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Research article

Immunohistochemical study of permeability glycoprotein expression in canine perianal tumors

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Abstract

Perianal gland tumors are androgenic hormone-dependent and commonly found in dogs. Permeability glycoprotein (PGP) is a member of the ATP-binding cassette transporter family, playing an essential role in reducing intracellular drug concentration and limiting drug cytotoxicity in cancer cells, leading to multi-drug resistance. This study aims to investigate PGP expression patterns in perianal gland tumors. Sixty-four specimens from 64 dogs were histologically classified as perianal gland adenoma (59.38%), perianal gland epithelioma (12.50%), and perianal carcinoma (28.13%). All samples are analyzed for PGP expression using immunohistochemistry, scoring for percentage positivity and intensity. Four cases (6.25%) have a positive expression of PGP with intense cytoplasmic staining. There was a significant difference in the PGP expression pattern among the groups *($p=0.01$)*. The expression of PGP may provide valuable insights into disease prognosis and prediction of clinical outcomes of chemotherapy treatment in dogs with perianal gland tumors.

Keywords: Dogs, Immunohistochemistry, Perianal gland tumor, Permeability glycoprotein expression.

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INTRODUCTION

A perianal tumor originates from a modified sebaceous gland, also known as a circumanal gland tumor or hepatoid gland tumor, located along the ventral midline from the perineum to the base of the skull, dorsal and ventral parts of the tail and the skin of the lumbar and sacral regions (Simeonov, 2019). Perianal gland tumors represented the sixth most common neoplasms, accounting for 4.62% of all canine cutaneous tumors in a previous study (Martins et al., 2022). Generally, canine perianal tumors can be classified into two types based on their behavior: benign (perianal adenoma) and malignant (perianal epithelioma and perianal carcinoma). A perianal adenoma is an androgenic hormone-dependent tumor commonly found in intact male dogs but rare in spayed males and females (Pereira et al., 2013). This tumor is the most common type, accounting for 58% to 96% of all canine perianal tumors (Berrocal et al., 1989; Petterino et al., 2004).

Perianal carcinoma is a rapid-growing tumor that commonly metastasizes to regional lymph nodes or distant organs (McCourt et al., 2018). Surgical excision of the cancer, together with hormone therapy, is the treatment of choice for perianal adenoma (Wilson and Hayes Jr, 1979; Brodzki et al., 2023). On the contrary, perianal carcinomas do not regress following castration and hormonal therapy. Patients without lymph node involvement and distant metastases are usually treated by a wide surgical excision in combination with cryosurgery or radiation (Tozon et al., 2005; Withrow et al., 2013). Moreover, electrochemotherapy is a choice, demonstrating a more effective, safe, and cost-effective local approach for the treatment of primary perianal tumors in dogs, especially in perianal adenoma and epithelioma (Tozon et al., 2010).

Several studies have demonstrated the expression of permeability glycoprotein (PGP), a member of the ATP-binding cassette (ABC) transporter family, in various tissues, including gastrointestinal epithelium, alveolar, blood-brain barrier, bronchiolar and bronchial epithelia, pancreatic ducts, renal distal tubules, salivary glands, bile canaliculi and ducts, adrenal glands, thyroid gland, urinary bladder, gall bladder, lymphocytes, and endothelia of various organs of both humans and dogs (Van der Heyden et al., 2011a; Saeed et al., 2014; Levi et al., 2019). PGP plays an essential role in human normal cells, acting as a protective mechanism against noxious xenobiotics (Bosch and Croop, 1996). For example, in the blood-brain barrier, PGP is highly expressed at the luminal side of the endothelial cells, where it acts as an efflux transporter, extruding substances from the brain to the blood (Demeule et al., 2001; de Lange, 2004; Lee and Bendayan, 2004). In addition, PGP pumps xenobiotics from intracellular space back to the capillary lumen and maintains the integrity of the blood-brain barrier while reducing the cerebral accumulation of substrate drugs (Stępień et al., 2012). Furthermore, PGP plays an essential role in maintaining homeostasis in the CNS, protecting the brain from an accumulation of potentially toxic substances (Fromm, 2004). PGP is also found in the brain capillaries, where it can restrict lipophilic drugs into the brain and export substances, such as beta-amyloid, from neuroparenchyma (Waghray and Zhang, 2017). In oncology, PGP acts as a pump drug out of cancer cells, reducing the intracellular drug concentration and limiting the cytotoxicity of the drug at its cellular site of action. Overexpression of PGP is one of the major factors leading to the multi-drug resistance phenotype (Sharom, 2011), resulting in cancer cells becoming resistant to a variety of commonly used antineoplastic drugs, including anthracyclines (doxorubicin, daunorubicin), vinca alkaloids (vincristine, vinblastine), taxanes (paclitaxel, docetaxel), epipodophyllotoxins (etoposide, teniposide), antibiotics (actinomycin D, mitomycin D), camptothecins (irinotecan, SN-38), and others (Bosch and Croop, 1996).

Therefore, the expression of PGP has been used as a prognostic factor for influencing treatment outcomes and patient prognosis in various human cancers. According to several studies, a high level of PGP expression has been associated

with poor response rates, shorter disease-free interval time, shorter survival time, and treatment failure after chemotherapy (Ieiri, 2012; Alfarouk et al., 2015).

In the veterinary field, few reports have described PGP expression in canine mammary tumors (Levi et al., 2016), lymphoma (Zandvliet et al., 2014), and transmissible venereal tumors (Chang et al., 2017). To our knowledge, no reports have described PGP expression in perianal gland tumors. Therefore, this study represents the expression pattern of PGP in canine perianal tumors. It may be used as a predictive biomarker in therapy and lead to the effective development of target treatment approaches, ultimately improving patient outcomes.

MATERIALS AND METHODS

Data collection

Formalin-fixed canine perianal gland tumor samples submitted from the Small Animal Hospital, Chiang Mai University Animal Hospital, Faculty of Veterinary Medicine, Chiang Mai University (between January 2015 and December 2020) were included in this study. The dogs had not received chemotherapy at the time of the biopsy. Medical information includes signalment, clinical signs, physical examination, and hematological and blood chemical profiles. All samples were re-examined independently by certified veterinary pathologists. The research protocols were approved by the Animal Ethics Committee of the Faculty of Veterinary Medicine, Chiang Mai University (S29/2563).

Immunohistochemical expression of PGP

After deparaffinization and rehydration, paraffin tissue sections 4-μm thick were immersed in a citric acid buffer with a pressure cooker for 30 min for antigen retrieval. All tissue sections were immersed in 10% hydrogen peroxide in methanol at room temperature and then incubated in 8% skim milk at 37 °C for 30 min to block non-specific reactions. All tissue sections were applied with 1:50 primary antibodies (rabbit anti-CD243 (ABCB1, P-glycoprotein 1) monoclonal antibody; Biolegend®, California, USA) at 4 °C overnight in a humidified chamber. The sections were then rinsed with Tris-buffered saline (TBS), applied with a biotinylated secondary antibody (ready-to-use; KPL, Seracare, Massachusetts, USA) at 37 °C for 1 hr, and subsequently incubated with streptavidin/HRP reagent (1:300, DAKO, Denmark A/S, Glostrup, Denmark) at room temperature for 40 mins. All tissue sections were rinsed with TBS before treatment with a DAB reagent set (ready-to-use; KPL, Seracare, Massachusetts, USA) and then counterstained with Mayer's hematoxylin (Biooptica, Italy). Normal canine liver was used as a positive control.

Immunoreactive score

According to a previous study, the immunoreactive score (IRS) system was evaluated using staining intensity and the percentage of positive tumor cells (Chang et al., 2017). Each sample was randomly examined using 20 high-power fields. Within each visual field, 100 cells were counted and randomly selected from various areas within each section. Staining intensity was assigned as follows: 0 = negative, 1 = weak, 2 = moderate, and 3 = strong in comparison with the expression level of the positive control. The percentages of positive tumor cells were classified as follows: 1 = < 10% positive tumor cells; 2 = 10–50% positive tumor cells; 3 = > 50% positive cells. The positive tumor cells were counted in randomly selected areas (hpf). The final score (0 to 9) was obtained by multiplying the information. The overall score was as follows: 0 to 1 = negative, 2 to 4 = weak, and 6 to 9 = strong (Chang et al., 2017).

Statistical analysis

The Kruskal-Wallis rank sum test and Pearson's Chi-squared test were used to analyze the immunoreactive score in all groups. Kaplan-Meier analysis was used to assess the median survival time. A p-value <0.05 was considered statistically significant.

RESULTS

Clinical characteristics

Sixty-four dogs were examined in this study: 60 males (93.75%) and four females (6.25%). The average age was 11.15 years (3 to 20 years). The sample comprised mixed breed dogs (n=20, 31.25%), Shih Tzus (n=18, 28.13%), Poodles (n=6, 9.38%), Siberian Huskies (n=6, 9.38%), Cocker Spaniels (n=3; 4.69%), Chihuahuas (n=2, 3.13%), Golden Retrievers (n=2, 3.13%), Miniatures n=2, 3.13%), Thai Bangkaews (n=2, 3.13%), Dachshunds (n=1, 1.56%), Dalmatians (n=1, 1.56%), Labrador Retrievers (n=1, 1.56%), and Spitz (n=1, 1.56%). The tumors were often observed in the perineal areas (n=56; 87.50%) and sometimes in tails (n=4; 6.25%), prepuces (n=3; 4.69%), and the inguinal area (n=1; 1.56%) (Figure 1).

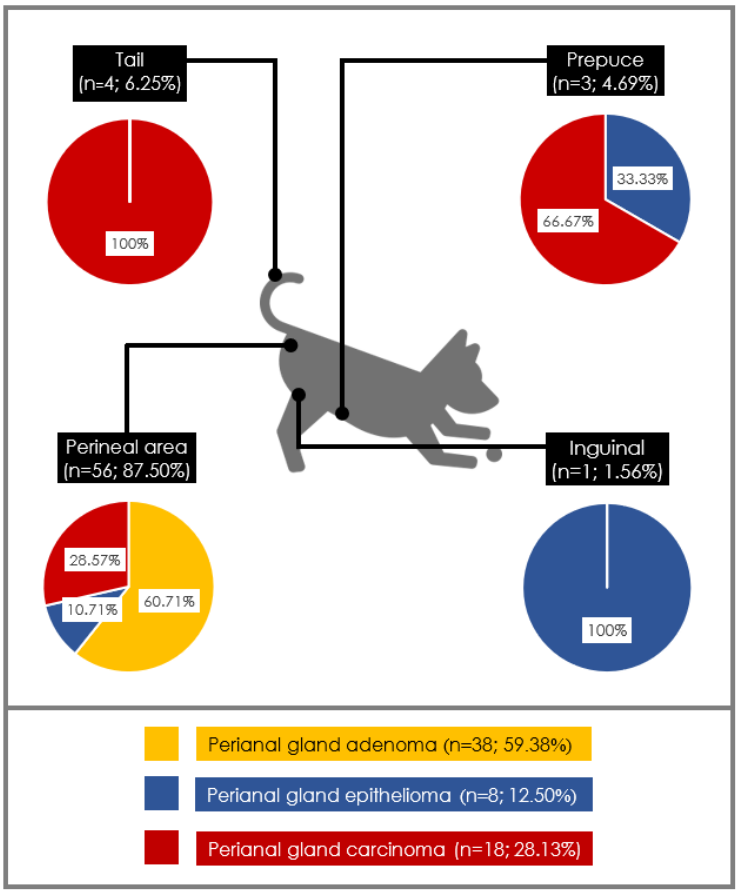

Figure 1 Anatomical locations of canine perianal gland tumor and the relative frequency of histological classification in each site

Histology

Sixty-four specimens were histologically classified into three groups as follows: perianal gland adenoma (n=38; 59.38%), perianal gland epithelioma (n=8; 12.50%), and perianal gland carcinoma (n=18; 28.13%) (Figures 1 and 2A–2C).

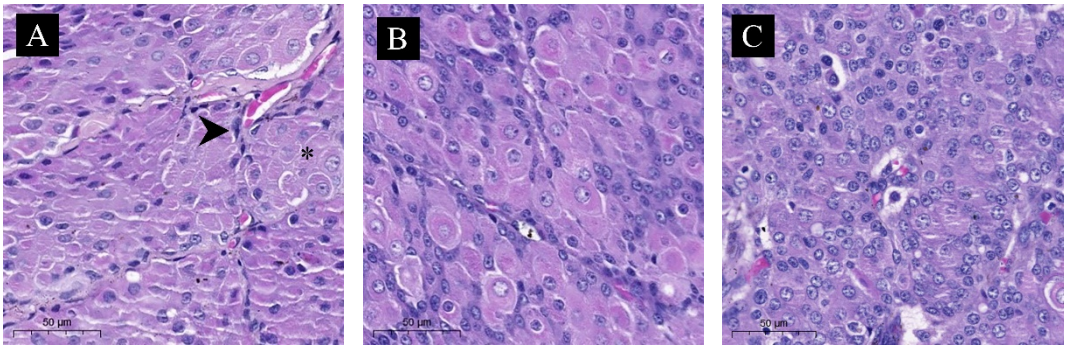

Figure 2 Perianal gland tumor. Dog. **(**A) Perianal gland adenoma: the tumor consists of reserve cells (arrowhead) and hepatoid cells (asterisk). The former is located surrounding the lobules of hepatoid cells with typical glandular architecture. (B) Perianal gland epithelioma; proliferating basaloid reserve cells are observed. (C) Perianal gland carcinoma, which is a poorly differentiated hepatoid cell, is observed. These cells are dissociated by reserve cells. Coarse chromatin pattern, anisocytosis, anisokaryosis, anisonucleoliosis, and angular nucleoli are noted. HE. Scale bar = 50 µm.

Immunohistochemical expression of p-glycoprotein (PGP)

Out of 64 perianal tumors, 47 (73.44%) revealed negative immunoreactivity to PGP (Table 1, Figure 3A). Diffuse cytoplasmic immunoreactivity to PGP was observed in 17 tumors (26.56%, Table 1). Tumor cells (6.25%) in four cases were positive for PGP with intense cytoplasmic staining (Figure 3B). Variable or weak cytoplasmic PGP immunoreactivity was noted in 13 cases (20.31%, Figure 3C). There was a significant difference in the PGP expression among the groups (p=0.01). Moreover, there was a significant difference in the positive PGP expression between the adenoma and carcinoma groups (p=0.01).

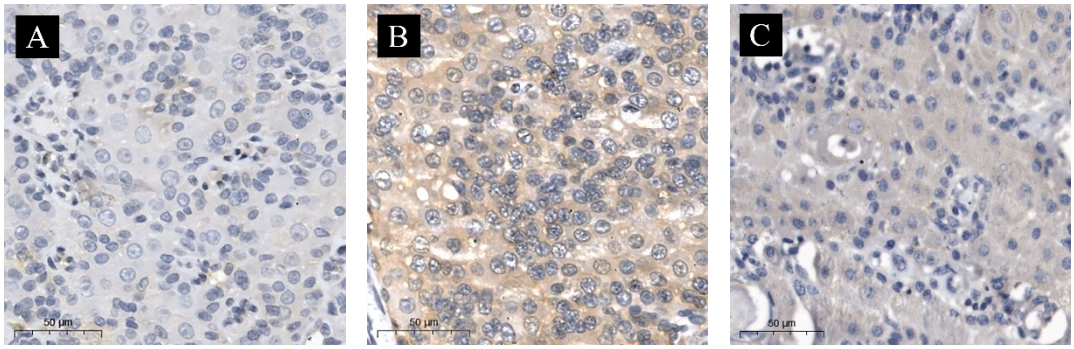

Figure 3 Perianal gland tumor. Dog. (A) Perianal gland adenoma with negative PGP immunoreactive score. (B) Perianal gland carcinoma with strong PGP immunoreactive score. (C) Perianal gland carcinoma with weak PGP immunoreactive score. IHC. Hematoxylin counterstain. Scale bar = 50 µm.

Table 1 Immunoreactive score in canine perianal gland tumor

Type	Immunoreactive score			Total
	Negative	Weak	Strong	
Adenoma	84.21% (32/38)	13.16% (5/38)	2.63% (1/38)	59.38% (38/64)
Epithelioma	87.50% (7/8)	12.50% (1/8)	0% (0/8)	28.13% (8/64)
Carcinoma	44.44% (8/18)	38.89% (7/18)	16.67% (3/18)	12.50% (18/64)
Total	**73.44% (47/64)**	**20.31% (13/64)**	**6.25% (4/64)**	**64**

Table 2 Immunoreactive score in each sample

Histological diagnosis	Immunoreactive score	Sample No.
Hepatoid gland adenoma	0	1,2,3,4,5,6,7,8,9,10,11,13,15,16,18, 21,22,24,25,26,29,30,33,34,36,38
	1	17,19,20,27,32,37
	2	12,31,35
	3	23,28
	4	14
Hepatoid gland carcinoma	0	39,40,42,45,49,51,53
	1	48
	2	41,46,56
	3	44,47
	4	43,54
	6	50,52,55
Hepatoid gland epithelioma	0	57,58,60,61,62,63
	1	59
	3	64

Survival time

The median survival times for dogs with perianal gland adenoma, epithelioma, and carcinoma were 530 days, 456 days, and 362 days, respectively. However, the median survival time was not statistically significant among these groups (Figure 4).

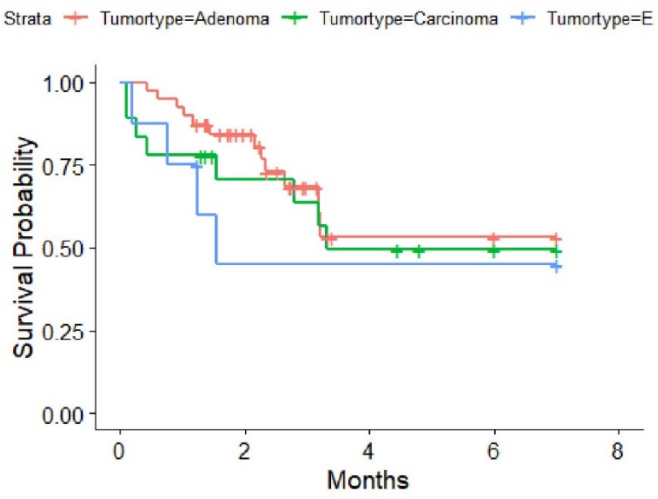

Figure 4 Kaplan-Meier survival curve of canine perianal gland tumor

DISCUSSION

In this study, most perianal gland tumor cases developed around the perianal area. Furthermore, these tumors had been found at the tail, inguinal region, and prepuce. In this research, perianal gland tumors were commonly observed in male dogs, particularly in mixed breeds, which differed from previous studies (Vail et al., 1990; Thomas and Fox, 1998; Petterino et al., 2004; Jakab et al., 2009; Kim et al., 2018). The etiology of perianal gland tumors remains unclear, but there is evidence to show that androgenic hormones, especially testosterone, might play a role in their development. The androgen binding sites identified in perianal adenomas indicate that androgenic hormones stimulate these tumors (Kim et al., 2018; Stern et al., 2018). In line with this, the present study demonstrates that intact male dogs exhibit a higher incidence of perianal gland tumor development than neutered male and female dogs.

PGP is a membrane protein found in various tissues throughout the human body, playing a role in cellular defense mechanisms and drug transport. PGP is also involved in multi-drug resistance in cancer cells. The results of this study indicate that 17 perianal gland tumor samples (26.56%) expressed PGP. The strong immunoreactive score of the malignant group was statistically significantly higher ($P=0.015$) compared to the benign group. These results align with previous studies in that most malignant tumor cases expressed PGP. Overexpression of this protein in cancer cells indicates drug (chemotherapy) resistance (Schneider et al., 1989; Linn and Giaccone, 1995; Baekelandt et al., 2000; Szakács et al., 2006; Kim et al., 2016).

The correlation of PGP expression with the survival rate, metastasis, tumor invasiveness, and the overall tumor, node, metastasis (TNM) stage has been demonstrated in several studies on humans and animals (Baekelandt et al., 2000; Van der Heyden et al., 2011b; Kim et al., 2016; Chang et al., 2017). PGP expression, therefore, seems to be used as a potential biomarker for cancer prognosis. The overexpression of this protein correlates with the possibility of lymph node metastasis, short disease-free survival and overall survival, and poor prognosis. In contrast, malignant cases with negative PGP seemed to have a better chemotherapy response (Baekelandt et al., 2000; Kim et al., 2016). In the present study, most perianal gland carcinoma cases expressed PGP and had the lowest median survival time compared with benign cases. Furthermore, our study demonstrated that the carcinoma group with a strong PGP score had a poor prognosis and the lowest median survival time compared to other groups. Therefore, we postulate that perianal carcinomas may not respond to chemotherapy. The results also revealed that only one sample from the adenoma group had a robust immunoreactive score. Several studies have demonstrated that various benign canine tumors, such as hepatoma, adrenal gland adenoma, and colorectal adenoma, expressed PGP (Weinstein et al., 1991; Ginn, 1996). Therefore, we postulate that a benign perianal tumor in dogs may express this protein. The limitations of this study were the small sample size, especially in the epithelioma and carcinoma groups. It might not be considered representative of dogs in both groups. Increasing the sample size might improve because of positive expression.

PGP expression patterns were not only used as a potential biomarker for cancer prognosis but also used as the decision to use targeted inhibitors of PGP in several human cancers to improve the therapeutic effects (Nanayakkara et al., 2018). In veterinary medicine, a PGP inhibitor (e.g., verapamil) was used as a competitive inhibitor to enhance the sensitivity of ivermectin (Ardelli and Prichard, 2013). However, no studies have demonstrated the effect of PGP inhibitors on cancer patients. Therefore, for further research, the application of this agent for chemoresistance in cancer to improve treatment outcomes should be considered.

In conclusion, altered expression of PGP may predict a chemotherapeutic response in canine perianal gland tumors. For further study, we would like to investigate the correlation between chemotherapy responsiveness and other parameters of malignant perianal gland tumors (i.e., metastatic rate and overall survival time) between the positive and negative PGP expression tumors. This investigation may provide valuable insights into disease prognosis and chemotherapy-based therapy outcomes in dogs with perianal gland tumors. Furthermore, this data can be used for further treatment plans or preventive care, such as recommendations for owners and veterinarians about early-age castration or health check-up programs.

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AUTHOR CONTRIBUTIONS

Authors 4 persons, participation in each of the following:

Nutchanon Pichaiya: Contribute to the conception and design of the study, Analyze and interpret the data (immunohistochemical examination and median survival time), Draft and revise the manuscript.

Pitchaya Matchimakul: Comment the manuscript.

Jirapat Arunorat: Comment the manuscript.

Atigan Thongtharb: Contribute to the conception and design of the study, Analyze and interpret the data (histopathological examination), Comment the manuscript.

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