Canine recurrent flank alopecia: a synthesis of theory and practice

Caniene recurrente flankalopecia: synthese van theorie en praktijk

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ABSTRACT

Canine recurrent flank alopecia is a non-inflammatory, non-scarring alopecia of unknown etiology and has a visually striking clinical presentation. Although this disease entity is relatively common in the northern hemisphere, there is only scant information in the literature regarding case descriptions. The aim of this article was to review the literature and to describe clinical presentations recognized in practice, which are not always extensively documented in the literature.

SAMENVATTING

Caniene recurrente flankalopecia wordt klassiek gekenmerkt door een niet-inflammatoire alopecia met onbekende etiologie. Deze dermatose wordt getypeerd door unieke huidsymptomen. Alhoewel de aandoening relatief frequent voorkomt in het noordelijk halfrond en dus ook in België, is er slechts beperkte informatie over te vinden in de literatuur. Het doel van dit overzichtsartikel is om enerzijds een samenvatting te geven van de literatuur en anderzijds de verschillende klinische presentaties die herkend worden in de dagelijkse praktijk maar niet vaak beschreven worden in de literatuur, te documenteren.

INTRODUCTION

Canine recurrent flank alopecia (CRFA) is a visually striking disease characterized by cyclic episodes of non-inflammatory hair loss (or coat changes) that can recur annually (Miller et al., 2013a). Several names have been proposed for this unique canine alopecic disease (canine flank alopecia, seasonal flank alopecia, idiopathic cyclic flank alopecia, cyclic follicular dysplasia) but none of the names fit perfectly: visually complete hair loss is not always seen, alopecia is not always confined to the flank area, and some dogs only experience one episode throughout their entire lives (Paradis, 2009). This intriguing disease was first reported in 1990 by Danny Scott (Scott, 1990). He described a clinically distinct form of waxing and waning non-scarring alopecia in five ovariohysterectomized dogs. Later, it became evident that dogs of either sex and reproductive status could be affected. Although the disease is well-recognized in practice, it remains poorly documented in the veterinary literature. The aim of this article is to make a synthesis of the current knowledge from the literature and the different clinical presentations that are recognized in practice, but which are not extensively mentioned in the literature.

ETIOLOGY AND PATHOGENESIS

The exact etiology of CRFA remains unknown. Studies evaluating thyroid function, reproductive hormones and growth hormones in affected dogs have not revealed abnormalities (Curtis et al., 1996; Daminet and Paradis, 2000). However, a localized change in the amount or sensitivity of the hair follicle receptors cannot be excluded (Miller et al., 2013a).

Because the disease is more prevalent in certain breeds, such as Boxers, Airedales, Schnauzers, English bulldogs, Affenpinschers, Griffon Korthals and Bearded collies, a genetic predisposition is suspected (Paradis, 2009; Waldman, 1995; Fontaine et al., 1998). Duration of daylight exposure or changes in light exposure appear to play a role in the development of the lesions. Several observations support the role of light in the pathogenesis of this disease. Firstly,

there is the seasonal nature and often annual recurrence of the disease. Interestingly, the onset of CRFA in the northern hemisphere is the reverse of what is seen in Australia and New Zealand, which means that in both hemispheres, the onset of alopecia coincides with the months with a shorter duration of daylight (Miller et al., 2013a; Paradis, 2012, Basset et al., 2005). Secondly, some cases that have been reported in the literature describe the development of lesions in dogs that were kept in abnormal light conditions; one dog in the northern hemisphere developed lesions in the summer when kept in a dark room (Waldman, 1995; Ando and Nagata, 2000). Light therapy has anecdotally been tried with success as a preventive therapy. In another study, dogs exposed to 100-200 Watt during 15 to 16 hours from September till April did not develop alopecia (Paradis, 1998).

There are two important photo-dependent hormones in the body: melatonin and prolactin. Melatonin is primarily synthesized in the pineal gland and acts at the level of the pars tuberalis of the pituitary. Its production is proportional to the length of the dark period. Decreased retinal daylight exposure results in increased melatonin production. Melatonin is important for reproduction, thermoregulation, coat color and hair cycling (Paradis, 2000; Stankov et al., 1994). It is known to be involved in the moulting of several mammalian species. Melatonin implants have been used in foxes and minks to manipulate seasonal coat changes (Valtonen et al., 1995; Rose et al., 1984).

Because of the familial incidence, the association with light exposure and the positive effects of melatonin supplementation, a decreased endogenous melatonin production in genetically predisposed animals is suggested to play a role in the pathogenesis of this disease (Paradis, 1995). Melatonin may act directly on the hair follicle or indirectly through modulation of melatonin stimulating hormone (MSH) and/or prolactin (Paradis, 1995; Fischer et al., 2008). Prolactin levels are known to inversely correlate with melatonin levels (Messenger, 1993). The increase of melatonin levels and subsequent decrease in prolactin levels induce the formation of a winter coat in sheep (Paradis, 2000; Nixon et al., 2002). Hair follicle cycling is governed by seasonal changes to produce a summer and winter moult, and the other photo-dependent hormone, prolactin, has been implicated as a principal regulator of this process (Messenger, 1993). Prolactin is synthesized in the pineal gland. It has been shown to inhibit growth of anagen follicles in mice and sheep (Nixon et al., 2002; Craven et al., 2006). It is believed to have inhibitory effects at different stages of the hair follicle cycle with the ability to reduce hair length, shorten anagen, induce shedding or lengthen the telogen phase (Nixon et al., 2006; Craven et al., 2006; Thompson et al., 1997). Prolactin may thus very well be an important player in CRFA but no studies have been done to assess its potential role.

CLINICAL PRESENTATION

The age of onset has a wide range: from one year of age to eleven years, with most cases developing clinical signs for the first time between three and six years of age (Miller et al., 2013a; Paradis, 2009; Paradis, 2012). Numerous breeds can be affected, but there seems to be a breed predilection in the Boxer, English bulldog, Airedale, Griffon Korthals, Affenpinscher, Labrador retriever, Golden retriever, Bouvier des Flandres, Dobermann and Schnauzer (Miller et al., 2013a; Paradis, 2009; Waldman, 1995; Fontaine et al., 1998; Cerundolo; 1999). Dogs of either sex and reproductive status can be affected. In practice, the typical clinical presentation of CRFA is a bilateral symmetrical, geographic-shaped, non-scarring and non-inflammatory alopecia in the thoracolumbar area. It is further characterized by a rapid onset of

Figure 1. Classical presentation of canine recurrent flank alopecia. A four-year-old Rhodesian ridgeback with bilateral symmetrical, geographic shaped alopecia on the thoracolumbar area and marked lesional hyperpigmentation.

Figure 2. Facial presentation with complete alopecia of the dorsal muzzle in a Golden retriever.

alopecia between the months of November and April in the northern hemisphere. The actual month of onset does not appear to be related to breed, age, sex or reproductive status (Miller et al., 2013a; Paradis, 2012). Hair regrowth can rarely take up to 18 months and permanent alopecia can be seen in chronic recurrent patients. Often, the area of alopecia remains visually recognizable, because regrown hair has a slightly different texture and/or color (Miller et al., 2013a; Paradis, 2012). Hyperpigmentation in the alopecic area may be striking but is not always present. The presence or absence of hyperpigmentation in response to light exposure depends on the breed and within certain breeds depends on the individual pigmentation profile of the dog. In some breeds and some individuals, hypermelanization of the skin resulting from endogenous production of factors that stimulate the melanocytes has never been noticed. Breed related lack of hyperpigmentation is usually seen in the Wirehaired pointer, Dalmatian, Dobermann, Vizsla and Weimaraner (Paradis, 2009; Declercq, 2008).

The classical distribution of the lesions is the lateral to dorsolateral thorax and lumbar region. Lesions consist of well-circumscribed patches of alopecia exhibiting a geographic and irregular pattern (Figure 1). The alopecic area ranges in size from 2 cm to almost the entire thoracolumbar area. Lesions most commonly are bilateral symmetrical, but one side is commonly more affected then the other. Unilateral lesions have been recognized. At the time of onset, there is lesional increased epilation (Miller et al., 2013a).

Several atypical presentations (facial presentation, generalized presentation, flank alopecia without an episode of visual flank alopecia and flank alopecia with interface dermatitis) have been recognized in practice (Declercq, 2008; Vandenabeele, 2007; Vandenabeele, 2014). They are called atypical because the distribution of the alopecia is not confined to or absent in the thoracolumbar area, or because instead of alopecia, there is only a discoloration and texture change of the coat. The factors that unify all of these cases are the often recurrent nature of the rapid onset of the non-pruritic lesions between November and April (except for the dogs with discoloration of the coat, where coat color changes and texture changes are seen later in the year and have an onset between April and September) and the spontaneous hair regrowth (Declercq, 2008; Cerundolo and Rest, 2013).

Facial presentation

In these patients, alopecia of the dorsal muzzle and sometimes associated mild alopecia in the periocular region are seen (Figure 2). This is most commonly noticed in the Golden retriever and Labrador retriever (Declercq, 2008; Cerundolo and Rest, 2013; Vandenabeele, 2007).

A visually more striking variation of this presentation is seen in the Bordeaux dog. These dogs present with alopecia and hyperpigmentation of the dorsal muzzle and facial folds. The affected dogs have no alopecia in the thoracolumbar area. The authors of the present study have also seen a Cane corso with this presentation, where the dog had three episodes of alopecia on the facial folds in three consecutive years (Figure 3). The alopecia started in April and hair regrowth was seen in July (Vandenabeele, 2014).

Figure 3. Facial presentation with alopecia and hyperpigmentation of the dorsal muzzle and facial folds in a Cane Corso (Picture courtesy of Ilona Schwarzkopf).

Generalized form

In these dogs, alopecia is present in the thoracolumbar area and other regions, such as the dorsal muzzle, periocular regions, base of the ears, perineum and base of the tail (Miller et al., 2013a; Declercq, 2008; Cerundolo and Rest, 2013) (Figure 4). This multifocal non-scarring alopecic form has been described in some Airedales, Golden retrievers, Griffon Korthals, Dobermanns, Wirehaired pointers and Giant Schnauzers (Paradis, 2009). Spontaneous regrowth is seen simultaneously in all of the affected areas.

Flank alopecia without an episode of visual alopecia

Coat color changes and/or changes in texture of the coat are seen in the flank and thoracolumbar area, without a visual episode of alopecia. These coat color changes are irregular in distribution and may have a geographic pattern. In the literature, aurotrichia has been described in Schnauzers without preceding alopecia (White et al., 1992). Interestingly, in the study

Figure 4. Generalized presentation of canine recurrent flank alopecia in a Wirehaired pointer. Note alopecia of the pinnae, flanks and distal extremities.

by White et al. (1992), the onset of the discoloration of the coat from silver or black hairs turning into a gold colored coat occurred during the months of April till September. This is later than what has been observed in the other forms of flank alopecia. One of the Schnauzers had two consecutive episodes of aurotrichia (White et al., 1992). Idiopathic aurotrichia has also been described in a Bichon frisé (month of onset not reported) (Miller et al., 2013b). The authors of the present study have seen recurrent aurotrichia in a Poodle, Lhasa apso, Cocker and Yorkshire terrier during the months of April till September (Figure 5). It is currently unknown why the coat color change of these dogs occurs at that time of the year. Possibly, the changes in the hair coat represent the recovery phase of the disease and are actually new grown hairs.

Flank alopecia in non-related dogs in the same household has been anecdotally noted. The case description of the flank alopecia in the Affenpinschers of Waldman (1995) mentions that multiple Affenpinschers developed flank alopecia in the winter, when kept in the conservatory, where there was no artificial heating or lighting. The authors of the present study have seen "an outbreak" of flank alopecia in a breeding facility where multiple Bichon frisé dogs developed alopecia at the same time. No more recurrences were seen when the day-night cycle was adjusted in the breeding facility. Another example which was observed by the authors of the present study is a household with three non-related English Staffordshire terriers where the three dogs develop flank alopecia simultaneously every year between December and February.

Flank alopecia with interface dermatitis

This entity was first described in 2003 by Rachid in Boxers and is characterized by a combination of flank alopecia and interface dermatitis/folliculitis (Rachid et al., 2003; Mauldin, 2005). In Europe, this presentation of flank alopecia has been reported by Van der Luer in an English bulldog (Van der Luer and Bonestroo, 2010). Also, the authors of the present study have seen this presentation in an English bulldog. The distribution of the lesions is very similar to the classical presentation of flank alopecia, with lesions confined to the thoracolumbar area. The difference is the concurrent presence of non-painful and non-pruritic multifocal circular scaly and crusted depigmented plaques within the alopecic area (Figure 6). The alopecia and the interface dermatitis demonstrate concurrent courses of remission and recurrence in these patients. The relationship between the two types of lesions is not known (Rachid et al., 2003; Mauldin, 2005). The possibility of a superimposed erythema ab igne (chronic radiant heat dermatitis) on CRFA lesions in some of those cases has been sug-

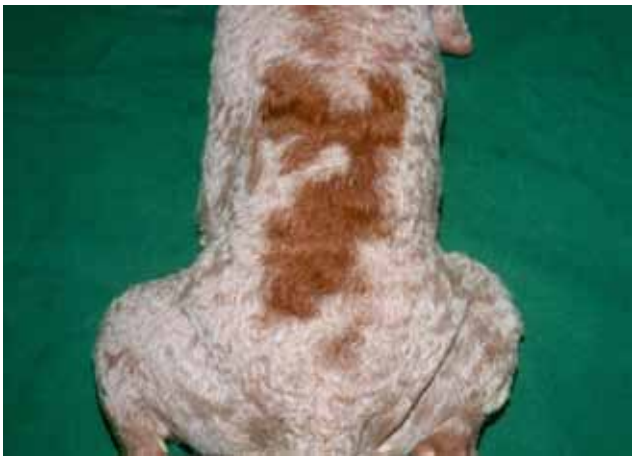

Figure 5. Presentation of canine recurrent flank alopecia without noticeable alopecia. Note the difference in coat color in an irregular pattern in the thoracolumbar area in this Poodle.

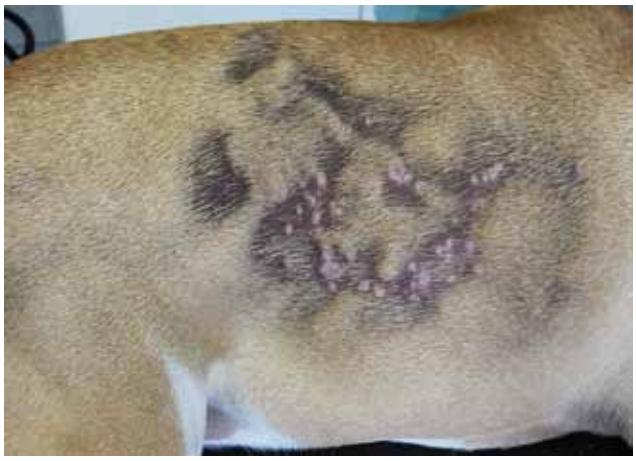

Figure 6. Flank alopecia with interface dermatitis in a 3-year-old English bulldog. Note the thoracolumbar distribution of the lesions with the presence of crusted depigmented plaques within the alopecic area (Picture courtesy of Anja Bonte).

gested (Paradis, 2009). However, the hypopigmentation bordered by the hyperpigmentation is unique to erythema ab igne (Declercq and Vanstapel, 1998). Moreover, histopathological changes typical of erythema ab igne, such as keratinocyte atypia and karyomegaly and a variable number of wavy eosinophilic elastic fibres ("red spaghetti"), are not seen in CRFA with interface dermatitis (Declercq and Vanstapel, 1998; Walder and Hargis, 2002; Rachid et al., 2003; Mauldin, 2005).

DIAGNOSIS

If a dog is presented with a history of annual recurring alopecia presenting with the typical lesions from November to April and spontaneous regrowth is evident, the diagnosis of CRFA can be made based on the history and striking clinical findings (Miller et al., 2013a; Paradis, 2012).

If a dog is presented for a first episode of CRFA with the typical clinical presentation endocrinopathies, such as hypothyroidism, breed specific hair cycle abnormalities, color dilution alopecia, post-shaving arrest, erythema ab igne (chronic radiant heat dermatitis), glucocorticoid injection reaction and post-rabies vaccination panniculitis need to be ruled out (Declercq, 2008).

It is of interest that certain breeds that are predisposed for CRFA, such as the Boxer, Airedale and German pointers, are also predisposed for hypothyroidism (Dixon et al., 1999; Paradis, 2009). Hypothyroidism usually presents as a slowly progressive alopecia, as opposed to the rapid onset of alopecia in CRFA. Usually, other coat changes are present in hypothyroid dogs such as a scaly or dull and brittle hair coat. Concurrent pyoderma and otitis are an occasional complaint in hypothyroid dogs (Paradis, 2009). Slow hair regrowth in clipped areas and a rat tail are other clinical findings suggestive of hypothyroidism. In CRFA, the quality and quantity of the coat in the non-lesional skin are normal. Another difference is that metabolic signs (weight gain, lethargy) are generally seen with hypothyroidism, but not in dogs with CRFA (Paradis, 2009).

Color dilution alopecia causes an initially dorsally oriented, slowly progressive diffuse, partial alopecia. A variable degree of alopecia can also be noted on the head and rarely, the extremities. Various breeds such as Dobermann, Chihuahua, Italian Greyhound, Yorkshire terrier, Whippet are predisposed for color dilution alopecia. It is associated with diluted colors of brown and black. These coat colors are referred to as blue, gray, fawn and red (Laukner, 1998). Affected dogs present with clinical signs before the age of 1 year and rarely later in life (Laukner, 1998).

There is a variety of breed-specific alopecic diseases in dogs that have erroneously been classified as follicular dysplasia. Because these forms of alopecia are not developmental abnormalities and do not represent one specific disease, it has been decided that hair cycle abnormalities would be a better denomination for this form of alopecia (Cerundolo et al., 2009). These hair cycle abnormalities have a true breed predisposition and have been reported in the Portuguese water dogs, Chesapeake Bay retriever, Curly Coated retriever and Irish water spaniels (Cerundolo et al., 2009; Laffort-Dassot et al., 2002; Cerundolo et al., 2005). The alopecia in these breeds can wax and wane, but there is no seasonal influence and the hair regrowth is never complete in these breeds. The caudal thighs and ventral neck are often involved and these are areas that are not affected in dogs with CRFA. Moreover, these dogs do not respond to melatonin treatment (Cerundolo et al., 2009; Cerundolo et al., 2005).

In post-clipping alopecia, there is a lack of regrowth at the site of previous clipping (Miller et al., 2013c).

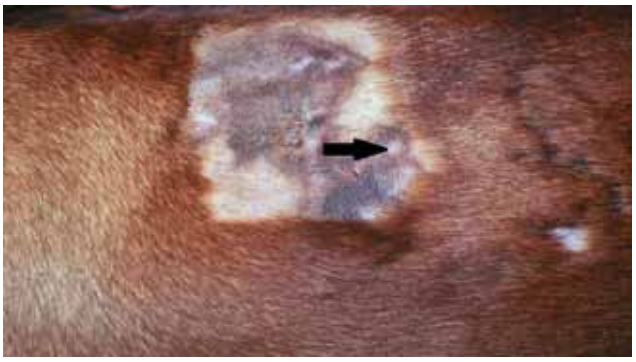

Figure 7. Clinical presentation of erythema ab igne. Note the alopecia with erythema and hypopigmentation bordered by hyperpigmentation (arrow) on the flank of this mixed breed dog subjected to a heat lamp post whelping.

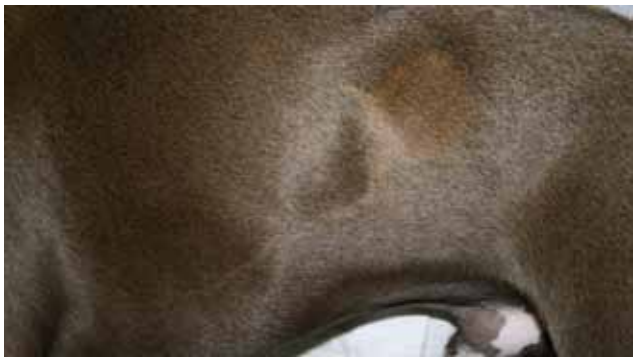

Figure 8. Focal discoloration of the coat with concurrent atrophy of the skin in a Weimaraner caused by a glucocorticosteroid injection.

Especially, if the dog was clipped in the thoracolumbar or dorsal area (as might be seen with epidural anesthesia), clinical resemblance with CRFA is possible. This disease usually effects Nordic breeds such as the Siberian husky, Alaskan malamute, Samoyed, Pomeranians and Chow Chows without age or sex predilection (Miller et al., 2013c; Gross et al., 2005a). It has been proposed that in those breeds, hair regrowth might take a lot longer because of a prolonged telogen phase that possibly developed to save energy in those cold climates. In this case, the prolonged telogen phase is responsible for the post-clipping alopecia (Credille, 2000). These breeds are not predisposed for CRFA, but post-clipping alopecia can be seen in other breeds too. Post-clipping alopecia is diagnosed by the signalment, the history of previous clipping and clinical presentation (Miller et al., 2013c; Gross et al., 2005a). Endocrinopathies, such as hypothyroidism, hyperadrenocorticism and alopecia X should be ruled out.

If a dog presents with unilateral alopecia in the thoracolumbar or dorsolumbar area, erythema ab igne and injection reactions need to be ruled out.

Erythema ab igne is a typically unilateral dermatosis that occurs at the site of repeated exposure to moderate heat. Lesions are commonly seen at the dorsolateral thoracic region and consist of irregular branching areas of alopecia with erythema and hypopigmentation bordered by hyperpigmentation (Miller et al., 2013d; Gross et al., 2005b; Walder and Hargis, 2002; Declercq and Vanstapel, 1998) (Figure 7). The distribution of the lesions and the irregular alopecia are similar to CRFA, especially flank alopecia with interface dermatitis. The hypopigmentation bordered by the hyperpigmentation is unique to erythema ab igne (Declercq and Vanstapel, 1998). Histopathological changes consist of keratinocyte atypia and karyomegaly, scattered apoptotic or vacuolated basal cells with an interface dermatitis, adnexal atrophy and a variable number of waxy eosinophilic elastic fibres ("red spaghetti") (Gross et al., 2005b). Erythema ab igne is diagnosed by a history of chronic access to heat sources, such as a heating pad, electric blanket, burning stove or heat lamp, with typical clinical signs and typical dermatopathological changes (Miller et al., 2013d; Gross et al., 2005b; Walder and Hargis, 2002; Declercq and Vanstapel, 1998). It is of interest to note that glucocorticosteroid injections also can cause either alopecia or changes in coat color and coat texture (Declercq, 2008; Miller et al., 2013e) (Figure 8). The alopecia is focal and often there is a concurrent atrophy of the skin with slight scaling. Mineralized injected material in the deep dermis can be seen or palpated; moreover, the underlying musculature can be atrophic in severe cases (Miller et al., 2013e). Another type of injection reaction, post-rabies vaccination panniculitis can be seen at the site of rabies vaccine deposition and is considered to be one of the vasculopathic syndromes under the group of ischemic dermatopathy (Gross et al., 2005c). Typically, the lesion is noted two to three months post vaccination. The lesion consists of a focal alopecia with minimal inflammation. The alopecic area may vary in size, and erythema is minimal or absent. Lesional hyperpigmentation can be seen (Miller et al., 2013e). Injection reactions can be diagnosed by history, clinical presentation and histopathology (Miller et al., 2013e; Gross et al., 2005b).

If a client does not want to wait for spontaneous regrowth, a biopsy and histopathological examination are warranted. In active lesions, the fairly typical histopathological changes consist of infundibular hyperkeratosis extending to secondary follicles and sometimes even into the sebaceous gland ducts (Figure 9). The hair follicles demonstrate an atrophic base and may be malformed. These fore-mentioned changes create a specific dysplastic appearance of the hair follicles resembling a malformed foot, hence called "witch's feet" or "octopus-like hair follicles" (Gross et al., 2005d). The size of the adnexae is normal, but sebaceous glands may be melanized. Melanin aggregates may also be present in the follicular lumen (Bagladi et al., 1996; Miller and Dunstan, 1993). The timing of the biopsies greatly influences the histopathological changes (Gross et al., 2005d; Paradis, 2009). When patients are biopsied early in the disease

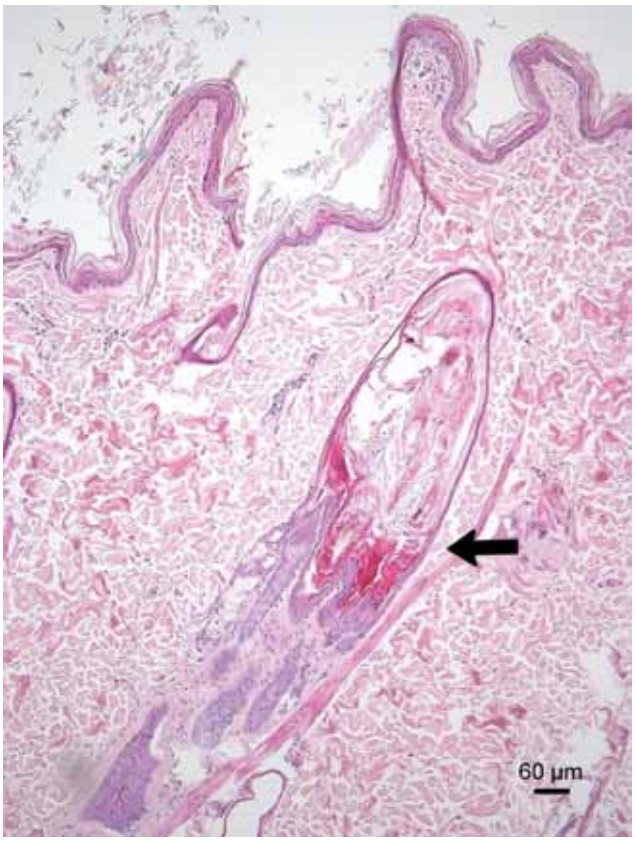

Figure 9. Photomicrograph. Hematoxylin and eosin stain. Note infundibular hyperkeratosis extending into the secondary follicles, creating the shape of a witches' foot (arrow).

process, most follicles are in the telogen or catagen phase. However, more often, patients are biopsied when the alopecia has been present for several months and is in the regression phase. If biopsied then, the follicles will often already be in anagen phase, and the infundibular orthokeratotic hyperkeratosis might not be prominently present (Fontaine et al., 1998). This is similar to what can be seen when the disease presents with just coat discoloration. In those cases, follicular hyperkeratosis and anagen follicles can be seen. The described follicular changes are suggestive but not pathognomonic for CRFA (Gross et al., 2005d; Paradis, 2009). Dysplastic hair follicles and abnormal melanin aggregation occur in both follicular dysplastic diseases and endocrine skin diseases (Rothstein et al., 1998).

CLINICAL MANAGEMENT

Dogs with this disease are otherwise healthy, and the disease should be considered as a cosmetic disease. As spontaneous hair regrowth does occur (albeit potentially incomplete with recurrent episodes), benign neglect can be a valid treatment option (Miller et al., 2013a; Paradis, 2009).

Because of a variable timing of the spontaneous regrowth and the unpredictable course of the alopecic periods, evaluation of treatment, either curative or as a preventive measure is very difficult to assess objectively.

Melatonin is considered the initial treatment of choice, if treatment is requested (Miller et al., 2013a). The optimal dose, best route of administration and the duration of treatment and best time of initiation of treatment are currently unknown, as placebo-controlled studies have not yet been published. A success rate of 50-75% has been reported based on anecdotal information (Paradis, 2009). Melatonin implants at 12mg/dog have been successfully used as a preventative treatment in dogs with recurrent episodes of CRFA (Paradis, 2000). Oral melatonin can be administered at a dose of 3 to 6 mg per dog twice to three times daily during 4 to 6 weeks (Paradis, 2000). This duration of treatment is based on a study in mink showing that melatonin induces the anagen hair cycle within a 4- to 6-week period (Paradis, 2000). However, once the hair cycle is restarted, melatonin is no longer necessary for continuous growth and maturation of the pelage (Valtonen et al., 1995). Treatment should be initiated shortly after the onset of the alopecia or 1 to 2 months before the anticipated onset of the alopecia. Melatonin is a safe drug, without side effects, but due to its interaction with reproductive hormones, it should not be used in breeding animals (Paradis, 2000).

In summary, canine recurrent flank alopecia is a fascinating disease unique to dogs with an unknown pathomechanism and with several clinical presentations. The proposed name does not fit perfectly for this disease entity. The course of the disease and its response to melatonin therapy are unpredictable.

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