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Epidemiological and histopathological analysis of 40 apocrine sweat gland carcinomas in dogs: a retrospective study

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Abstract

Introduction: Apocrine sweat gland carcinomas (ASGCs) are malignant neoplasms of dogs and other animals, rarely reported worldwide. The aim of this study was to summarise the occurrence of this cancer in a population of dogs in Poland between 2009 and 2014 with regards to histological features and body location of the tumours, as well as age, sex and breed of the cancer-affected dogs. **Material and Methods:** The study involved 40 canine ASGC cases diagnosed in five national veterinary pathology laboratories. The material was processed according to routine histological methods. **Results:** Histological types of the tumours involved simple and complex apocrine carcinoma of cystic/papillary (62.5%), solid (15%), and tubular type (12.5%), as well as apocrine ductal carcinoma (10%). The epidemiological analysis revealed peak incidence of the cancer in dogs between 8 and 14 years of age, with the most commonly affected sites being forelimbs and thorax. The highest number of the cancer cases was diagnosed in mixed breed dogs and German Shepherds; no sex predilection was noted. **Conclusion:** To the authors' knowledge, this is the first report recounting the study on canine malignant apocrine sweat gland tumours in Poland providing detailed phenotypical and histological data, which are otherwise rarely described in veterinary literature. This type of cancer appears to be diagnosed more frequently in dogs than in humans. Being an easily accessible material for research, canine ASGCs might serve as a relevant animal model for studies related to pathogenesis of sweat gland tumours.

Keywords: dog, apocrine sweat gland carcinoma, epidemiology, histopathological analysis.

Introduction

Apocrine sweat gland carcinomas (ASGCs) are malignant skin neoplasms and in dogs they have been estimated to account for about 2% of skin-associated tumours, which are the most common canine primary neoplasms (2, 11). These tumours are rarely reported in veterinary literature and in the last decade no widely available epidemiological reports have been published on the topic. They have been described to have a variable macroscopic appearance and unless it is not an inflammatory, rapidly growing variant of the neoplasm, the malignant tumour might be misdiagnosed as a benign lesion due to slow nodular growth (8). Wide excision is usually a the treatment of choice; however, the cancer has been reported to have

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a tendency to recur, invade the lymphatic system, and develop distant metastases associated with poor outcome (2, 11, 16). The purpose of this report is to summarise epidemiological data and histological features of canine ASGCs diagnosed in five veterinary laboratories in Poland between 2009 and 2014 and to compare the results with reports of other authors.

Material and Methods

Material. Material for the study consisted of archival paraffin blocks of ASGC tissues of dogs diagnosed with this cancer in Poland between 2009 and 2014 in five national veterinary pathology laboratories.

Histopathological examination. In order to classify the collected tumours according to the World Health Organization International Histological Classification of Tumours of Domestic Animals (7), all the paraffin blocks of the tumour tissues were submitted for histopathological re-evaluation. The paraffin-embedded tissue samples were cut to 5 μm sections, stained with haematoxylin and eosin (HE), and then submitted to light microscopic examination and further classification, based on their histological features, into solid, cystic/papillary, tubular, and ductal apocrine sweat gland carcinomas. Additional subdivision of the tumours into simple and complex types was based on the presence of proliferation of myoepithelial cells surrounding the neoplastic structures of epithelial origin. Each slide was subsequently evaluated for the presence of cancer-associated inflammation, desmoplasia, necrosis, and invasion of the surrounding tissue.

Epidemiological and statistical analysis. All available details regarding tumour location, age, sex, and breed of the dogs were collected and analysed. All clinical data except for breed were submitted to statistical analyses using STATISTICA Software, version 10, 2011, Stat Soft, Inc. Furthermore, the analyses aimed to verify whether any parts of the body were affected by this type of cancer significantly more often. These analyses involved the two-sided test between two structure indicators with Bonferroni correction for multiple comparison of the locations based on their ratio values (adjusted significance level $\alpha = 0.001389$). In addition, the percentage of males and females was compared using two-sided test between two structure indicators, based on chi-square test. For an evaluation of a normality of age distribution, Shapiro-Wilk test was used.

Results

Overall, 40 ASGC tissues of dogs were collected. As shown in Table 1, histologically, four tumours were recognised as apocrine ductal carcinomas characterised by sheets of double layers of cells resembling apocrine duct epithelium displaying cellular pleomorphism and nuclear hyperchromatism (Fig. 2). The remaining cases were estimated as apocrine sweat gland carcinomas showing cystic, solid or tubular appearance (Fig. 3, 5, 6). Malignant neoplastic epithelial cells were characterised by large round hyperchromatic nuclei with prominent nucleoli and usually large amount of cytoplasm with variable mitotic activity. Cellular and nuclear pleomorphism was mostly prominent in less differentiated, solid or papillary tumours. The apocrine secretory activity of the neoplastic cells marked by the presence of eosinophilic exudate in lumina of the neoplastic glandular structures was particularly observed in the cystic and tubular tumours (Fig. 7). Among all the apocrine sweat gland adenocarcinomas the largest subtype consisted of 25 (62.5%) cystic tumours which mostly appeared as papillary due to proliferation and invagination of the neoplastic cells into lumina of the cysts (Fig. 4). There were also 6 (15 %) cases recognised as solid tumours and 5 (12.5%) tubular ones. Both the tubular and ductal carcinomas consisted of simple tumours, while 21 (81%) cystic/papillary carcinomas and 3 (50%) solid ones were recognised as complex carcinomas which accounted for 60% of all the studied tumours. An invasion of the surrounding tissue was visible in all ductal carcinomas, then in 88% of cystic/papillary, 50% of solid, and 80% of tubular tumours. No invasion of the vasculature was noticed in any of the examined cases. Marked desmoplasia was visible in all tubular tumours, in 66.7% of the solid, 25% of the ductal, and 20% of the cystic ones. Necrosis of variable degree was observed in 36% of the cystic/papillary ASGCs, as well as in 50% and 40% of the solid and the tubular tumours, respectively, but in none of the ductal carcinomas. Infiltration of the neoplastic tissue by inflammatory cells including plasmocytes, granulocytes, or lymphocytes was present in 72% of the cystic/papillary tumours, as well as in 66.7% of the solid, 60% of the tubular, and 50% of the ductal carcinomas.

In a group of cystic/papillary ASGCs comprising 25 tumours, the age details were known in 23 cases and ranged from 5 to 17 years. The sex was known in 22 cases, of which 10 were female and 12 were male. The dogs with specified breed in this group included nine mixed breeds, four German Shepherds, two Dachshunds, two Yorkshire Terriers, and one of each of the following: Poodle, Labrador, Alaskan Malamute, Cocker Spaniel, Newfoundland, and Staffordshire Bull Terrier.

Regarding the solid carcinomas (six cases), the age details were provided for five dogs, the youngest of which was a 3.5-year-old male German Shepherd and the oldest a 14-year-old Dachshund of unknown gender. The cases with specified breeds in this group involved three Dachshunds, one German Shepherd,

and one Boxer. The sex was known for two cases which included one previously mentioned male and one female Dachshund.

The group of ASGCs of tubular type with the age details provided involved two 9-year-old dogs, one 11-year-old, and one 14-year-old. There were three males in this group, whereas the sex of the remaining two was not provided. The group consisted of single representatives of the following breeds: German Shepherd, Giant Schnauzer, Boxer, Siberian Husky, and mixed breed.

The four cases of ductal ASGCs involved a 7-year-old female American Staffordshire Terrier and three mixed breeds, one of which was a 12-year-old male and two were 9- and 10-year-old females.

The analysis of the available epidemiological data involving all ASGCs under study revealed that among 31 cases with determined sex, 17 were found in males and 14 in females. The chi-square analysis of sex predilection revealed no statistically significant relationship between gender and ASGC occurrence. The age details were provided for 35 dogs and the age ranged from 3.5 to 17 years with an average of 9.93 ± 3.21 years. The highest number of ASGC cases was found in 11-year-old dogs (Fig. 1). The normality of the age distribution was confirmed by Shapiro-Wilk test ($P = 0.35$).

Anatomic location was known in 32 cases and, as seen in Table 2, the body area in which the highest number of tumours was found was forelimb (25% excluding a finger area), particularly axillary area (15.6%). Other body locations included thorax (15.6%), abdomen (12.5%), head (12.5%), finger (12.5%), neck (9.4%), back (3.1%), and hind limbs (3.1%). All finger area tumours were diagnosed in males, whereas 80% of the axillary tumours were diagnosed in females. There was no other correlation noted between sex and the body locations, nor any association between breed and body location. Statistical analysis did not reveal any significant differences among the particular parts of the body regarding the prevalence of ASGCs.

Among 37 animals for which breed was specified, most cancer cases were found in crossbred animals (35.1%), followed by German Shepherds (16.2%), and Dachshunds (13.5%) (Table 3).

Table 1. Prevalence of histological types and histological features of 40 cases of canine ASCSs

Histological type	N	Histological features				Complex ASGCs
		Invasion of stroma/capsule	Desmoplasia	Inflammation	Necrosis	
Cystic/papillary	25	22	5	18	9	21
Solid	6	3	4	4	3	3
Tubular	5	4	5	3	2	0
Ductal	4	4	1	2	0	0

N - number of cases

Table 2. Body locations of 40 cases of ASGC according to the histopathological subdivision

Body location	Cystic/papillary (N)	Solid (N)	Tubular (N)	Ductal (N)	ASGCs in summary (N)
Head	2	1	-	1	4
Neck	3	-	-	-	3
Back	-	1	-	-	1
Thorax	3	-	-	2	5
Abdomen	4	-	-	-	4
Limb					
Arm	2	-	-	-	2
Axilla	4	-	1	-	5
Elbow	1	-	-	-	1
Foot	1	-	-	-	1
Finger	1	1	2	-	4
(Area not-specified)*	2	-	-	-	2
Unknown body location	2	3	2	1	8

N – number of cases
*particular parts of a limb were not specified in these cases

Table 3. Number of dogs and sex distribution for each breed among 37 dogs with apocrine sweat gland carcinoma

Breed	N	M	F	NS
Mixed breed	13	6	4	3
German Shepherd	6	3	2	1
Dachshund	5	0	3	2
Boxer	2	2	0	
York Terrier	2	1	0	1
Poodle	1	1	0	
American Staffordshire Terrier	1	0	1	
Giant Schnauzer	1	1	0	
Labrador	1	0	1	
Alaskan Malamute	1	0	1	
Siberian Husky	1	1	0	
Staffordshire Bull Terrier	1	0	1	
Cocker Spaniel	1	0	1	
Newfoundland	1	1	0	

N – number of cases in each breed, M – number of males, F – number of females, NS – number of dogs for which sex was not specified

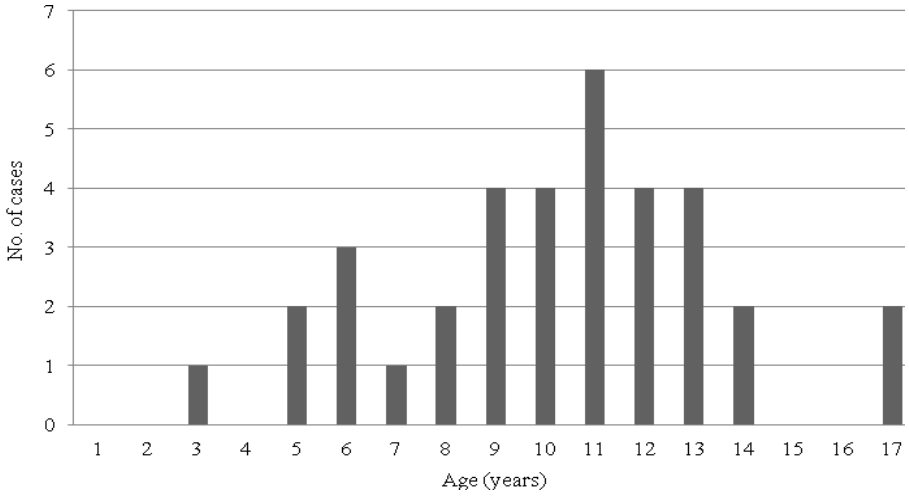

Fig. 1. Age distribution of 35 dogs with apocrine sweat gland carcinoma

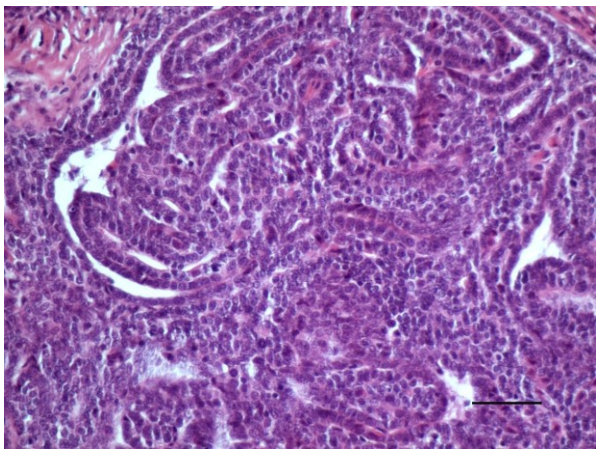

Fig. 2. Apocrine ductal carcinoma. Tumour is formed by double layers of pleomorphic cells resembling epithelium of apocrine sweat gland ducts. HE. Bar = 50 µm

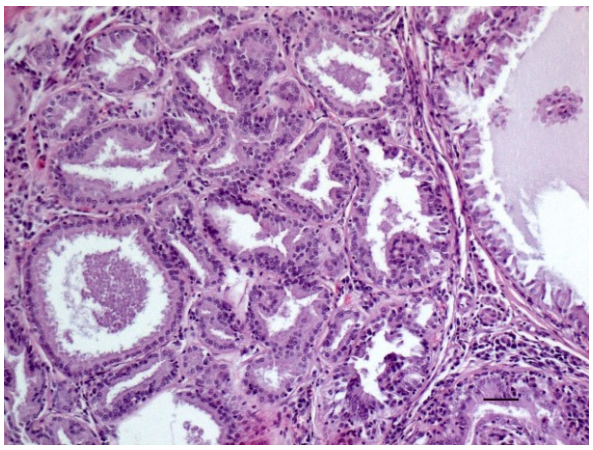

Fig. 3. Canine apocrine sweat gland carcinoma, cystic type. Pleomorphic neoplastic cells displaying secretory activity. Eosinophilic exudate expanding the lumen of a cystic structure is visible on the left side of the image. interlobular stroma is infiltrated multifocally by inflammatory cells. HE. Bar = 50 µm

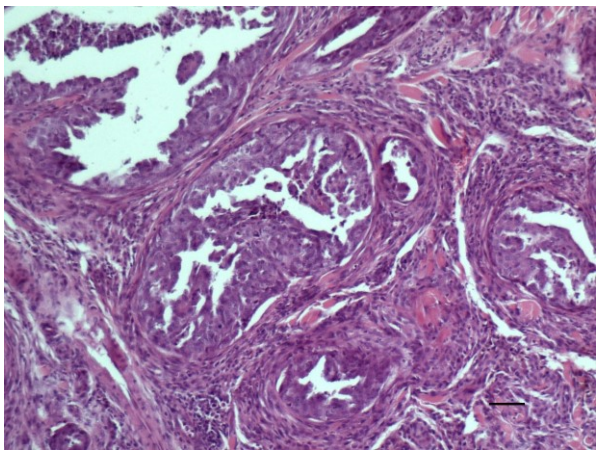

Fig. 4. Canine apocrine sweat gland carcinoma complex, cystic/ papillary type. The lumina of the cystic structures are filled with invaginations of neoplastic epithelial cells forming papillae. HE. Bar = 50 µm

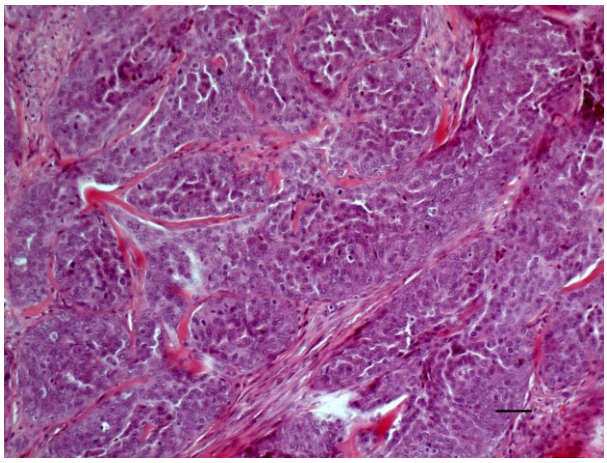

Fig. 5. Canine apocrine sweat gland carcinoma, solid type. Densely packed neoplastic cells divided by trabeculae of connective tissue. HE. Bar = 50 µm

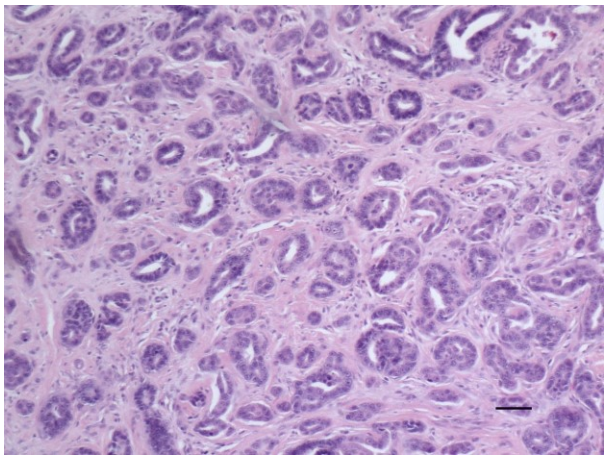

Fig. 6. Canine apocrine sweat gland carcinoma, tubular type. There are multiple lobules of neoplastic cells forming tubules divided by large amount of connective tissue. HE. Bar = 50 µm

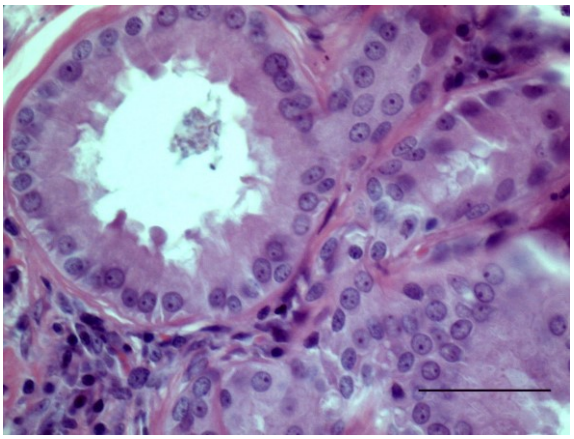

Fig. 7. Canine apocrine sweat gland carcinoma, cystic type. Neoplastic apocrine epithelial cells displaying decapitation secretion characterised by apical blebbing. HE. Bar = 50 µm

Discussion

The results of the study regarding histological classification of the collected tumours show that the majority of the neoplasms were apocrine sweat gland adenocarcinomas while only single cases were apocrine ductal carcinomas, and this proportion is similar to previous reports by other authors (7 – 9, 16). Among the tumours showing differentiation to a sweat gland secretory epithelium, tumours of cystic/papillary subtype were the most common. Although this observation is consistent with several previous reports (7 – 9, 16), other authors indicate the solid subtype as more frequently occurring (11, 19). However, in our report, the tumours of the solid subtype accounted for only 15% of the total. Furthermore, among the ASGCs analysed in the present study, tubular tumours which accounted for 12.5 % of all the analysed ASGCs were also identified, whereas only a single report noted the occurrence of this subtype in a population of 44 ASGCs-affected dogs at 25% (16). Other authors describing this subtype either mentioned its occurrence with no data on its prevalence (4, 19) or did not report their occurrence at all, like Kalaher *et al*. (11), who analysed histological features of similar number of canine sweat gland carcinomas.

Regarding histological features the invasion of surrounding stroma or capsule was apparent in the majority of the cases (82.5%), consistently with the information provided in available literature. Similar observations (63.6%) were reported by Simko *et al.* (16), who additionally noted invasion of blood vessels in 11.3% of studied cases, while Kalaher *et al.* (11) observed invasion of the lymphatic system in 22.5% of ASGCs. An invasion of blood vessels and lymphatics was not observed in the present study; however, this evaluation was based on routine haematoxylin and eosin staining only. Immunohistochemical staining, allowing the identification of the vasculature invasion, was not performed in this study.

Among all body parts, limbs, particularly forelimbs, were most frequently affected by ASGC in the present study, which is consistent with reports by other authors (9, 11, 16). Thorax, abdomen, and head were also amongst the most affected body locations according to the results of the present and previous studies (9, 11, 16). On the limbs, axilla and finger were the most common locations. Low number of cases in each of the body locations precluded an estimation of the location prevalence of any statistical significance. For the same reason no association between any of the body locations and particular histological features, such as inflammation, desmoplasia, necrosis, or invasion of the surrounding tissue could be found. Although according to Goldshmidt *et al.* (9) inflammatory cancers tend to occur more frequently in an axillary area, the present study did not provide any evidence to support this thesis, as among 27 ASGCs displaying characteristics of inflammation only five were found in the said region.

The results of the study regarding age distribution are consistent with epidemiological data reported previously by other authors who observed a mean age of 9 (5, 9) or 10 years (7). Similarly to the present results, other authors also reported that the majority of cases were diagnosed in dogs 8-year-old and older (8, 9, 16); however, while in the present study the youngest dog was 3.5-year-old, the cancer was reported, in single cases, in even younger dogs, *i.e.* 1.5-year-olds (9). Based on the results of the present and other authors' studies it may be concluded that although ASGCs may occur in any age, the most susceptible to the cancer development are dogs aged 8 years and older.

Gender details were not specified for significant percentages (22.5 %) of the cases in the present study; however, statistical analysis of the remaining cases did not reveal any significant sex predilection, which other authors did not observe (9, 11, 16). Furthermore, there was no statistically significant difference regarding the prevalence of females and males in each dog breed involved in the present study. The analysis of the present results in regard to breeds indicates that dogs of mixed breeds were the most affected, whereas among pure bred dogs, German Shepherd was a breed in which the highest number of ASGCs was diagnosed. Other authors variably reported breed predisposition to the cancer in dogs (8, 9, 11) and only one source showed results similar to those presented here, indicating mixed breed dogs and German Shepherds as the most affected (9). Breeds at increased risk indicated by other authors included Golden Retriever (11), Old English sheepdog, Lhasa Apso, Shih Tzu, and Cocker Spaniel (8, 9); however, only one case of the latter appeared in our survey. The third most affected breed in the present study was the Dachshund, which was previously never indicated as a breed at risk of ASGC development. Undoubtedly, more frequent cancer occurrence in a given breed might be associated with a higher prevalence of the breed in comparison to others in a studied population of dogs. Unavailability of data on a prevalence of different canine breeds in Poland in a studied period made it impossible to conclude on any breed predilection. Given that this type of cancer is rare in dogs and that the majority of cases have been diagnosed in mixed breeds, the issue of breed predisposition requires further studies, perhaps even involving similar research in other countries.

The size of the population involved in the present study accounted for 40 cases diagnosed during six-year period in five main veterinary pathology laboratories in Poland. Available literature provides very few reports on epidemiological and histological aspects of these neoplasms in dogs, of which 2% detailed analyses of similar-sized groups including one of 40 cases diagnosed during three-year period in north-eastern USA (11) and one of 44 cases diagnosed during 11 years by three laboratories in Canada (16). There is only one source presenting several epidemiological data for larger group comprising over 200 ASGC cases diagnosed in USA during undisclosed period (9). Therefore, based on the results obtained in the present and previous studies it is difficult to estimate a real predisposition to ASGC development with regard to breed, sex, or body location. To date, little is known about an aetiopathology of this neoplasm in dogs. Mutations of several genes, particularly gene p53, were previously described in several malignant tumours of the sweat gland in humans, with indication of ultraviolet radiation as one of inducting factors (3). Low incidence of the cancer precludes not only clinical trials, but also possibilities of extensive research on this tumour in human medicine, as only isolated cases of human apocrine sweat gland cancer have been reported in the literature worldwide (1, 6, 10, 13, 14). Moreover, in humans, apocrine sweat gland carcinomas are classified as a subtype of sweat gland tumours, which account for around 0.01% of primary skin tumours (1). Apocrine sweat glands are not as widely distributed on the human body as they are in dogs, thus an occurrence of the cancer might be even less frequent in humans (1). In fact, due to the rarity of the disease, histological diagnostic criteria of ASGCs and their classification in humans remain unclear (5, 17). This in return causes difficulties in establishing proper treatment, which is an important issue, as the development of this cancer is associated with metastases leading to negative prognosis (6, 14). This type of cancer, although rare, appears to be diagnosed more frequently in dogs than in humans (10), therefore, canine apocrine sweat gland carcinoma might serve as an animal model for research on aetiopathology of this cancer.

According to previous reports, canine apocrine sweat gland carcinomas accounted for 2%–3% of all tumours diagnosed in dogs at the same time (11, 15). The major limitation of the present study was the lack of available data on all cancer cases diagnosed in dogs during the described period, which made the estimation

of the ASGC prevalence and incidence in Polish population of cancer-affected dogs impossible. The authors are also aware that, similarly to other reports of this type, certain data on age, sex, breed, or location were not available in some of the studied cases. Moreover, post-excisional follow-up information was not available in any of the studied cases, which excluded the possibility of analysis of correlation between the histopathological features and the disease outcome. While such obstacles are unavoidable in retrospective studies of this type, they could be prevented in the future if animal cancer registries were established, similar to those that exist in several countries or comparable to those in human oncology. This would undoubtedly help in analysis of epidemiological patterns (4, 12, 18). Nevertheless, the present report is the first in recent years describing the study on canine malignant apocrine sweat gland tumours providing phenotypical information valuable for both veterinary professionals and researchers conducting comparative studies aiming to identify possible risk factors of the cancer occurrence both in dogs and humans.

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