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Multiple follicular abnormalities in a 1-year old cat consistent with basaloid follicular hamartomas

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Background – In humans, basaloid follicular hamartomas are benign follicular tumours, that can be solitary or multiple, in which case they show autosomal dominant inheritance.

Hypothesis/Objectives – This study describes clinical and histopathological findings observed in a young cat, which could be consistent with basaloid follicular hamartomas.

Case description – Multiple follicular abnormalities, consistent with cutaneous diffuse basaloid follicular hamartomas, were observed in skin samples from a one-year old neutered domestic short hair cat. Clinical signs were diffuse symmetrical alopecia with exaggerated skin markings (ventral abdomen, thorax and medial aspects of the limbs) and intense follicular-centred thickening (face and feet). Microscopic lesions were characterised by multiple proliferative follicular abnormalities in all samples. The epidermis showed a very irregular surface with the follicles filled with variably pigmented keratin. The epithelial walls of the follicles had multiple small hyperplastic basaloid cells foci. In the superficial dermis under the epidermis and around the follicles, fibroblastic spindle-shaped mesenchymal cells with a homogeneous moderate density were present in the collagenous connective tissue. The interfollicular epidermis was also abnormal with multiple small proliferating trichoblastic foci originating from the basal layer. RNAscope testing for feline papillomavirus was negative.

Conclusions and clinical relevance – This case report provides the first evidence of clinical and histopathological findings of multiple follicular abnormalities, consistent with cutaneous diffuse basaloid follicular hamartomas in a cat.

Background

In humans, basaloid follicular hamartomas are benign follicular tumours that can be solitary or multiple, in which latter case they show autosomal dominant inheritance.[1] In animals, to the best of the authors' knowledge, no cases have been reported. This study describes clinical and histopathological findings observed in a young cat, which could be consistent with basaloid follicular hamartomas.

Case report

A 1-year old neutered domestic short hair cat was referred for a pruritic and alopecic diffuse dermatitis of a few weeks' duration. Previous systemic antibiotic and glucocorticoid therapies had little to no effect. A fungal culture had returned negative.

On admission, the general physical examination revealed no abnormalities apart from a depressed demeanour (Figure 1a). Diffuse symmetrical alopecia affected mainly the ventral abdomen and thorax as well as the medial aspects of all four limbs. The skin markings were exaggerated with a pronounced loss of elasticity (Figure 1b). Diffuse and mild erythema with focal hyperpigmented areas was observed (Figure 1b). The face and the feet were alopecic and severely thickened (Figure 1c). On close examination, the thickening seemed to be follicular-centred (Figure 1d,e).

A complete serum biochemical analysis and complete blood count showed all values within normal limits. The cat tested negative for feline immunodeficiency virus/feline leukaemia virus. Microscopic lesions, in three 6 mm skin biopsy specimens from the face, were characterised by multiple proliferative follicular abnormalities in all samples. The epidermis showed a very irregular surface with the follicles filled with variably pigmented keratin (Figure 2a,b). The epithelial walls of the follicles had

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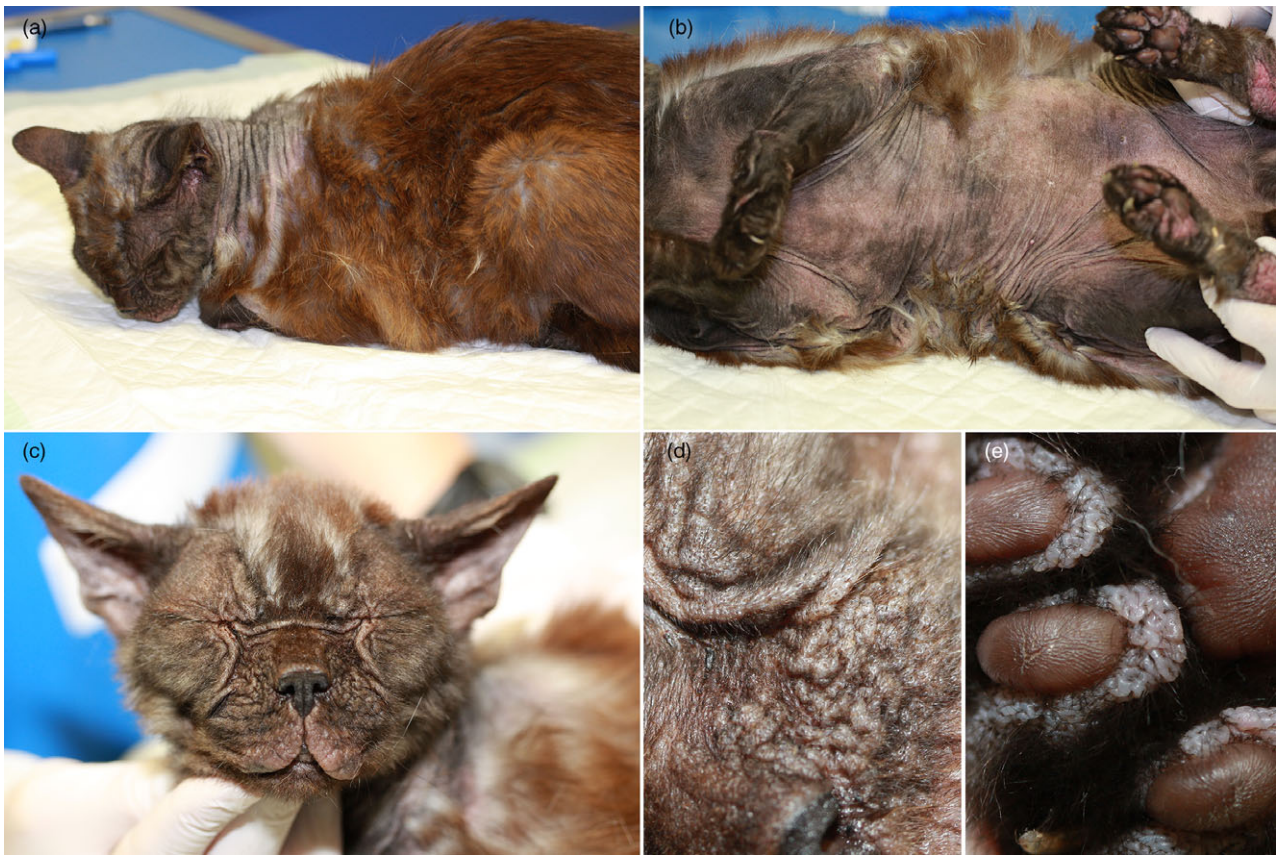

Figure 1. Clinical findings of a 1-year-old cat with basaloid follicular hamartomas.
The cat had a depressed demeanour (a), extensive symmetrical alopecia on the ventral abdomen with erythema, focal hyperpigmentation and excessive skin markings with loss of elasticity (b). The face was alopecic and severely thickened (c). Close examination of the face (d) and around the footpads (e) reveals follicular-centred thickening.

multiple small hyperplastic basaloid cell foci (Figure 2c). In the superficial dermis under the epidermis and around the follicles, fibroblastic spindle-shaped mesenchymal cells with a homogeneous moderate density were present in the collagenous connective tissue (Figure 2d). The interfollicular epidermis also was abnormal with multiple small proliferating trichoblastic foci originating from the basal layer. The sebaceous glands and epitrichial sweat glands were normal. RNAscope assay was assessed using a 13ZZ probe named V-FPV-E6-E7[2] and RNAscope 2.5 HD Assay RED according to the manufacturer's recommendations (Bio-techne SAS; Noyal-Chatillon-sur-Seiche, France) with a protease incubation time of 15 min. A probe to the bacterial gene dihydrodipicolinate reductase (*dapB*) served as the negative control, as well as normal skin; cutaneous viral plaques/squamous cell carcinoma and mucosal papilloma on feline cases served as positive controls. *In situ* hybridisation tested negative for *Felis catus* papillomavirus 2 (FcaPV-2) *E6* and *E7* gene transcription (Figure 3a–e).

The cat was euthanised owing to poor quality of life. Necropsy did not reveal any gross or microscopic abnormalities of any other organs apart from strikingly thickened fascia and articular capsules of the hips and shoulders. Their microscopic examination revealed only severe fibrous hyperplasia; additional skin biopsies obtained from the head, thorax and abdomen showed similar results as before.

The final clinicopathological diagnosis was cutaneous diffuse basaloid follicular hamartomas.

Discussion

Cutaneous hamartomas (nevi) are circumscribed developmental defects of the skin, characterised by hyperplasia of one or more skin components.[3] They are uncommon in dogs and cats and may be congenital or not. Their exact mechanism of formation is unknown.[3]

In humans, basaloid follicular hamartomas were previously often diagnosed as trichoepitheliomas or basal cell carcinomas.[1,4] They can be hereditary, in which case they are generalised or localised, or nonhereditary with solitary, localised or multiple lesions.[4] The generalised basaloid follicular hamartoma syndrome subtype carries an autosomal inherited pattern and affected patients show additional lesions such as milium cysts, comedones, alopecia or hypotrichosis. It is generally associated with an autoimmune disease.[5] Multiple basaloid follicular hamartomas associated with myasthenia gravis and diffuse alopecia form the Brown–Crounse syndrome.[6] However, some reported cases of multiple basaloid follicular hamartomas failed to demonstrate an autosomal dominance inheritance and the causative gene is unknown.[7] The pathophysiological aetiology of the lesion has been suggested to be an abortive growth of secondary hair germs, with differentiation occurring only in the upper

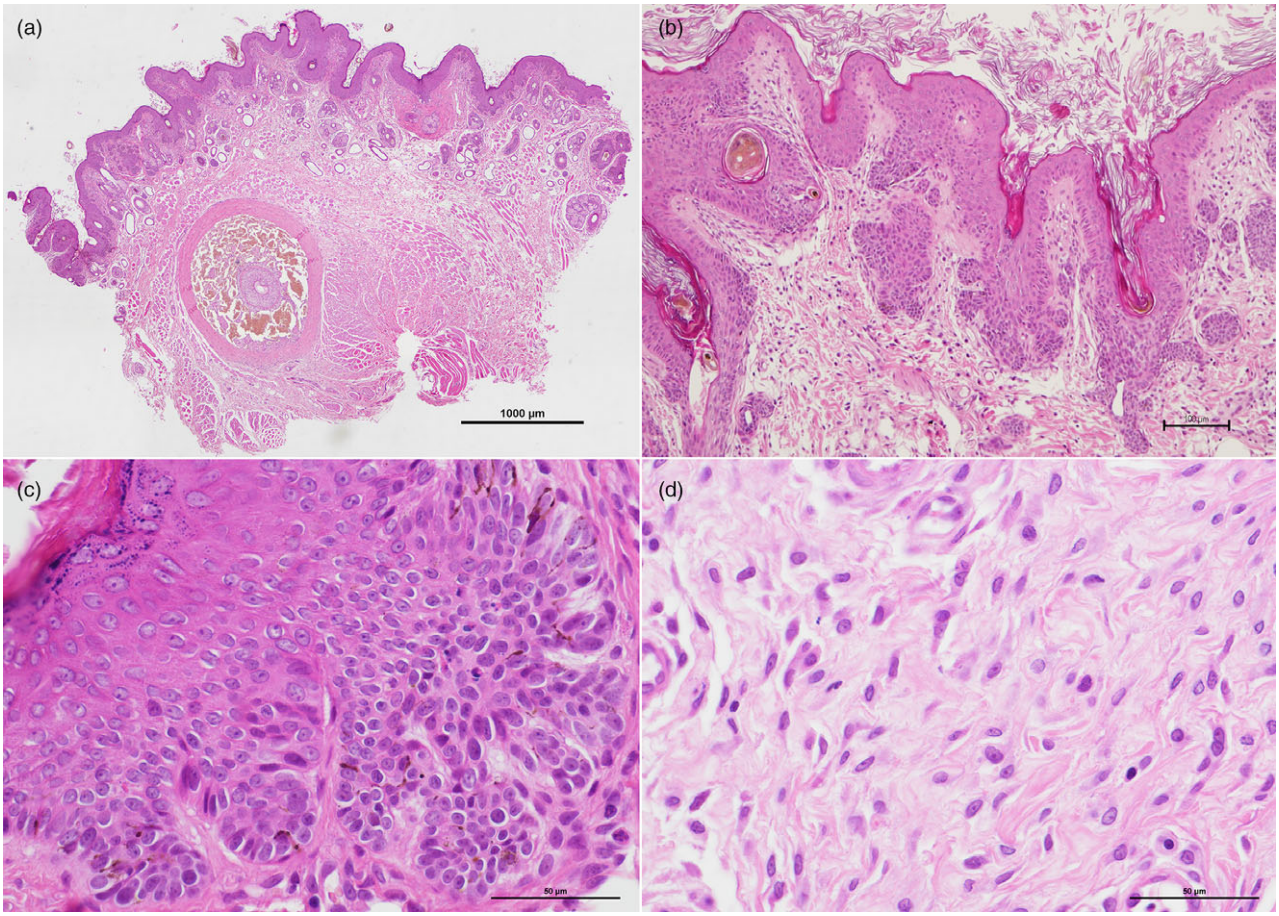

Figure 2. Histopathological findings in skin biopsy samples taken from the face of a 1-year-old cat with basaloid follicular hamartomas. (a) Hyperplastic epidermis with a very irregular surface (haematoxylin & eosin, ×40). (b) Multiple small hyperplastic trichoblastic foci of basaloid cells originating from the epithelial wall of the follicles and the basal layer of epidermis; follicles filled with variably pigmented keratin (H&E, ×100). (c) Epithelial walls of the follicles with multiple small hyperplastic basaloid cells foci (H&E, x400). (d) Homogeneous and moderate density of fibroblastic spindle-shaped mesenchymal cells in the dermis (H&E, x400).

part of the follicle.[8] Basaloid follicular hamartomas are morphologically similar to infundibulocystic basal cell carcinoma and immunoreactivity with cytokeratin 20 is similar, which makes some authors consider both lesions to be identical.[9] However, the anastomoses and strands of basaloid cells are localised in the dermis opposed to the infundibulocystic basal cell carcinoma, which may involve the subcutaneous fat and skeletal muscle. In both lesions, the strands are embedded in a loose, fibrous stroma.[4,7] Moreover, mitoses and single cell necrosis are rare while a high number of these are more consistent with basal cell carcinoma.[1]

In this feline case, the main diagnostic pitfalls are papillomavirus-induced lesions (viral plaques), trichoepitheliomas and basal cell carcinomas. Recent evidence suggests that FcaPV-2 is the predominant cause of feline viral plaques/Bowenoid *in situ* carcinomas, although FcaPV3, FcaPV4 and FcaPV5 also may cause development of lesions. Viral plaques typically present as multiple pigmented or nonpigmented, nonpruritic lesions commonly on face, head and neck.[10,11] Histologically, there is mild to moderate epidermal and infundibular hyperplasia that may progress to dysplasia and atypia in Bowenoid *in situ* carcinomas.[11] The RNAscope assay used here enabled the involvement of FcaPV-2 in the lesions to be excluded. Trichoepitheliomas are thought to originate from keratinocytes differentiating toward all three segments of the hair follicle.[12] They are polymorphic tumours as their histological appearance depends on their origin (follicular sheath or hair matrix) and degree of differentiation. Malignant transformation is uncommon and lesions tend to be solitary.[3,12] Basal cell carcinomas in cats are common, solitary, well-circumscribed, firm and round small tumours that have metastasis potential. They originate from pluripotential epithelial cells in the basal layer and adnexa. Histologically, they appear as multiple basaloid cells aggregates within a stroma bed and mitotic abnormalities are common, while the mitotic activity is variable.[3]

In humans, when not associated with a systemic disease, the prognosis of basaloid follicular hamartomas is good and the issue is mainly cosmetic provided that no suspicious changes arise.[1,4,7] Retinoids have been used to decrease the size of lesions in generalised conditions[5] and various excision therapies are available.

In this feline case, no equivalence or specific reason for the thickened fascia and articular capsules were found and there was no evidence of another systemic disease. The fibroblastic spindle-shaped mesenchymal cells which were observed in the dermis of the cat are not reported in

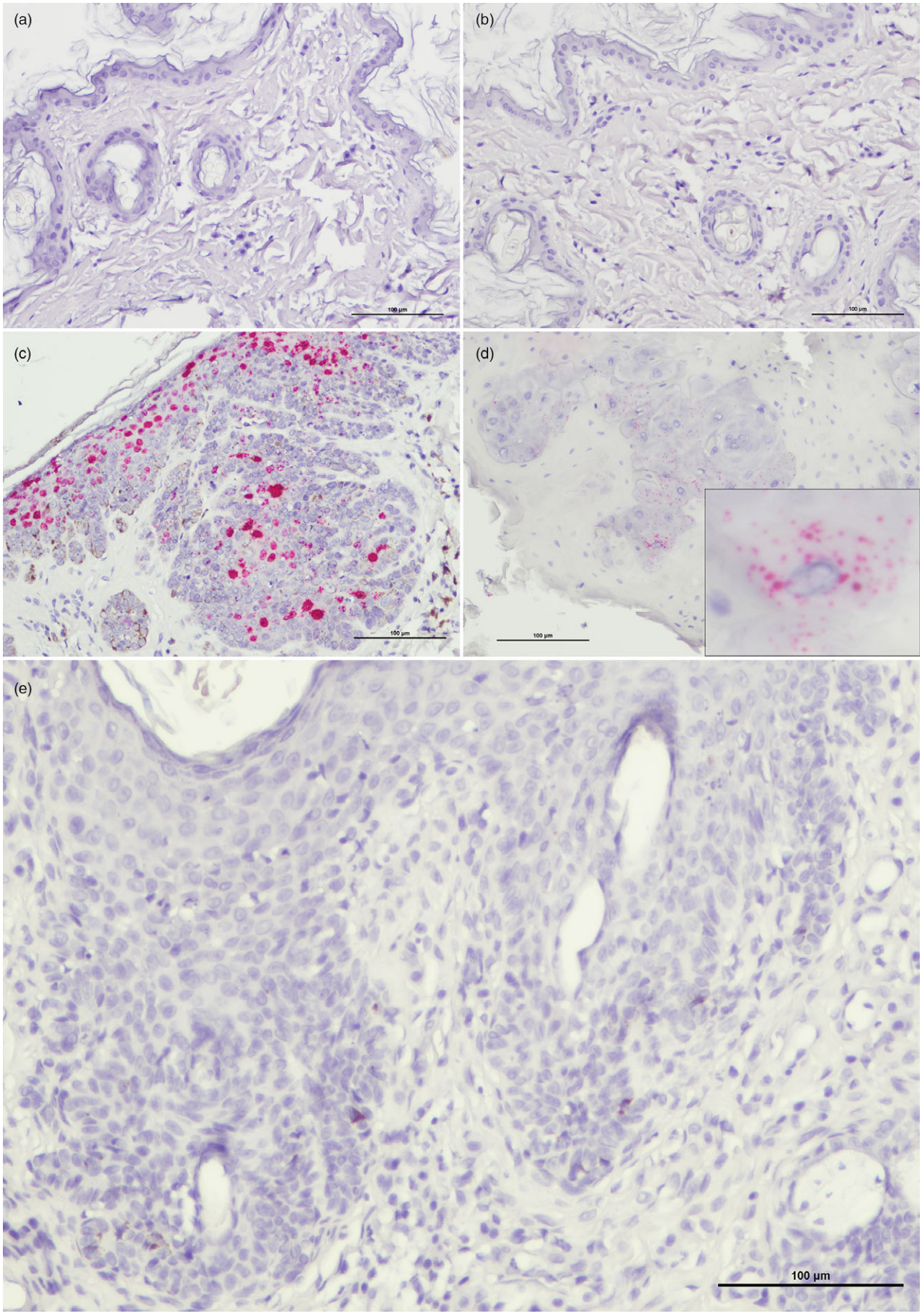

Figure 3. *In situ* hybridisation for *Felis catus* papillomavirus 2 (FcaPV-2) *E6* and *E7*.
(a) Negative control – normal skin, cat, bacterial gene dihydrodipicolinate reductase (*dapB*) served as the negative probe control: absence of hybridisation signals. (b) Negative control – normal skin, cat: absence of hybridisation signals. (c) Positive control – cutaneous viral plaque and *in situ* squamous cell carcinoma, cat: strong, diffuse, hybridisation signals are evident within keratinocyte nuclei in upper layers of the epidermis. (d) Positive control – mucosal papilloma, cat: dot-like signals are evident within the cell cytoplasm. (e) Tested sample – cutaneous diffuse basaloid follicular hamartomas, cat: absence of hybridisation signals. x200.

human cases.[4,7] A potential link between the abnormalities of the dermal connective tissue and fascia/articular capsules is unclear. Information about the siblings and parents of this case was not available and no genetic testing could be done, making it impossible to hypothesise a familial/inherited condition.

This case report provides the first evidence of clinical and histopathological findings, including negative RNAscope testing for feline papillomavirus, of multiple follicular abnormalities, consistent with cutaneous diffuse basaloid follicular hamartomas in a cat.

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Author Contributions

Fabien Moog: Investigation; writing – original draft; writing – review and editing. **Véronique Demorieux:** Investigation; writing – review and editing. **Nicolas Gaide:** Investigation; methodology; writing – review and editing. **Marie-Odile Semin:** Investigation; writing – review and editing. **Jerome Abadie:** Methodology; writing – review and editing. **Zacharopoulou Maria:** Investigation; writing – review and editing. **Lucrecija Marinovic:** Investigation; writing – review and editing. **Maxence Delverdier:** Investigation; methodology; supervision; writing – review and editing. **Frédérique Degorce-Rubiales:** Investigation; methodology; writing – review and editing. **Marie-Christine Cadiergues:** Conceptualization; investigation; methodology; supervision; writing – review and editing.

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Résumé – De multiples anomalies folliculaires, compatibles avec des hamartomes folliculaires basaloïdes diffus cutanés, ont été observées dans des échantillons de peau d'un chat domestique à poils courts castré âgé d'un an. Les signes cliniques étaient une alopécie diffuse symétrique avec des marques cutanées exagérées (abdomen ventral, thorax et face médiale des membres) et un épaississement folliculaire intense (face et pieds).

Resumen – Se observaron múltiples anomalías foliculares, consistentes con hamartomas foliculares basaloides difusos cutáneos, en muestras de piel de un gato doméstico de pelo corto castrado de 1 año. Los signos clínicos fueron alopecia simétrica difusa con marcas cutáneas exageradas (abdomen ventral, tórax y cara medial de las extremidades) e intenso engrosamiento de la piel centrado en los folículos (cara y pies).

Zusammenfassung – In Hautproben einer einjährigen kastrierten Europäischen Kurzhaarkatze wurden multiple follikuläre Abnormaitäten beobachtet, die mit kutanen diffusen follikulären Hamartomen konsistent waren. Die klinischen Zeichen bestanden aus einer diffusen symmetrischen Alopezie mit übertriebenen Markierungen auf der Haut (ventrales Abdomen, Thorax und mediale Aspekte der Extremitäten) sowie deutliche Follikel-zentrierte Verdickungen (Gesicht und Füsse).

要約 – 1歳の去勢されたドメスティック・ショートヘアの猫の皮膚に、皮膚びまん性basaloid follicular hamartomaに一致する複数の毛包異常が観察された。臨床症状は、強調された皮膚の模様を伴うびまん性対称性脱毛　(腹部腹側、胸部、四肢内側) および強い毛包中心性肥厚 (顔面、足部) であった。

摘要 – 在一只1岁去势家养短毛猫的皮肤样本中观察到多发性毛囊异常,与皮肤弥漫性基底样毛囊错构瘤一致。临床体征为弥漫性对称性脱毛, 伴皮肤纹理加深(下腹部、胸部和四肢内侧) 和明显的的毛囊中心增厚(面部和爪部) 。

Resumo – Múltiplas anormalidades foliculares, consistentes com hamartomas cutâneos foliculares basaloides difusos, foram observadas em amostras de pele de um gato doméstico de pelo curto castrado de um ano de idade. Os sinais clínicos foram alopecia simétrica difusa com marcações cutâneas exuberantes (abdômen, tórax e aspecto medial dos membros) e espessamento folicular central intenso (face e patas).

