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Neoplastic disease

Cutaneous apocrine gland neoplasia in 16 captive African wild dogs (*Lycaon pictus*)

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ABSTRACT

This retrospective study documents the occurrence of single and multiple cutaneous apocrine gland tumours (CATs) on the dorsal midline of 16 captive African wild dogs (AWDs, *Lycaon pictus*) derived from 161 submissions to diagnostic laboratories in South Africa, France and Germany between 1997 and 2022. Animals included in the study came from zoological institutions in South Africa (n = 2), France (n = 5) and Germany (n = 1) and ranged from 5 to 14 years of age. Fifteen affected animals were female (94%) and one was male. CATs presented as raised, hairless, multilobular, grey firm masses, consistently located along the dorsal midline. Apart from a single cutaneous apocrine adenoma and a cystadenoma occurring concurrently with two non-cystic adenocarcinomas, neoplasms were consistent with malignant cutaneous apocrine adenocarcinomas with lymphatic spread and visceral metastases. Advanced age and female sex were identified as risk factors. A genetic component or association with the increasing use of GnRH agonist contraceptives was suspected but could not be established. This study highlights the need for close clinical monitoring of AWDs over the age of 5 years for the development of CATs along the dorsal midline and supports early surgical intervention. More research is needed to determine the role of inbreeding, endocrine changes and husbandry factors that may play a role in the development of CATs on the dorsal midline of AWDs.

1. Introduction

The African wild dog (AWD, *Lycaon pictus*), also known as the Cape hunting dog, African hunting dog or painted dog, once ranged throughout much of Sub-Saharan Africa, the central Sahara and the grasslands and woodlands of South Africa [1]. Due to a dramatic decline in population, the AWD is listed as 'Endangered' on the International Union of Conservation of Nature Red List of Threatened Species [2]. AWDs commonly live in packs of 5–15 adults and yearlings with a complex social structure. The alpha male and female have almost exclusive reproductive privileges, while the other members of the pack rarely breed but help rear the pups [3]. Worldwide, 600 AWDs are currently kept in captivity [4]. The management of individuals in human care is challenging and a wide range of social and physiological factors need to be taken into consideration for animal welfare reasons [5]. Neoplasms have been reported infrequently in AWDs [6]. These include clinical reports of cutaneous apocrine gland tumours (CATs) as well as haemangiosarcomas, multilobular tumour of bone, peripheral odontogenic

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fibroma, adrenocortical adenoma and carcinoma, osteosarcoma and mammary and uterine neoplasia [7,8]. A recent retrospective review of morbidity and mortality of 140 captive AWDs in the UK also identified soft tissue sarcoma of the mandible and bronchoalveolar carcinoma [4]. Overall, females have a higher incidence of neoplasia than males, with an increased occurrence of reproductive tract neoplasms [4,6,8].

The current study describes the features of dorsal midline cutaneous apocrine gland neoplasms in 16 AWDs in zoological collections in France, Germany and South Africa between 2000 and 2022.

2. Materials and methods

Pathology reports stored in the South African National Biodiversity Institute's National Zoological Gardens (NZG) and the Zoological Information Management System were searched for captive AWD cases. A total of 161 pathology reports from cases between 1997 and 2022 were identified and retrospectively analysed (by MSH) for the presence of CATs. Pathology records were derived from the Department of Veterinary Pathology of the Ludwig-Maximilians-University (LMU) Munich (n = 7), the pathology laboratory of the NZG (n = 113) and Vet Diagnostics Laboratoire (VDL, n = 41). Case material from the LMU originated from one German zoo, NZG cases were collected from two South African facilities and cases were submitted to the VDL from five French zoos.

Sixteen of the 161 (9.94%) submissions had CATs and were included in the study. Data collected from pathology reports for each individual included origin, signalment, contraceptive status, weight, nutritional condition (based on fat stores and skeletal muscle mass) and pathology findings. Concurrent lesions were tabulated. In all cases, tissues were routinely processed for histology following fixation in neutral buffered formalin and stained with haematoxylin and eosin (HE) according to standard operating procedures. Apocrine gland origin was confirmed in a subset of tumours (n = 4) by immunohistochemistry using Mouse Monoclonal Antibody to Cytokeratin (CAM5.2) (CliniSciences, www.clinisciences.com) following standard laboratory protocols. Initial histopathological evaluations were performed by veterinary pathologists (AF, EM, KL, MM). Two cases from the Institute of Veterinary Pathology of the LMU Munich underwent additional review by one of the authors (MH) under supervision (DD, MM). All pathological findings were tabulated. Data were collated and analysed utilizing Microsoft Excel spreadsheets and pivot tables.

3. Results

Detailed data including case number, zoological collection of origin, date of sampling, samples available for examination (biopsy/post-mortem material), tissue submitted, sex, age, type of cutaneous apocrine gland tumour and occurrence of metastases are provided in Table 1. Five of the 16 cases derived from the Ann van Dyk Cheetah Centre, 4/16 from the Zoo de Montpellier and 2/16 originated from Munich Zoo Hellabrunn. One case was from each of the UBhetyan-O-Africa, Réserve Africaine de Sigean, Zoo d'Amnéville, Zoo de Cerza – Normandie and Zoo de la Palmyre.

Cases of CATs were diagnosed between 2000 and 2022. Three AWDs from two institutions (Zoo de Montpellier and Zoo de la Palmyre) had serial tumours over the course of up to 7 years. Nine (56%) of the cases had been first diagnosed in 2014 and 2015. Nine of the tumours were diagnosed on biopsy samples and 11 were identified from samples taken during post-mortem examinations. The animals ranged from 5 to 14 years of age and the average age of initial tumour occurrence was 10.13 years. One male and 15 females comprised the study population.

Grossly, CATs were located along the dorsal midline of the neck, between the shoulder blades and, to a lesser extent, along the back to the lumbar region (Fig. 1A). Neoplasms ranged from 1 cm in diameter to 13 × 8 × 0.5 cm and presented as raised, hairless, multilobular, often ulcerated, grey firm masses (Fig. 1B). Cut surfaces were firm, lobulated and mottled pale grey to brown (Fig. 1C). In two cases, cutaneous apocrine gland adenocarcinomas (CAAs) infiltrated cranially into the muscles of the head and neck.

Neoplasms in 14 animals were classified as CAAs, one animal had a cutaneous apocrine adenoma and a cystadenoma occurred concurrently with two non-cystic adenocarcinomas in another animal. Seven out of 16 animals had a single CAA and 7/16 presented with more than one CAA. In one case, a single CAA was initially diagnosed on biopsy in 2011 and was present when the animal was necropsied 1 year later. One animal had single CAAs in 2012 and 2015 before presenting with multiple CAAs and metastases in 2019. Two further cases had single CAAs 7 and 2 years apart, respectively.

Histologically, CAAs consisted of variably tightly packed islands, tubules and lobules of neoplastic epithelial cells separated by a thin fibrous connective tissue stroma (Fig. 2B). In early lesions, neoplastic transformation of individual glands could be observed (Fig. 2A). Neoplastic cells were polygonal to columnar with moderate to abundant amounts of eosinophilic cytoplasm with clearly defined cell margins and occasional apical blebbing. The nuclei were central to basal with finely clumped chromatin and 1–3 small magenta nucleoli (Fig. 2C). Moderate anisocytosis and anisokaryosis were present with rare mitotic figures (<1/high-power field). In two cases (nos. 1 and 12) the tumours extended cranially into the muscles of the neck and skull. Visceral metastases were observed in three cases, affecting primarily the lungs (n = 3), adrenal glands (n = 2) and lymph nodes (n = 2). Widespread visceral metastases as well as a CAA on the left hindleg were documented in the male AWD. Neoplastic cells were observed in lymphatics adjacent to the CAAs in one animal. Deep sections of the CAAs were often necrotic and infiltrated by large numbers of neutrophils. In early lesions, neoplastic transformation of individual glands was observed.

The apocrine adenoma was histologically similar, but its cells were more uniform with inconspicuous nucleoli and no malignancy features. The cystadenoma was a well delineated but unencapsulated mass with multiple clear cystic cavities lined by simple to pseudostratified cuboidal to columnar epithelial cells with eosinophilic cytoplasm and frequent small apical buds. Nuclei were round and basal with coarsely clumped chromatin and inconspicuous nucleoli. No mitoses were seen in benign lesions. Single or aggregated haemosiderin or lipofuscin-laden macrophages, as well as small numbers of lymphocytes, plasma cells and macrophages, were present multifocally throughout all the tumours.

Immunohistochemical labelling of a subset of tumours revealed consistent cytoplasmic immunoreactivity of moderate to marked intensity within neoplastic epithelial cells (Fig. 2D). Non-neoplastic apocrine glands within the adjacent dermis were immunoreactive, whereas the stratified squamous epithelium of the epidermis, follicular epithelium and cutaneous sebaceous glands, when present in sections, were negative.

Contraceptive history, body weight and condition and details of other lesions detected are available in Supplementary Table 1.

4. Discussion

Only limited clinical reports are available on CATs in captive AWDs [6]. While CATs were also previously identified in pathology reports submitted to the AWD Species Survival Plan programme,

Table 1
Origin, sex, sample date and type, age, type of tumour and presence or absence of metastases in 16 African wild dogs with cutaneous apocrine gland tumours

Case number	Collection of origin	Date of sampling (dd/mm/y)	Sample method/tissue	Sex	Age at presentation (y)	Apocrine tumours	Metastases
1	1	08/11/2000	PM	M	10	Multiple CAAs	Omentum, liver, spleen, pituitary, lung, adrenal glands, bronchial lymph node; neck, temporal, biceps femoris muscle
2	8	07/03/2012	B (skin)	F	5	Single CAA	
		27/08/2015	B (skin)		8	Single CAA	
		09/08/2016	B (skin, ovaries, uterus)		10	Not detected	
		26/09/2019	PM		12	Multiple CAAs	Lung and unidentified lymph node
3	3	15/05/2012	PM	F	11	Two CAAs, single ACA	Neoplastic cells in lymphatics
4	1	22/05/2014	PM	F	11	Multiple CAAs	N
5	1	19/09/2014	PM	F	13	Multiple CAAs	N
6	1	28/10/2014	PM	F	9	Single CAA	N
7	1	06/11/2014	PM	F	12	Multiple CAAs	N
8	3	17/11/2014	PM	F	10	Single AA	N
9	8	27/08/2015	B (skin)	F	8	Single CAA	
		09/08/2016	B (ovaries, uterus)		10	Not detected	
		27/02/2021	PM		14	Single CAA	N
10	8	27/08/2015	B (skin)	F	8	Single CAA	
		09/08/2016	B (ovaries, uterus)		10	Not detected	
11	8	27/08/2015	B (skin)	F	10	Single CAA	
		09/08/2016	B (ovaries, uterus)		11	Not detected	
12	2	01/12/2015	PM	F	13	Multiple CAAs	Oesophagus, kidney, adrenal gland, lung, occipital muscles
13	2	03/12/2015	PM	F	10	Multiple CAAs	N
14	5	14/11/2017	PM	F	12	Single CAA	N
15	7	27/11/2020	B (skin)	F	11	Single CAA	
		23/11/2021	B (skin)		12	Single CAA	
		29/12/2021	PM (liver, intestine, kidney, heart, spleen, stomach)		12	Not detected	N
16	6	13/07/2021	B (skin, vagina)	F	9	Single CAA	
		26/04/2022	PM		10	Single CAA	N

1, Ann van Dyk Cheetah Centre; 2, Munich Zoo Hellabrunn; 3, Réserve Africaine de Sigean; 4, Ubehtyan-O-Africa; 5, Zoo d'Amnéville; 6, Zoo de Cerza – Normandie; 7, Zoo de la Palmyre; 8, Zoo de Montpellier.
PM, post-mortem examination; B, biopsy.
CAA, cutaneous apocrine adenocarcinoma; AA, apocrine adenoma; ACA, apocrine cystadenoma.
N, no metastases recorded at post-mortem examination.

this entity was not detected during a recent morbidity and mortality review of 140 individuals from 10 UK institutions [4,6]. This retrospective study provides the first detailed pathological description of CATs in 16 AWDs from several European and South African institutions, outlines the gross and histological features, highlights biological behaviour and discusses possible underlying factors.

Chemical signalling facilitates short- and long-range communication in most taxa [9]. The apocrine glands of AWDs produce a distinctive pungent musky odour utilized with vocalization to maintain pack cohesion during hunting and social communications [10–12]. Sex hormones influence sweat gland function, and sebaceous and apocrine glands produce sex hormones with intracrine and paracrine functions [13]. The dorsal midline is a common location of specific scent-marking glands in animals that practice scent marking by back rolling. Grossly, CATs in AWDs had a clear predilection for this dorsal midline location and consistently presented as raised, hairless, multilobular, grey firm masses with frequent surface ulceration. In animals with multiple CAAs, extension from between the shoulders to the lumbar area was observed in some cases. The anatomical location of apocrine glands in AWDs appears similar to domestic dogs. However, in domestic dogs the neck, head and dorsal trunk are common sites for apocrine adenomas, while CAAs are more frequent on the head, legs and inguinal and axillary areas [14,15]. In European ground squirrels (*Spermophilus citellus*) and Richardson's ground squirrels (*Urocitellus richardsonii*) apocrine adenocarcinomas have also been reported in the dorsal glands, which play an important olfactory role in these species [16,17]. The dorsal location of apocrine glands used for marking and the longer hair on the shoulders and back compared to the flanks and legs of AWDs, may explain the distribution of CATs observed in AWDs. Preputial hair of male AWDs is also very long but this area is associated with mainly sebaceous glands and no neoplasms were observed in the genital area [11,12]. It may be noteworthy that case no. 3 presented with concurrent multiple anal sac apocrine carcinomas with lymphatic invasion (Supplementary Table 1), although anal sac secretions do not appear to play a major role in AWD communication [12].

The histological appearance of the neoplasms in these AWDs was compatible with the morphological features of apocrine tumours in domestic cats and dogs, although no ductal, complex or mixed, ceruminous, or inflammatory type tumours were seen in AWDs [14]. Among the included cases, 17/19 neoplasms were malignant (89%) and metastases occurred in 4/17 animals with CAAs (23.5%). Multiple concurrent CAAs occurred in 7/16 animals and 7/16 developed more than one CAA over time. The biological behaviour of CAAs in domestic dogs is variable with minimal supporting statistical data [14,15]. In cases no. 1 and 12, CAAs infiltrated cranially into the muscles of the head and neck and were associated with distant metastasis. It is unclear whether extensive linear tumour growth was a representation of linear infiltration or the simultaneous development of malignant neoplasia in multiple adjacent sweat glands. Likewise, it could not be established whether separate tumours diagnosed at different time points in the same animal represented a recurrence of the same neoplasm, newly arisen tumours or correlated with a failure to detect small early tumours that had expanded subsequently. The biological behaviour of CATs in AWDs warrants early surgical intervention and detailed recording of tumour

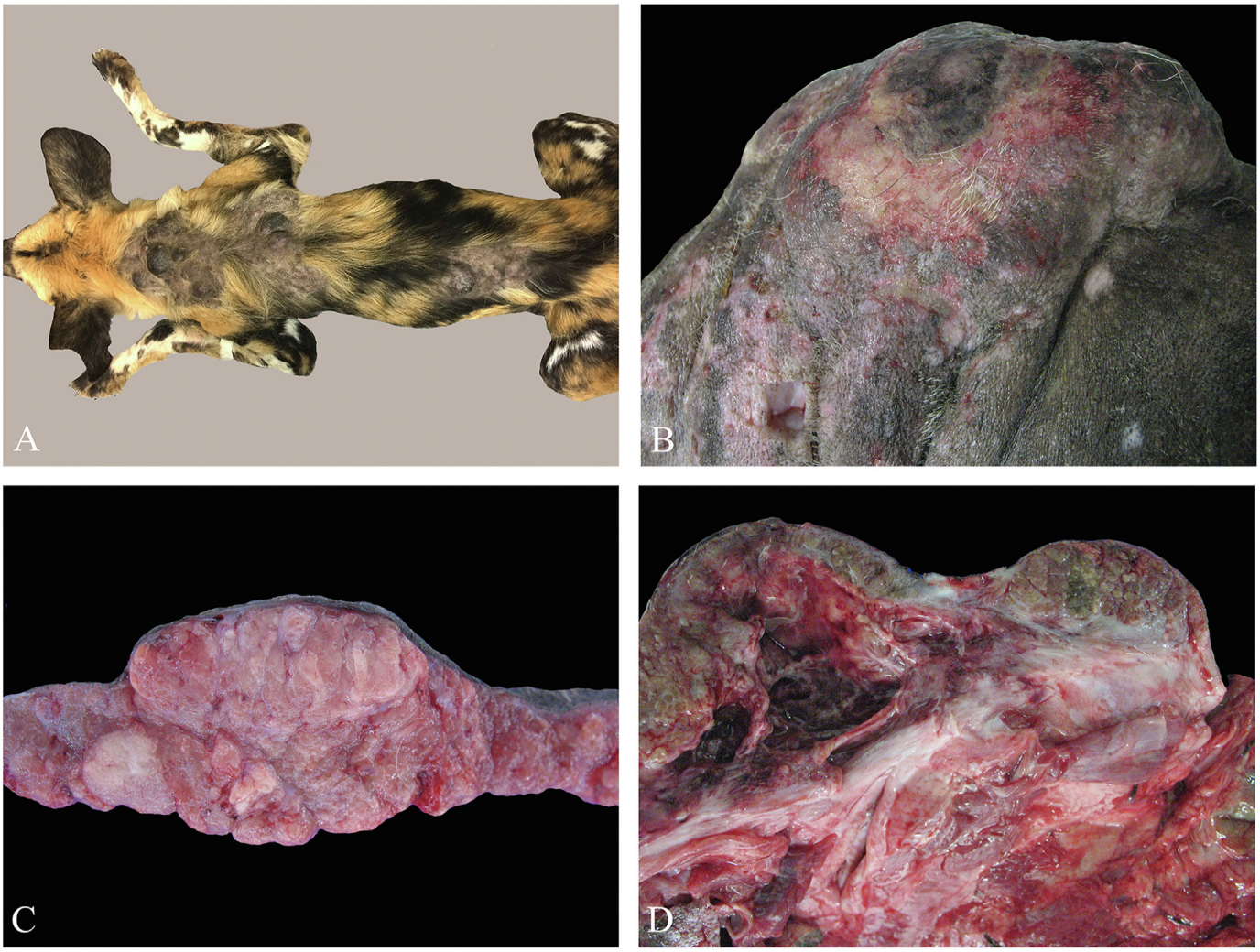

Fig. 1. Cutaneous apocrine gland carcinoma, skin, African wild dog. (**A**) Confluent areas over back are hairless and characterized by multinodular, raised, firm neoplastic nodules. Elsewhere haircoat along dorsal midline is long. (**B**) Skin devoid of hair and extensively ulcerated over multinodular neoplasm. (**C**) Coalescing mottled pink to white infiltrative mass extending laterally in subcutis. (**D**) Neoplasm has necrohaemorrhagic centre and infiltrates overlying skin.

locations on excision to allow for better correlation with potential subsequent lesions, and also highlights the importance of continued clinical monitoring of affected animals.

The overall incidence of cutaneous apocrine tumours among skin tumours of domestic dogs ranges from 1.7% (cystic and/or secretory apocrine adenomas) to 0.6–2.2% (adenocarcinomas) in available studies [14,19] In the present study, 10% (16/161) of submissions presented with these tumours, although the study included more than one submission per animal.

Predisposition to the development of neoplasia is probably multifactorial and may relate to a range of influencing factors including gender, genetics, age, diet and environmental conditions, and several of these factors may have played a role in the development of these neoplasms in the present AWDs. There was a strong predisposition of female AWDs to develop CAAs. No sex predilection has been recorded for CATs in domestic dogs and cats [14,15]. However, it has been reported that women may be more at risk of developing sweat gland ductal tumours than men [18]. Prior to completion of the study, the authors had speculated on a possible correlation of the development of CATs in AWDs with the contraceptive regime in captivity, but this hypothesis was not substantiated by the study findings. However, concurrent reproductive pathology was noted in 6/16 cases (Supplementary Table 1) in the ovary (adenocarcinoma, granulosa cell tumour, subserosal cystadenocarcinoma), uterus (leiomyoma, leiomyosarcoma), vaginal leiomyosarcoma, mammary carcinoma, adrenocortical carcinoma, skin (lipoma), abdominal cavity (lipoma) and urinary system (bladder fibro-/leiomyoma, haemangiosarcoma) potentially suggesting a higher overall prevalence of neoplasms in this species than previously indicated.

It cannot be excluded that a genetic component may play a role in the development of CATs in AWDs. Breed predispositions to the development of apocrine adenomas are recorded in domestic dogs and cats, with Great Pyrenees, Chow Chows, Malamutes, Old English Sheepdogs, Persian and Himalayan cats, Coonhounds, Norwegian Elkhounds and Siamese cats appearing to have a higher risk of developing CAAs [19]. The basis for breed predispositions is not well documented, but genetic factors are likely to play a role and breeding-related narrowing of the gene pool may explain breed-dependent overrepresentations of different tumour types. Analysis of the family trees of the 16 animals included in the study revealed that the male (case no. 1) was in direct F2 generation to two females (cases no. 5 and 6). Cases no. 12 and 13 were also related to each other in the F2 generation. The significance of these

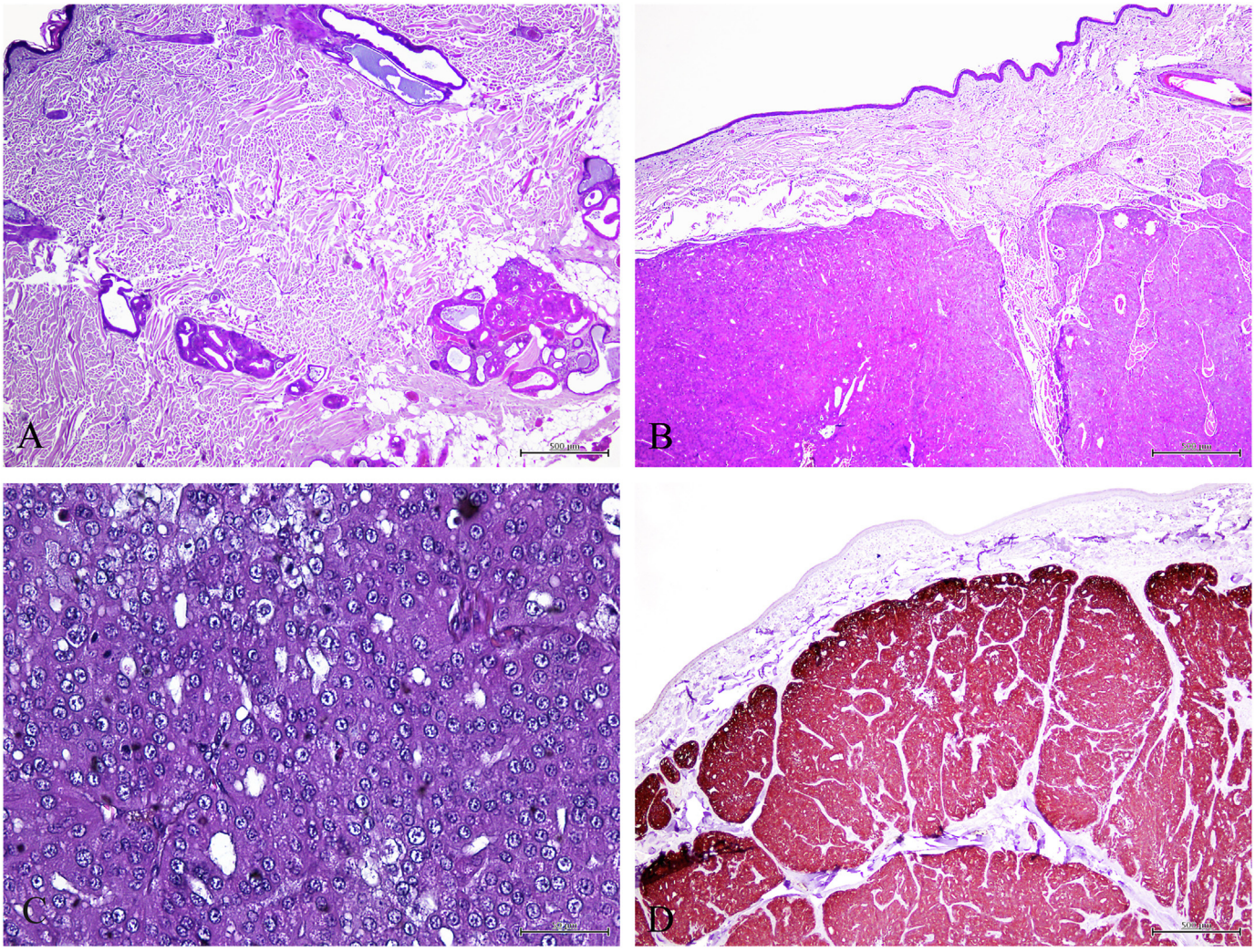

Fig. 2. Cutaneous apocrine gland carcinoma, skin, African wild dog. (**A**) Early neoplastic transformation of apocrine gland characterized by dense nodule of neoplastic cells adjacent to adnexal structures. HE. Bar, 500 μm. (**B**) Unencapsulated invasive neoplastic epithelial cells form irregular lobules of tightly packed acini and tubules separated by connective tissue. HE. Bar, 500 μm. (**C**) Columnar neoplastic cells with round nuclei, coarsely clumped chromatin, abundant eosinophilic cytoplasm and apical blebs form sheets and acini. HE. Bar, 50 μm. (**D**) Neoplastic cells intensely immunolabelled for glandular cytokeratin (CAM 5.2). IHC. Bar, 500 μm.

findings is, however, uncertain and case numbers were insufficient to reliably confirm a genetic component as has been suggested [20]. It is noteworthy, that due to the regular importation of breeding animals as part of population management, AWDs in European zoos were found to have a genetic diversity comparable with free-ranging Southern African populations and a higher diversity than AWDs in South African zoos [21,22]. Cases included in this study were derived from both South African and European facilities. Available data do not allow for reliable comparison of the incidence of neoplasia between South African and European cases, and the role of genetic diversity in the pathogenesis of CATs in AWDs remains uncertain.

In the present study, neoplasms occurred predominantly in AWDs 8 years of age or older. One animal was 5 years of age and the average age of affected animals was 10 years. In humans, full maturity of apocrine glands is considered a prerequisite to lesion development, and age of onset in both domestic animals and the AWDs in this case series suggests similar considerations [23]. No CATs were detected during a survey of 46 free-ranging AWDs in South Africa, although at least 80% of animals were less than 4 years of age [24]. In the wild, AWDs live approximately 7 years, while the average lifespan is 10 years in captivity [6,25]. Based on the study findings, advanced age is a major risk factor for the development of CATs in AWDs. It is noteworthy that advanced age may also be a contributing factor for the concurrently observed neoplastic lesions in the reproductive tract in the study population (Supplementary Table 1).

For AWDs in which the relevant organs were sampled for histology in the present study, the prevalence of ovarian tumours (6/7), cystic endometrial hyperplasia (9/10), mammary gland hyperplasia (4/4), thyroid C cell hyperplasia (2/4), adrenocortical hyperplasia (4/5), adrenocortical carcinoma (2/5) and parathyroid gland hyperplasia (1/1) further suggests the possibility of endocrine abnormalities. Adrenocortical adenoma and carcinoma, as well as mammary and uterine neoplasia, have been documented in AWDs but the relationship between the various hyperplastic and neoplastic conditions seen in the present study is unclear and no clear correlation could be made to the development of CATs [6,24].

Pituitary and mammary tumours as well as lipomas have been described in rats treated with GnRH analogs [26]. Pituitary adenomas are, however, common in older rats, and may be associated with age, genetic factors, overnutrition and parity [27]. Pituitary tumours could potentially account for the high number of endocrine-producing or endocrine-responsive tumours seen in our AWDs. The time frame of the upsurge in cases of CATs (2014–2015)

corresponds to the increasing use of GnRH agonist contraceptives [28,29]. Cases nos. 4–7 occurred in one institution in 2014. Repeated pseudopregnancies (due to GnRH-mediated contraceptive treatment in males) were believed to be responsible for increased numbers of cases of cystic endometrial hyperplasia (CEH) and pyometra requiring unplanned ovariohysterectomy in AWDs from the same facility from 2008 [5]. Synthetic progestin and GnRH analog contraceptive treatment in domestic and wild canids, particularly AWDs, has been shown to increase the likelihood of ovarian neoplasia, CEH and pyometra, as well as hydrometra (one case had mucometra) and adenomyosis, especially in older canids [23,30–34]. This effect is mitigated if AWDs are treated with progestogens at the time of implant placement [30]. Adenomyosis was seen in 5/7 AWDs for which the uterus was submitted (71%) and has been previously reported in this species [24,35]. However, these conditions also occur in AWDs that do not receive contraceptive treatment and 50% of the AWDs in this series were not treated with GnRH agonist contraceptives [32]. This indicates a limited role for contraceptive treatment in the development of CATs. Unfortunately, hormone levels were not determined and the pituitary was not available for histological examination in the present study cases.

The potential importance of environmental conditions and diet in the development of neoplasia, both in humans and animals, has been discussed in many previous studies. It could be speculated that altered marking behaviour in captivity could result in secretory retention or overstimulation of the cutaneous apocrine glands of AWDs, thereby constituting a possible factor predisposing to neoplastic transformation. A study comparing the social behaviour and structure of wild and captive groups of AWDs demonstrated that captive groups express many of the behaviours displayed by wild groups, and highlighted that urinating and scent marking are important aspects of the dominance posturing of males and alpha females [36]. Investigations into the possibility that a captive environment, in which animals have less hunting possibilities, reduced roaming availability and human impacted social structures, may stimulate increased dominance posturing could shed further light on important behavioural differences in wild versus captive populations.

It is also interesting to note that the hierarchical social organization of AWDs results in an alpha pair dominating the pack and monopolizing breeding. Correlation of dominance data with the occurrence of CATs in female AWDs was not possible as part of the present study. Providing these data alongside biopsy or post-mortem submissions of AWDs could provide further insights and may aid additional investigations.

5. Conclusion

This study highlights the susceptibility of captive aged (>8 years) female AWDs to the development of apocrine skin tumours on the dorsal midline. Most of the tumours were malignant and more than one can develop in affected animals over time. Therefore, monitoring AWDs over the age of 5 years, and those that have presented with CAT previously, is advisable. CAT detection warrants early surgical intervention. Advanced age and female sex were important risk factors for tumour development. No association with GnRH agonist contraceptive treatment was found. The possible role of genetic, environmental, dietary and endocrine abnormalities in the pathogenesis of this condition requires future research.

Availability of data and material

Part of the case material included in the present study that derived from France was included in a poster presentation on familial occurrence of CATs in AWDs (cases 2, 9, 10 and 11) [19]. These cases and cases 3 and 8 were also included in a poster presentation as part of a retrospective study on neoplasms in AWDs in French zoological collections [7].

Statement of author contributions

E.P. Mitchell: Conceptualization, Data curation, Formal analysis, Investigation, Visualization, Writing - original draft/review and editing. **D. Denk**: Conceptualization, Data curation, Formal analysis, Investigation, Project administration, Supervision, Writing - original draft/review and editing. **M. Henker**: Data curation, Formal analysis, Methodology, Writing - original draft/review and editing. **K. Lemberger**: Data curation, Investigation, Writing - original draft/review and editing. **C. Gohl**: Investigation. **M. Majzoub-Altweck**: Investigation. **A. Falkenau**: Investigation. **P. Caldwell**: Investigation. **B. Chenet**: Investigation. **M. Mosca**: Investigation. **D. Pin**: Investigation.

Declaration of competing interests

The authors declared no conflicts of interest in relation to the research, authorship and publication of this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcpa.2023.10.005.

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