Atopic dermatitis                                         | 82                   | 1                       | 1                      | 0.00006, 8                             |
| With bacterial folliculitis                               | 14                   | 0                       | 0                      | 0, 27                                  |
| With bacterial folliculitis and furunculosis             | 4                    | 0                       | 0                      | 0, 60                                  |
| With yeast dermatitis                                     | 22                   | 16                      | 73                     | 50, 88                                 |
| With bacterial folliculitis and yeast dermatitis         | 2                    | 2                       | 100                    | 20, 100                                |
| With hypothyroidism                                       | 2                    | 0                       | 0                      | 0, 80                                  |
| Bacterial folliculitis                                    | 31                   | 0                       | 0                      | 0, 14                                  |
| With furunculosis                                         | 53                   | 1                       | 2                      | 0.1, 11                                |
| Bacterial furunculosis                                    | 9                    | 0                       | 0                      | 0, 37                                  |
| Blastomycosis                                            | 1                    | 0                       | 0                      | 0, 95                                  |
| Bullous pemphigoid                                        | 1                    | 0                       | 0                      | 0, 95                                  |
| Castration-responsive dermatosis                          | 1                    | 0                       | 0                      | 0, 95                                  |
| Cheyletiellosis                                           | 1                    | 0                       | 0                      | 0, 95                                  |
| Contact dermatitis                                        | 5                    | 0                       | 0                      | 0, 54                                  |
| Demodexis (generalized)                                  | 25                   | 0                       | 0                      | 0.17                                   |
| With bacterial folliculitis and furunculosis             | 1                    | 0                       | 0                      | 0, 95                                  |
| Dermatomyositis                                           | 4                    | 0                       | 0                      | 0, 60                                  |
| Dermatophytosis                                           | 10                   | 0                       | 0                      | 0, 34                                  |
| Discoid lupus erythematosus                              | 11                   | 0                       | 0                      | 0, 32                                  |
| Drug eruption                                             | 3                    | 0                       | 0                      | 0, 69                                  |
| Eosinophilic folliculitis and furunculosis                | 8                    | 0                       | 0                      | 0, 40                                  |
| Erythema multiforme                                       | 2                    | 0                       | 0                      | 0, 80                                  |
| Estrogen-responsive dermatosis                            | 3                    | 0                       | 0                      | 0, 69                                  |
| Flea allergy dermatitis                                   | 15                   | 3                       | 20                     | 5, 49                                  |
| With bacterial folliculitis and furunculosis             | 1                    | 0                       | 0                      | 0, 95                                  |
| With bacterial folliculitis and yeast dermatitis         | 2                    | 1                       | 50                     | 3, 97                                  |
| With yeast dermatitis                                     | 7                    | 6                       | 86                     | 42, 99                                 |
| Follicular dysplasia                                      | 14                   | 0                       | 0                      | 0, 27                                  |
| With bacterial folliculitis                               | 2                    | 0                       | 0                      | 0, 80                                  |
| With bacterial folliculitis and furunculosis             | 2                    | 0                       | 0                      | 0, 80                                  |
| Food allergy                                              | 21                   | 1                       | 5                      | 0.002, 26                              |
| With bacterial folliculitis                               | 1                    | 0                       | 0                      | 0, 95                                  |
| With bacterial folliculitis and yeast dermatitis         | 1                    | 1                       | 100                    | 5, 100                                 |
| With yeast dermatitis                                     | 5                    | 4                       | 80                     | 30, 99                                 |
| With hypothyroidism                                       | 1                    | 0                       | 0                      | 0, 95                                  |
| Growth hormone-responsive dermatosis                     | 2                    | 0                       | 0                      | 0, 80                                  |
| Hyperadrenocorticism (spontaneous)                        | 14                   | 0                       | 0                      | 0, 27                                  |
| With bacterial folliculitis                               | 1                    | 0                       | 0                      | 0, 95                                  |
| With calcinosis cutis                                     | 5                    | 1                       | 20                     | 1, 70                                  |
| Hyperadrenocorticism (iatrogenic)                         | 2                    | 0                       | 0                      | 0, 80                                  |
| With calcinosis cutis                                     | 4                    | 0                       | 0                      | 0, 60                                  |
| Hyperestrogenism                                          | 2                    | 0                       | 0                      | 0, 80                                  |
Table 1. continued

| Diagnosis                                                        | Total # of specimens | # of specimens with PD* | % of specimens with PD | 95% CI for the % of specimens with PD |
|------------------------------------------------------------------|----------------------|-------------------------|------------------------|----------------------------------------|
| Hypothyroidism                                                  | 46                   | 1                       | 2                      | 0.1, 13                                |
| With bacterial folliculitis                                     | 12                   | 0                       | 0                      | 0, 30                                  |
| With bacterial folliculitis and furunculosis                    | 4                    | 0                       | 0                      | 0, 60                                  |
| With bacterial folliculitis and yeast dermatitis                 | 1                    | 0                       | 0                      | 0, 95                                  |
| With yeast dermatitis                                           | 6                    | 4                       | 67                     | 24, 94                                 |
| Ichthyosis                                                      | 1                    | 0                       | 0                      | 0, 95                                  |
| Juvenile cellulitis                                             | 1                    | 0                       | 0                      | 0, 95                                  |
| Lichenoid dermatitis (idiopathic)                               | 3                    | 0                       | 0                      | 0, 69                                  |
| Mucocutaneous pyoderma                                          | 1                    | 0                       | 0                      | 0, 95                                  |
| Normal skin                                                     | 28                   | 0                       | 0                      | 0, 15                                  |
| Pattern baldness                                                | 2                    | 0                       | 0                      | 0, 80                                  |
| Pemphigus erythematosus                                         | 4                    | 0                       | 0                      | 0, 60                                  |
| Pemphigus foliaceus                                             | 12                   | 0                       | 0                      | 0, 30                                  |
| With yeast dermatitis                                           | 1                    | 0                       | 0                      | 0, 95                                  |
| Pemphigus vulgaris                                              | 3                    | 1                       | 33                     | 2, 87                                  |
| Pituitary dwarfism                                              | 5                    | 0                       | 0                      | 0, 54                                  |
| Primary seborrhea                                               | 7                    | 0                       | 0                      | 0, 44                                  |
| With yeast dermatitis                                           | 4                    | 3                       | 75                     | 22, 99                                 |
| With bacterial folliculitis                                     | 2                    | 0                       | 0                      | 0, 80                                  |
| With bacterial folliculitis and furunculosis                    | 1                    | 0                       | 0                      | 0, 95                                  |
| With hypothyroidism                                             | 1                    | 0                       | 0                      | 0, 95                                  |
| Pyotraumatic dermatitis                                         | 1                    | 0                       | 0                      | 0, 95                                  |
| Sarcoptic mange                                                 | 31                   | 2                       | 6                      | 1, 23                                  |
| With bacterial folliculitis                                     | 5                    | 0                       | 0                      | 0, 54                                  |
| With bacterial folliculitis and yeast dermatitis                 | 3                    | 1                       | 33                     | 2, 87                                  |
| With yeast dermatitis                                           | 12                   | 8                       | 67                     | 35, 89                                 |
| With hypothyroidism                                             | 1                    | 0                       | 0                      | 0, 95                                  |
| Schnauzer comedo syndrome                                       | 2                    | 0                       | 0                      | 0, 80                                  |
| Sebaceous adenitis                                              | 5                    | 0                       | 0                      | 0, 54                                  |
| Sertoli cell syndrome                                           | 2                    | 0                       | 0                      | 0, 80                                  |
| Sterile panniculitis (idiopathic)                               | 6                    | 0                       | 0                      | 0, 48                                  |
| Sterile pyogranuloma syndrome                                   | 3                    | 0                       | 0                      | 0, 69                                  |
| Subcorneal pustular dermatosis                                  | 5                    | 0                       | 0                      | 0, 54                                  |
| Systemic lupus erythematosus                                    | 7                    | 0                       | 0                      | 0, 44                                  |
| Toxic epidermal necrolysis                                      | 2                    | 0                       | 0                      | 0, 80                                  |
| Uveodermatologic syndrome                                       | 1                    | 0                       | 0                      | 0, 95                                  |
| Vasculitis                                                       | 7                    | 0                       | 0                      | 0, 44                                  |
| With bacterial folliculitis and furunculosis                    | 4                    | 0                       | 0                      | 0, 60                                  |
| With bacterial furunculosis                                     | 1                    | 0                       | 0                      | 0, 95                                  |
| Vesicular cutaneous lupus erythematosus                         | 2                    | 0                       | 0                      | 0, 80                                  |
| Yeast dermatitis                                                | 22                   | 20                      | 91                     | 69, 98                                 |
| With bacterial folliculitis                                     | 9                    | 9                       | 100                    | 63, 100                                |
| Zinc-responsive dermatosis                                      | 11                   | 3                       | 27                     | 7, 61                                  |

*PD = pilosebaceous dysplasia.
PD, as evaluated in this study, consisted of each of the following histological findings (Figs. 1 and 2): (1) the infundibula of hair follicles were hyperplastic and exhibited variable degrees of intercellular edema (spongiosis), intracellular edema of keratinocytes, and lymphocytic exocytosis (infiltrative lymphocytic mural folliculitis); (2) the sebaceous glands were hyperplastic but not inflamed; (3) the sebaceous ducts, secondary hair follicles, and sebaceous glands were oriented lateral and/or dorsal to the primary hair follicles; (4) the surrounding dermis exhibited edema, perivascular-to-interstitial accumulations of predominantly lymphocytes and plasma cells, and rare mild fibrosis.

After all specimens were examined and recorded, the diagnoses were made available to the blinded evaluators (DCF and JPK). Three groups were created without consideration of the PD prevalences or counts of individual cases: Group 1 represents normal dogs; group 2 represents dogs with yeast dermatitis or yeast dermatitis in combination with other non-yeast dermatoses; group 3 represents dogs with only non-yeast dermatoses.

This statistical analysis using Statistix 10 (Analytical Software, Tallahassee, FL 32317-2185 USA) sought to answer two questions: (1) does the prevalence of PD differ according to diagnostic group?; (2) among the dogs with PD, is the percentage of pilosebaceous units with PD the same between groups? A chi-square test, 95% confidence intervals (CI; calculated by the Wilson score method with continuity correction), and a box-and-whisker plot were used to compare the prevalence of PD according to diagnostic groups. Because the data were not assumed to be bell-shaped (Gaussian), a Wilcoxon rank-sum test was performed at the p≤0.05 cutoff to statistically evaluate the percent of pilosebaceous units with PD between groups.

Results

Of the 698 specimens examined (Table 1) there were 28 dogs in group 1, 98 dogs in group 2, and 572 dogs in group 3. PD was not observed in any specimen from group 1 (0%; 95% CI 0%, 20%). PD was observed in 76 of 98 (78%; 95% CI 68%, 85%) specimens from group 2 and in 14 of 572 (2.4%; 95% CI 1.4%, 4.2%) specimens from Group 3. Of the 14 dogs with PD that did not have a diagnosis of yeast dermatitis, 3 had zinc-responsive dermatitis, 3 had food allergy, 1 had pemphigus vulgaris, 1 had bacterial folliculitis and furunculosis, 1 had atopic dermatitis, 1 had hypothyroidism, and 1 had spontaneous hyperadrenocorticism with calcinosis cutis.

There was a significantly (chi-square = 424.49, degrees of freedom = 2, p<0.0001) higher prevalence of PD among dogs in group 2 than among the other two groups. The fact that the percentage of PD in group 3 lies within the CI of group 1 means that the two groups are not significantly different at the p<0.05 cutoff.

The percentage of pilosebaceous units with PD within specimens with PD varied from 12% to 100% (median 75%) and 3% to 100% (median 30%) in groups 2 and 3, respectively. The null hypothesis was that the percent of pilosebaceous units with PD had similar distribution between groups 2 and 3. This was rejected because group 2 had a significantly (p=0.0002) higher percentage of units affected than did group 3.

Discussion

To our knowledge, this is the first study to characterize the histological appearance, prevalence, and association of PD in dogs with yeast (presumptively Malassezia) dermatitis. Histopathological criteria of yeast dermatitis have been reported and do not include PD or any pilosebaceous abnormality that is similar to our description of PD.

1. Idiopathic sebaceous gland hyperplasia is characterized by marked, non-inflammatory hyperplasia of sebaceous glands. Affected dogs show a greasy, matted hair coat without pruritus or inflammation.
2. Abnormal sebaceous gland differentiation (sebaceous gland dysplasia) is characterized by non-inflammatory, small, poorly-formed sebaceous glands composed of aggregates of haphazardly arranged, basaloid keratinocytes and sebocytes. Affected dogs manifest progressive, non-pruritic hair loss, scaling, and a harsh, dry hair coat.
3. Follicular dysplasia syndromes are characterized by non-inflammatory hair follicle dysplasia and variable
abnormalities of melanization²,³,⁸. Affected dogs show non-pruritic and non-inflammatory patterns of hair loss.

4. Sebaceous gland hamartomas (nevi) and hair follicle hamartomas (nevi) are characterized by non-inflammatory nodules formed by hyperplastic sebaceous glands or hair follicles, respectively²,³,⁶,⁹. Pilosebaceous (organoid) hamartomas (nevi) feature non-inflammatory nodular hyperplasia of both elements⁵,⁶. Affected dogs present with single or multiple non-pruritic cutaneous nodules.

PD was observed in 76 of 98 (78%) of dogs with yeast dermatitis and in 14 of 572 (2.4%) of dogs with non-yeast dermatitis. PD was also not observed in any normal dogs, which is consistent with the fact that no pilosebaceous abnormality fitting our description has been reported in normal dogs⁵. While the presence of PD is significantly associated with yeast dermatitis, it is not diagnostic for the disease.

In addition to finding the prevalence of PD, we also sought to find out whether the percentage of pilosebaceous units with PD (among cases with PD) was the same between dogs with yeast dermatitis versus non-yeast dermatitis. In this study, dogs with yeast dermatitis had a median of 75% of their pilosebaceous units (within a section) affected. In contrast, dogs with non-yeast dermatitis and a finding of PD only had a median of 30% of pilosebaceous units affected.

Fourteen of 572 (2.4%) dogs with non-yeast dermatitis had skin-biopsy specimens with PD. One explanation for these findings is that these diseases can present with secondary infections and they might have had undiagnosed yeast dermatitis⁵. This could not be determined due to the retrospective nature of the study. Because all of these 14 dogs responded to appropriate therapy for their respective diseases, we could speculate that any undiagnosed secondary yeast dermatitis may have spontaneously resolved. It is not known whether there is an association between the percentage of pilosebaceous units with PD and the severity of the yeast dermatitis. If there is an association then this could explain why a dog with a low percentage of pilosebaceous units affected could have had undiagnosed yeast dermatitis at the time of biopsy.

In conclusion, the finding of PD is significantly associated with yeast dermatitis and, when present in dogs with yeast dermatitis, might be seen in a majority of the pilosebaceous units within a given section. These findings suggest that the finding of PD in skin-biopsy specimens of dogs is significantly associated with yeast dermatitis and could be considered when making this histological diagnosis.

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