

Veterinary Pathology Online

<http://vet.sagepub.com/>

The Clinical and Morphologic Features of Nonepidermolytic Ichthyosis in the Golden Retriever

E. A. Mauldin, K. M. Credille, R. W. Dunstan and M. L. Casal

Vet Pathol 2008 45: 174

DOI: 10.1354/vp.45-2-174

The online version of this article can be found at:

<http://vet.sagepub.com/content/45/2/174>

Published by:



<http://www.sagepublications.com>

On behalf of:

American College of Veterinary Pathologists, European College of Veterinary Pathologists, & the Japanese College of Veterinary Pathologists.

Additional services and information for *Veterinary Pathology Online* can be found at:

Email Alerts: <http://vet.sagepub.com/cgi/alerts>

Subscriptions: <http://vet.sagepub.com/subscriptions>

Reprints: <http://www.sagepub.com/journalsReprints.nav>

Permissions: <http://www.sagepub.com/journalsPermissions.nav>

>> [Version of Record - Mar 1, 2008](#)

[What is This?](#)

The Clinical and Morphologic Features of Nonepidermolytic Ichthyosis in the Golden Retriever

E. A. MAULDIN, K. M. CREDILLE, R. W. DUNSTAN, AND M. L. CASAL

Departments of Pathobiology (EAM) and Clinical Studies (MLC), University of Pennsylvania, School of Veterinary Medicine, Philadelphia, PA; Eli Lilly and Co., Indianapolis, IN (KMC); and Biogen Idec, Cambridge, MA (RWD)

Abstract. A scaling disorder specific to Golden Retriever dogs has been recognized by both dermatologists and pathologists, but to date has not been well characterized. At the University of Pennsylvania's Laboratory of Toxicology and Pathology, 46 cases of ichthyosis were diagnosed histologically in Golden Retriever dogs from January 2004 to January 2007. A total of 22 dogs had skin lesions documented at younger than 1 year of age; 3 dogs between 1 and 2 years of age; 13 dogs developed lesions at older than 2 years; and the time of onset was unknown for 8 dogs. A total of 25 dogs were female, and 21 were male. All dogs had strikingly similar histopathologic changes that consisted of mild to moderate laminar orthokeratotic hyperkeratosis with an absence of epidermal hyperplasia and dermal inflammation. Ultrastructural analysis using a ruthenium tetroxide fixation method was performed on punch biopsy samples from 5 dogs and compared with 2 control dogs (1 clinically and histologically normal sibling of an affected dog and 1 Cairn Terrier). All affected dogs had retained and convoluted membranes with crystalline structures in the stratum corneum. Scattered keratinocytes in the granular cell layer had prominent, clear, membrane-bound, cytoplasmic vacuoles. Pedigree analysis of 14 dogs was compatible with autosomal recessive inheritance, but incomplete dominance could not be ruled out. This unique hyperkeratotic/scaling disorder in Golden Retrievers has distinctive clinical, histologic, and ultrastructural features, which are consistent with a primary cornification defect.

Key words: Canine; cornification; Golden Retrievers; hyperkeratosis; ichthyosis.

Ichthyoses encompass a heterogeneous group of hereditary and generally congenital diseases that are all characterized by faulty formation of the outer layer of the epidermis, the stratum corneum, with resultant scaling.^{15,16} The stratum corneum is composed of terminally differentiated keratinocytes (corneocytes), which together with layers of lipid, serve as the major structural barrier between the body and the environment.¹⁰ In humans, ichthyosiform disorders vary greatly in the clinical phenotype, with the more severe hereditary disorders being evident at birth and some others developing later in life. For example, in humans, ichthyosis vulgaris is a relatively mild autosomal dominant disorder with an incidence as high as 1 in 250. In humid climates, patients may have clinically normal skin that becomes symptomatic (dry, scaly) when those individuals move to cold, dry climates.¹⁶

Ichthyoses are classified by the clinical presentation (e.g., character of scale, distribution of lesions, erythroderma, abnormalities in other parts of the skin and internal organs) as well as the age of onset/pattern of inheritance and histopathologic and/or ultrastructural features. Over the past two

decades, molecular characterization of ichthyosiform disorders has greatly expanded the understanding of cornification.¹⁶ In veterinary medicine, the term *ichthyosis* has been limited to rare congenital or hereditary disorders believed to be due to primary defects in the formation of the stratum corneum.³⁰ To date, several ichthyosiform disorders have been characterized in companion animals;^{5–8,11–12,18,21,26–28} only rarely has the molecular mechanism been elucidated.^{8,11} In contrast, most cornification disorders in dogs are secondary to other diseases, such as allergies, metabolic/endocrine abnormalities, and/or bacterial infections.³¹

Veterinary dermatologists and pathologists have recognized a scaling disorder specific to the Golden Retriever dog for about a decade. Anecdotally, this disorder causes mild to moderate scaling with characteristic histopathologic features. To date, one case report has documented this defect, yet it is routinely diagnosed by specialists in dermatopathology and dermatology.²¹ The aim of this study was to document the histopathologic, clinical, and ultrastructural features and investigate the mode of inheritance.

Materials and Methods

A computer search of the University of Pennsylvania Laboratory of Pathology and Toxicology (UPENN-LPT) biopsy database was performed from January 1, 2004, to January 31, 2007, for cases coded as either "lamellar ichthyosis" or "Golden Retriever ichthyosis." The history, signalment, and hematoxylin and eosin (HE)-stained glass slides were reviewed. The veterinarian from each case was contacted, and a 5-generation pedigree was requested of the affected dog. The vertical pedigrees were drawn by hand and scrutinized to see whether the assumed phenotypes and the genotypes in each generation were suggestive of simple Mendelian inheritance.

During the same time period, 6 dogs with suspected Golden Retriever ichthyosis were recruited for ultrastructural analysis. Clinical criteria for inclusion were the following: 1) Golden Retriever; 2) moderate to severe scaling in absence of pruritus or inflammation (e.g., erythema, crusts, ulcers, etc.); history of allergic skin disease or endocrinopathy; 3) pedigree; and 4) lesional photographs of the dog.

Specimens for histopathologic and ultrastructural analysis were obtained from lesional skin of the 6 dogs with local anesthesia by the submitting veterinarian. Two 6-mm punch biopsy samples from each dog were fixed in 10% neutral-buffered formalin, routinely processed, sectioned at 5 μm , and stained with HE. One 6-mm punch biopsy sample was placed in modified Karnovsky fixative (2.5% glutaraldehyde, 2% paraformaldehyde in 0.1 M cacodylate buffer, pH 7.2) for electron microscopy (EM). Samples from 2 normal dogs, an age-matched sibling of an affected Golden Retriever, and a 1-year-old male Cairn Terrier were used as controls for both histopathology and ultrastructural analysis.

Skin samples for conventional transmission EM (TEM) were processed by standard techniques.^{3,24} The skin samples for the detection of lipid leaflets were processed following the protocols reported by Elias, with minor modifications.¹⁷ Briefly, the samples were trimmed into 1-mm cubes and fixed in modified Karnovsky solution at 4°C for overnight. After rinse with sodium cacodylate, the samples were postfixed with 1% reduced osmium tetroxide (OsO₄) for 2 hours in the dark. The samples were then incubated in freshly made 0.25% ruthenium tetroxide for 45 minutes in the dark, followed by conventional procedures of dehydration and embedding. The blocks were polymerized at 68°C for 48 hours. Sections of 80–90 nm were obtained from the epidermis mounted on copper grids, stained with uranyl acetate and lead citrate, and examined with a FEI Tecnai T-12 transmission electron microscope operated at 80 kV.

An assessment of cornified envelope (CE) integrity was performed on scales from 1 affected dog by subjecting the corneocyte to a detergent. A corneocyte with a normal cross-linked envelope (via transglutaminase enzymes) should tolerate an ionizing detergent and



Fig. 1. Pelage; Golden Retriever with nonepidermolytic ichthyosis. Note the large, white, and loosely adherent scale.

reducing agent, whereas an abnormal (non-cross linked) envelope will deteriorate. An age-matched normal Golden Retriever dog and a dog with hypohidrotic ectodermal dysplasia were used as controls.⁹ Briefly, 10 mg of scales were obtained from the affected and control animals. The scales were placed in 10 ml Dulbecco's Minimum Essential Medium plus 2% 2-mercaptoethanol and 2% sodium dodecyl sulfate, boiled for 10 minutes, and vortexed for 10 minutes, and envelopes were counted via a hemocytometer under the light microscope.²³

Results

A total of 46 cases of ichthyosis were diagnosed histopathologically in Golden Retriever dogs over a 23-month period (January 2004 to December 2005). This included 5 dogs recruited for ultrastructural analysis. One dog recruited for ultrastructural analysis was excluded from the study due to incompatible histopathologic changes (hyperplastic eosinophilic superficial dermatitis) and clinical features.

A total of 25 dogs were female, and 21 were male. The age at the time of clinical onset ranged from 8 weeks to 12 years (median = 2.29 years). A total of 22 dogs had hyperkeratosis documented at younger than 1 year; 3 dogs between 1 and 2 years of age; 13 dogs developed scaling at older than 2 years; and the time of onset was unknown for 8 dogs. All dogs had dry scaling, which was described as moderate to severe with variable ventrally oriented hyperpigmentation. The scaling was not associated with inflammation. The character of the scale was consistent in all cases: large, loosely adherent, soft, white-to-gray scales that were often referred to as "snowflake-like" (Fig. 1). A total of 45 of the 46 dogs were described as having generalized scaling. In 1 dog, the scaling

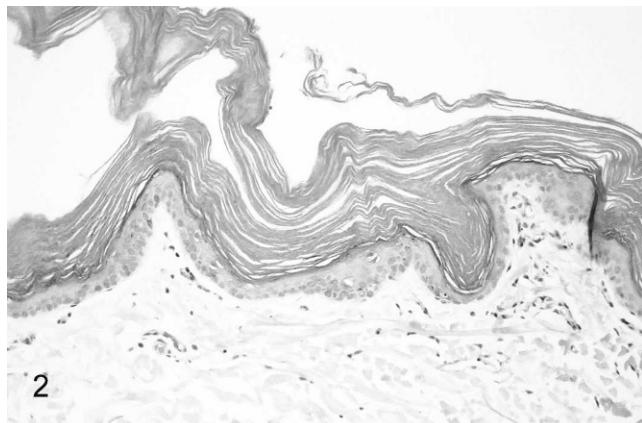


Fig. 2. Haired skin; Golden Retriever with nonepidermolytic ichthyosis. Diffuse laminar orthokeratotic hyperkeratosis is present in absence of epidermal hyperplasia or dermal inflammation. HE.

was primarily distributed on the ventrolateral thorax and abdomen. Changes noted on the ventrally oriented skin (axilla, thorax, abdomen) included hyperpigmentation (10 dogs) and/or erythema (4 dogs). A total of 8 of the 46 dogs were reported to be mildly pruritic. Of those, 3 had signs compatible with mild allergic skin disease, and two had mild pruritus attributed to concurrent pyoderma.

All dogs had strikingly similar histopathologic changes of hyperkeratosis that varied from mild to moderate. The main feature was laminar orthokeratotic hyperkeratosis with minimal to no epidermal hyperplasia and an absence of dermal inflammation. All adnexal structures were within normal limits. The corneocytes were arranged in closely packed layers compared with the open basket-weave pattern associated with normal skin (Fig. 2). Scattered keratinocytes in the outer spinous layer contained large, clear intracellular spaces (Fig. 3) of unknown origin. Keratoxyaline granules were

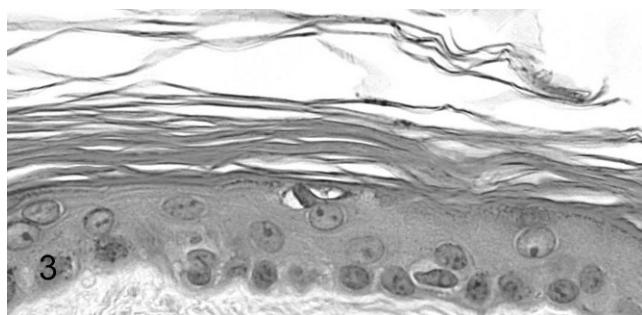


Fig. 3. Hairy skin; Golden Retriever with nonepidermolytic ichthyosis. The stratum corneum has diffuse laminar orthokeratotic hyperkeratosis with scattered vacuolated keratinocytes in the stratum granulosum. HE.

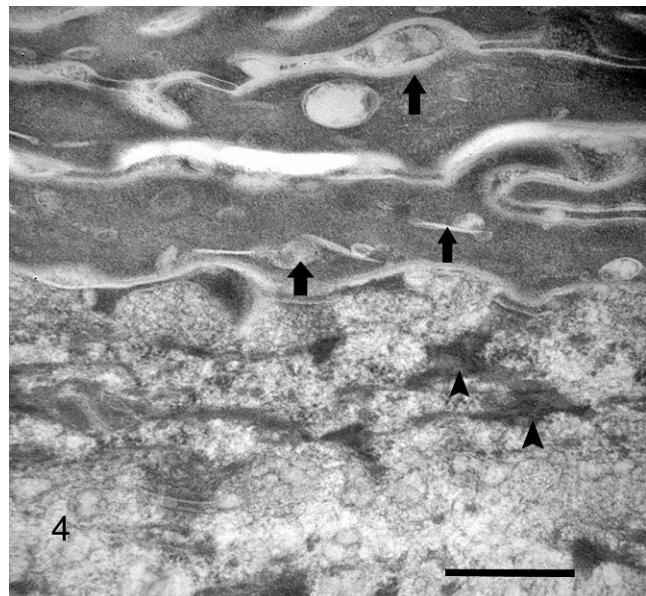


Fig. 4. Stratum corneum and granular cell layer; Golden Retriever with nonepidermolytic ichthyosis. Note the convoluted membranous material in the stratum corneum (arrows). Arrowheads = keratoxyaline granules. Bar = 500 nm.

intermittently present, a normal feature of canine skin.³³

On ultrastructural examination, the most prominent change in the stratum corneum was the presence of many convoluted membranes and crystalline material (Figs. 4 and 5). Some spinous and granular layer keratinocytes contained vacuoles with a small amount of wispy granular

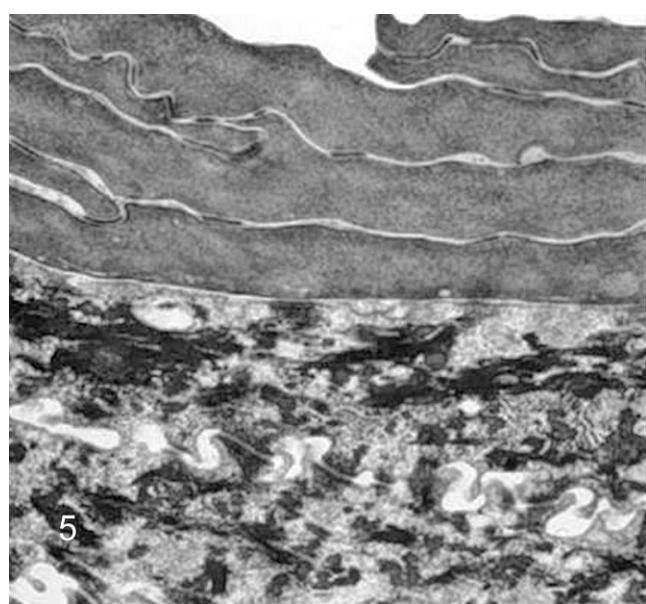


Fig. 5. Stratum corneum and granular cell layer; normal stratum corneum in an unaffected dog.

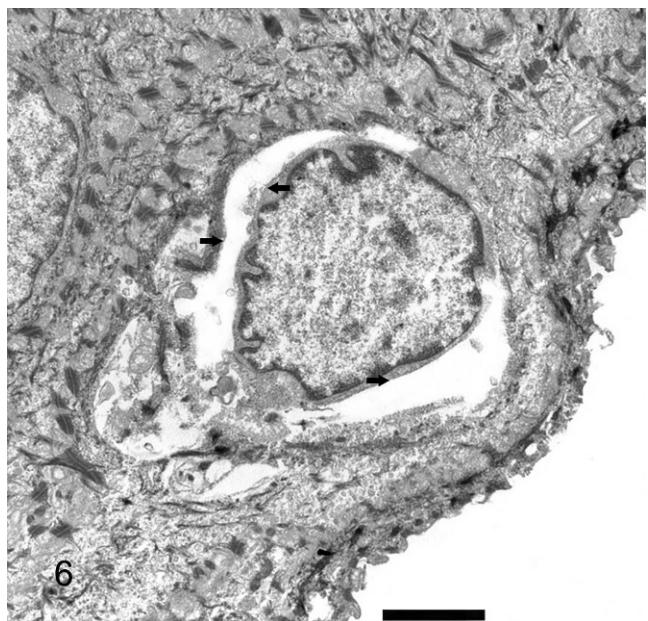


Fig. 6. Epidermis; Golden Retriever with non-pidermolytic ichthyosis. Partially membrane-bound vacuoles (arrows) are located in spinous layer keratinocytes. Bar = 2 μ m.

material that may correspond with the clear spaces observed histologically (Fig. 6). No abnormalities were seen in the cornified envelope. Clear assessment of the lipid lamellae was difficult to discern. Scant, membranous material was evident in the

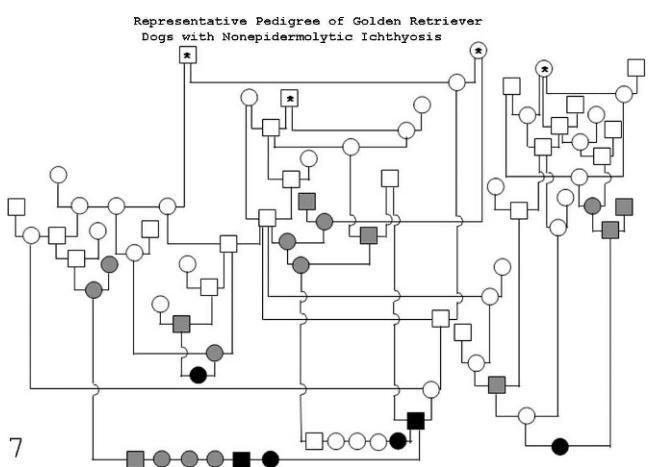


Fig. 7. Excerpt from pedigree of Golden Retrievers with ichthyosis. Squares and circles represent males and females, respectively. Open, shaded, and filled-in symbols designate dogs with no clinical information, phenotypically normal dogs as assessed by a veterinarian, and affected Golden Retrievers, respectively. All dogs in this pedigree have common ancestors and are related via the dogs indicated with an asterisk in the middle of the symbol.

control Cairn Terrier but not in the normal sibling of an affected Golden Retriever.

No abnormality in the cornified envelope could be defined using the detergent procedure. It should be noted that a positive control for this method (a dog with a known cross-linking defect) could not be found.

Pedigrees were made available from 15 of the 46 affected dogs with clear identifiers, such as date of birth, age at death, and gender. Information regarding the health status of littermates and parents of 3 affected dogs was also obtained. Dogs were considered phenotypically unaffected if none of the typical clinical signs of scaling were noted by a veterinarian. A representative portion of the larger pedigree relationship between the dogs affected with ichthyosis is shown in Figure 7. The median inbreeding coefficient for affected dogs and their relatives in which pedigrees were made available was 6.25% from 10 generations, with a range of 0.2 to 12.50%. Observations made from the combined pedigrees include: 1) males and females were equally affected, 2) affected dogs were mostly born to healthy parents, and 3) breedings between an affected and an unaffected dog resulted in a mix of affected and unaffected offspring in the same litter. The small number of pedigrees made available and the lack of health information on ancestors and littermates did not allow for segregation analysis and heritability calculations using standard methods.^{14,29}

Discussion

The process of cornification is complex and involves coordination of a number of different biochemical processes that lead to the final product: a fully differentiated anucleate keratinocyte (corneocyte) that is sandwiched between layers of lipid and is eventually shed into the environment. This “bricks” and “mortar” arrangement (bricks represent corneocytes, and mortar is analogous to the intercorneocyte lipids) creates a structural barrier for the skin, preventing transepidermal water loss and the entry of pathogens or xenobiotics.²² The process of cornification involves a form of programmed cell death called terminal differentiation with simultaneous nuclear degradation, creation of a strong cornified envelope to replace the cell membrane (mediated by transglutaminases), and formation of an inner protein core by aggregating keratin tonofilaments (mediated by filaggrin—“filament aggregating protein”). Much of the lipid in the stratum corneum is supplied by liposome-like structures, lamellar granules that are formed in the upper stratum spinosum and released

into the intercellular space at the stratum corneum junction.⁹ Ichthyosis results from either increased stratum corneum production or decreased corneocyte desquamation (retention hyperkeratosis).¹⁵

To date, relatively few ichthyosiform disorders have been documented in dogs, and most are reported as single cases.^{5-8,11-12,18,21,26-28} The Golden Retrievers presented herein have histopathologic, ultrastructural, and clinical changes that warrant classification as a primary disorder of cornification and specifically ichthyosis. Although the general term *seborrhea* can describe scaling disorders, it is nonspecific, and the histologic changes here are very different from those of seborrheic dermatitis, as occurs in several breeds.³¹

The wide age distribution reflects the subtle nature of the phenotype. Determining an exact age of onset is difficult, as mild scaling could have been easily overlooked. Twelve cases were well-documented at 1 year of age or less, and many when the puppies were only a few weeks to months of age. Hereditary ichthyosis is often present at birth, but it is not uncommon for signs to develop later in adulthood. The most common ichthyosis in humans, ichthyosis vulgaris, may be precipitated by changes in the environment and allergen exposure. Some patients appear clinically normal until moving to a dry, cold climate.¹⁶ It is reasonable to hypothesize that other factors (environment, concurrent disease states, etc.) lower the stratum corneum's ability to compensate and trigger the appearance or exacerbation of clinical lesions.

Ichthyosiform disorders are difficult to classify, but the most straightforward way to view them is as epidermolytic or nonepidermolytic forms based on light microscopic examination. Epidermolytic ichthyosis (epidermolytic hyperkeratosis) has histopathologic features of suprabasal keratinocyte vacuolation with hyperkeratosis that are uniquely correlated to mutations in epidermal keratins.¹⁶ This disorder has been identified in dogs and well-characterized in a family of Norfolk Terriers.^{8,11,27} The histopathologic changes seen in the Golden Retriever are nonepidermolytic; thus, it is unlikely that a mutation in epidermal keratins is the etiology.

The light microscopic features of the non-epidermolytic ichthyoses (e.g., congenital ichthyosiform erythroderma, lamellar ichthyosis, ichthyosis vulgaris) are overlapping, and clear distinction is often difficult by histopathology alone.¹ The disorders are characterized by clinical onset, inheritance, type of scale, and distribution in combination with ultrastructural and molecular analysis.¹⁶ Another recently described form of

nonepidermolytic ichthyosis in dogs occurs in Jack Russell terriers.^{12,20,26} This disease has a much more severe phenotype than that of the Golden Retrievers, with large, thick, adherent parchment paper-like scales and corresponding marked, tightly laminated, orthokeratotic hyperkeratosis.

In humans, some forms of nonepidermolytic ichthyosis have been related to mutations in the gene encoding for transglutaminase 1 (TGM1), with a resulting deficiency of this enzyme.^{1,15,16} A detergent method that is used to aid in the diagnosis of TGM1 deficient ichthyosis in humans was applied to the scale from 1 affected dog. Corneocytes with a defective cross-linking of the CE should not withstand the detergent, whereas a corneocyte with a normal CE should be resistant.²³ No changes were seen between dogs with normal corneocytes and the affected dog; however, a positive canine control was not available. Because canine microsatellite markers near canine TGM1 are available, as is the coding sequence, molecular biology studies could potentially rule out defects in TGM1 as a cause of the disease in Golden Retrievers.¹³

Ultrastructural analysis may reveal specific structural abnormalities diagnostic of some heritable ichthyoses and blistering genodermatoses. For example, ichthyosis vulgaris is characterized by few intact or complete absence of keratohyalin granules in the granular layer, which is correlated with loss of profilaggrin or filaggrin.^{4,19} The stratum corneum of the Golden Retrievers contained a marked amount of retained membranous material. Similar material has been noted by some of the authors (EAM, RWD, and KMC) in normal dogs, albeit not to the degree of that in the Golden Retrievers. Retained and convoluted membranes also have been reported in a Jack Russell Terrier with ichthyosis,¹² and they may represent a common but nonspecific finding in nonepidermolytic ichthyosis. The cornified envelopes appeared within normal limits. The intercorneocyte lipid layer was difficult to evaluate, despite ruthenium fixative, a technique used to optimize lipid lamellae assessment.¹⁷ Repeat analysis should be performed in the future. The scattered, single vacuoles seen on light microscopy in spinous and granular keratinocytes were initially assumed to be artifactual, but these vacuoles contained clear spaces which appeared at least partially membrane bound. The origin or significance of this change is unclear.

The pedigree analysis suggested an autosomal recessive trait, as males and females were equally affected, and 11 of the 15 dogs with pedigrees were siblings with normal parents confirmed by the

examining veterinarian and an experienced breeder. However, the analysis should be viewed in light of the variable age expression and difficulty in confirming the status of "normal" in siblings or parents of affected dogs. Because the age of onset is variable, it is difficult to confirm that all parents of affected dogs were normal or confirm that these dogs will not develop ichthyosis in the future. Therefore, an incomplete dominant mode of inheritance cannot be ruled out. Further studies examining the mode of inheritance are underway. A better understanding of the inheritance may allow selective breeding to reduce the incidence of the disorder.

Golden Retriever ichthyosis is not a rare diagnosis in one author's (EAM) dermatopathology diagnostic service (~1% of submissions), and it is likely that mild cases go undetected or simply ignored. The diagnosis of Golden Retriever ichthyosis is based on typical clinical features of loose truncal scale, breed, and characteristic histopathologic changes of laminated orthokeratotic hyperkeratosis with minimal epidermal hyperplasia. Although mild, the disorder may predispose to pyoderma, can be aesthetically displeasing for the pet owner, and will be a lifelong condition. Treatment involves topical therapy with emollients and moisturizers as needed. In an older dog, the scaling may resemble the exfoliative form of cutaneous lymphoma, although Golden Retriever ichthyosis lacks the erythema and has softer scales.³² Pruritus is not a feature of Golden Retriever ichthyosis unless secondary pyoderma or allergic skin disease develops.

Based on morphologic changes, Golden Retriever ichthyosis is unlikely to be due to mutation in TGM1, epidermal keratins, or filaggrin. Further assessment should be performed to evaluate role of lipid ratios, lipid content, or transporter proteins of the stratum corneum. Some forms of lamellar ichthyosis are related to abnormalities in lipid-carrier proteins.²⁵

Acknowledgements

This study was supported by a departmental research grant from the University of Pennsylvania, School of Veterinary Medicine, Department of Clinical Studies, and by a grant from the National Institutes of Health (RR02512).

References

- 1 Akiyama M, Sawamura D, Shimizu H: The clinical spectrum of nonbullous congenital ichthyosiform erythroderma and lamellar ichthyosis. *Clin Exp Dermatol* **28**:235–240, 2003
- 2 Alhaidari Z, Ortonne JP, Pisani A: Congenital ichthyosis in two cavalier King Charles spaniel littermates. *Vet Derm* **5**:117–121, 1994
- 3 Allen E, Yu QC, Fuchs E: Mice expressing a mutant desmosomal cadherin exhibit abnormalities in desmosomes, proliferation, and epidermal differentiation. *J Cell Biol* **133**:1367–1382, 1996
- 4 Anton-Lamprecht I: Ultrastructural identification of basic abnormalities as clues to genetic disorders of the epidermis. *J Invest Dermatol* **103**:6S–12S, 1994
- 5 August JR, Chickering WR, Rikihisa R: Congenital ichthyosis in a dog: comparison with the human ichthyosiform dermatoses. *Comp Cont Ed Prac Vet* **10**:40–45, 1988
- 6 Baker JR, Ward WR: Ichthyosis in domestic animals: a review of the literature and a case report. *Br Vet J* **141**:1–8, 1985
- 7 Barnett KC: Congenital keratoconjunctivitis sicca and ichthyosiform dermatosis in the cavalier King Charles spaniel. *J Small Anim Prac* **47**:524–528, 2006
- 8 Barnhart KF, Credille KM, Ambrus A, Dunstan RW: A heritable keratinization defect of the superficial epidermis in Norfolk terriers. *J Comp Pathol* **130**:246–254, 2004
- 9 Casal ML, Jezyk JM, Greek JM, Goldschmidt MH, Patterson DF: X-linked ectodermal dysplasia in the dog. *J Hered* **88**:513–517, 1997
- 10 Chu DH, Haake AR, Holbrook K, Loomis CA: The structure and development of the skin. In: Fitzpatrick's Dermatology in General Medicine, ed. Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz SI, 6th ed., pp. 58–88. McGraw-Hill, New York, 2003
- 11 Credille KM, Barnhart KF, Minor JS, Dunstan RW: Mild recessive epidermolytic hyperkeratosis with a novel keratin 10 donor splice-site mutation in a family of Norfolk terrier dogs. *Br J Dermatol* **153**:51–58, 2005
- 12 Credille KM, Peterson AD, Song MD, Dunstan RW: Heterogeneity in nonepidermolytic ichthyosis in a cat and two dogs. In: Advances in Veterinary Dermatology, ed. Kwochka KW, Willemse T, von Tscharner C, vol 3, pp. 925–927. WB Saunders, Philadelphia, PA, 1998
- 13 Credille KM, Venta PJ, Breen M, Lowe JK, Murphy KE, Ostrander EA, Galibert F, Dunstan RW: DNA sequence and physical mapping of the canine transglutaminase 1 gene. *Cytogenet Cell Genet* **93**:73–76, 2001
- 14 Davie AM: The 'singles' method for segregation analysis under incomplete ascertainment. *Ann Hum Genet* **42**:507–512, 1979
- 15 DiGiovanna JJ: Ichthyosiform disorders. In: Fitzpatrick's Dermatology in General Medicine, ed. Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz SI, 6th ed., pp. 481–505. McGraw-Hill, New York, 2003
- 16 DiGiovanna JJ, Robinson-Bostom L: Ichthyosis: etiology, diagnosis, and management. *Am J Clin Dermatol* **4**:81–95, 2003
- 17 Elias PM, Cullander C, Mauro T, Rassner U, Komuves L, Brown BE, Mennon GK: The secretory granular cell: the outermost granular cell as a

- specialized secretory cell. *J Invest Dermatol Symp Proc* **3**:87–100, 1998
- 18 Helman RG, Rames DS, Chester DK: Ichthyosis-form dermatosis in a soft-coated Wheaten terrier. *Vet Derm* **8**:53–58, 1997
- 19 Getling ZN, Kuklin VT: Ultrastructural changes in the epidermis in ichthyosis vulgaris. *Vestn Dermatol Venerol* **6**:17–20, 1989
- 20 Gross TL, Ihrke PJ, Walder EJ, Affolter VK: Diseases with abnormal cornification. In: *Skin Diseases of the Dog and Cat*, 2nd ed., pp. 174–179. Blackwell Science, Ames, IA, 2005
- 21 Hall JA, Yager J: Diagnostic dermatology. *Can Vet J* **45**:872–873, 2004
- 22 Jackson SM, Elias PM: Skin as an organ of protection. In: *Fitzpatrick's Dermatology in General Medicine*, ed. Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz SI, 6th ed., pp. 107–118. McGraw-Hill, New York, 2003
- 23 Jeon S, Djian P, Green H: Inability of keratinocytes lacking their specific transglutaminase to form cross-linked envelopes: absence of envelopes as a simple diagnostic test for lamellar ichthyosis. *Proc Natl Acad Sci U S A* **95**:687–690, 1998
- 24 Kobinger GP, Weiner DJ, Yu QC, Wilson JM: Filovirus-pseudotyped lentiviral vector can efficiently and stably transduce airway epithelia in vivo. *Nature (Biotechnol)* **19**:225–230, 2001
- 25 Lefevre C, Audebert S, Jobard F, Bouadjar B, Lakhdar H, Boughdene-Stambouli O, Blanchet-Bardon C, Heilig R, Foglio M, Weissenbach J, Lathrop M, Prud'homme JF, Fischer J: Mutations in the transporter ABCA12 are associated with lamellar ichthyosis type 2. *Hum Mol Genet* **12**: 2369–2378, 2003
- 26 Lewis DT, Ford MJ, Kwochka KW: Characterization and management of a Jack Russell terrier with congenital ichthyosis. *Vet Derm* **9**:111–118, 1998
- 27 Mecklenburg L, Hetzel U, Ueberschär S: Epidermolytic ichthyosis in a dog: clinical, histopathological, immunohistochemical and ultrastructural findings. *J Comp Pathol* **122**:307–311, 2000
- 28 Muller GH: Ichthyosis in two dogs. *J Am Vet Med Assoc* **169**:1313–1316, 1976
- 29 Nicholas FW: Is it inherited? *Veterinary Genetics*, pp. 217–231. Clarendon Press, Oxford, UK, 1987
- 30 Scott DW, Miller WH, Griffin CE: Congenital and hereditary defects. In: *Muller and Kirk's Small Animal Dermatology*, 6th ed., pp. 922–925. WB Saunders, Philadelphia, PA, 2001
- 31 Scott DW, Miller WH, Griffin CE: Keratinization defects. In: *Muller and Kirk's Small Animal Dermatology*, 6th ed., pp. 1022–1054. WB Saunders, Philadelphia, PA, 2001
- 32 Scott DW, Miller WH, Griffin CE: Neoplastic and non-neoplastic tumors. In: *Muller and Kirk's Small Animal Dermatology*, 6th ed., pp. 1330–1342. WB Saunders, Philadelphia, PA, 2001
- 33 Scott DW, Miller WH, Griffin CE: Structure and function of the skin. In: *Muller and Kirk's Small Animal Dermatology*, 6th ed., pp. 26–27. WB Saunders, Philadelphia, PA, 2001

Request reprints from E. A. Mauldin, University of Pennsylvania, School of Veterinary Medicine, Laboratory of Pathology and Toxicology, 3800 Spruce Street, Philadelphia, PA 19104-6051 (USA). E-mail: emauldin@vet.upenn.edu.