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Canine Anal Sac Adenocarcinomas: Clinical Presentation and Response to Therapy

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A retrospective study of 43 dogs with anal sac adenocarcinoma (ASAC) was performed to characterize the clinical presentation and response to treatment. Clinical signs at presentation varied considerably, with signs related either to sublumbar nodal metastasis (tenesmus or constipation) or hypercalcemia (polyuria-polydipsia and anorexia) being the most frequent findings. At the time of presentation, 23 (53%) dogs had hypercalcemia and 34 (79%) had metastases, with the regional lymph nodes (31 dogs, 72%) being the most common site of metastasis. A variety of chemotherapeutic agents were administered, with partial remission (PR) recorded in 4 of 13 (31%) dogs treated with cisplatin and in 1 of 3 (33%) dogs treated with carboplatin. The median survival for all dogs was 6 months (range, 2 days–41 months). There was no statistical association between the presence of hypercalcemia and survival, although the power of the study to detect an increase in survival of 3 months was low (.33). We conclude that platinum chemotherapy has antitumor activity in canine apocrine gland carcinoma and that further study of these agents is warranted.

Key words: Anal tumors; Chemotherapy; Dog; Surgery.

Anal sac disease in the dog is common and affects approximately 12% of the canine population.[1] The majority of anal sac disease consists of impactions and infections,[1] with neoplasia being an uncommon occurrence.[2] Tumors in the perineal area, however, are common in the dog, with the majority being adenomas of the perianal glands.[3] Perianal adenomas are seen most frequently in intact male dogs because of the tumor's testosterone dependence.[3] The most common malignancy in the perineal area in older female dogs is anal sac adenocarcinoma (ASAC). These tumors arise from the apocrine glands of the anal sac.[3] ASAC accounts for approximately 2% of skin tumors in the dog.[2]

ASACs are malignant neoplasms with a propensity to metastasize initially to the regional lymph nodes, and then to the liver, spleen, lungs, and other sites.[4,5]

Reports of ASAC are limited in the veterinary literature.[2–5] There is some conflicting information regarding gender predisposition. In 2 reports, 11 of 14[4] and 30 of 32[5] dogs with ASAC were female. A large study of 238 dogs, however, suggested a similar occurrence in males and females, with 56% being female.[2] ASAC is a disease of older dogs, with the mean age at presentation reported to be 10.2–10.8 years, having a range of 3–17 years.[2–5] There is limited information on breed predisposition. German Shepherds accounted for 3 of 14[4] and 4 of 32[5] patients in 2 small studies. In the larger report of 238 dogs, several breeds including the English Cocker Spaniel, Dachshund, Alaskan Malamute, English Springer Spaniel, and German Shepherd were reported to be at increased risk of developing ASAC.[2]

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Clinical signs of ASAC are varied, and signs relate to the size of the tumor at presentation and whether hypercalcemia is present. In a study of 32 dogs with ASAC, the diagnosis was made as an incidental finding in 11 dogs. Tenesmus, constipation, or change in stool shape was observed in 10 dogs, a perineal swelling was present in 9 dogs, and polyuria and polydipsia were noted in 5 dogs. A variety of other clinical signs were seen in the remaining dogs and included limb swelling and dysuria.[5] In another study of 14 dogs with ASAC, the major complaint was perineal swelling (11 dogs), and the tumor was an incidental finding in the remaining 3 dogs.[4]

In dogs that presented with polyuria and polydipsia, hypercalcemia was usually present. Polydipsia, polyuria, and hypercalcemia have been reported to be due to parathyroid hormone-related polypeptide produced by the tumor cells.[6–9] This results in pseudohyperparathyroidism or hypercalcemia of malignancy, the most common cause of hypercalcemia in the dog.[10] In the study of 32 dogs with ASAC, hypercalcemia was present in 8 dogs, only 5 of which had polydipsia and polyuria.[5]

ASAC has been treated with surgery, chemotherapy, and radiation. There is limited information on the results of these treatments. In the study of 32 dogs, 27 underwent resection of the primary tumor. Ten of the 27 dogs also had removal of the iliac lymph nodes. Of the 27 dogs having surgery, the median survival was 8.3 months (mean, 12.7 months) in 21 dogs that survived at least 1 month after surgery. Hypercalcemia and metastasis at the time of diagnosis were poor prognostic factors. The median survival of dogs with either hypercalcemia or metastasis was 6 months, compared to 11.5 months for dogs with normocalcemia and 15.5 months for those free of metastasis. Only 3 dogs received chemotherapy (doxorubicin and cyclophosphamide), with a median survival of 2 months.[5]

This retrospective study was performed to determine the response of anal sac tumors to therapy in order to identify potential treatments that could be tested in prospective clinical trials.

Materials and Methods

The Veterinary Medical Data Base was used to identify medical records of dogs with ASAC at the Purdue University Veterinary Teaching Hospital from 1980 to 2000. Inclusion criteria included a histo-

pathologic diagnosis of apocrine gland adenocarcinoma of the anal sac, clinical staging information that included at least abdominal radiographs or abdominal ultrasonography and thoracic radiographs, and a complete historical, clinical, and clinicopathologic record. The histopathological diagnoses were reviewed by a boarded pathologist (DBD). Follow-up information was obtained from the medical record and, where applicable, by telephone contact with the owner or referring veterinarian. Responses to chemotherapy were classified as follows: complete remission (CR)—complete clinical resolution of the tumor; partial remission (PR)—reduction in tumor volume ≥50%; stable disease (SD)—tumor size remaining within 50% of the original size; and progressive disease (PD)—increase in tumor volume ≥50% or new lesions being present. The response was assessed on the dog's total tumor burden and was based on radiographic or ultrasonographic measurements in 3 dimensions for all lesions. In animals that had had surgery, the response was assessed from the postoperative measurements of disease. Survival was measured from the time of diagnosis to the time of death, or if that date was not known, the dog was censored from the data at the date the dog was last known to be alive. At the time of writing, all dogs were either dead or lost to follow-up. Dogs that were discharged from the hospital alive and had no follow-up from that time were not included in the survival analysis. Postmortem examination information was available for 1 dog.

The distribution of survival time for dogs with hypercalcemia compared with dogs that had normocalcemia and the comparison between the different treatment groups were computed by product-limit survival estimates.[a] Comparisons of equality of survival time over the strata were done by log-rank and Wilcoxon statistical tests. A difference in survival of 3 months was considered clinically significant. A P value $<.05$ was considered statistically significant. Post hoc analysis of power to detect a 3-month increase in survival was performed on the comparison of survival between the dogs that were normocalcemic and those that were hypercalcemic, and this was .33. It was estimated that at least 50 dogs would need to be in each group to achieve a power of .80 and to detect the clinically significant difference of 3 months.

Results

Forty-three dogs were included in this study. There were 25 males (2 intact) and 18 females (3 intact). The most common breed was mixed breed (19 dogs). There were 16 purebreds, including the German Shepherd (3), Golden Retriever (3), Cocker Spaniel (2), Bouvier des Flandres (2), Labrador Retriever (2), Shetland Sheepdog (2), and 1 each of Standard Poodle, Miniature Poodle, Boxer, Dachshund, Maltese, Border Collie, Irish Setter, Alaskan Malamute, Lhasa Apso, and Brittany Spaniel. The age at presentation ranged from 7 to 19 years, with a median of 11 years. Most dogs had more than 1 presenting complaint, and there was no clear relationship between the various findings (Table 1). A large number of the dogs with tenesmus were found to have enlarged sublumbar lymph nodes but not large masses in the anal area.

Twenty-two dogs (51%) had hypercalcemia. Serum calcium concentrations in the dogs with hypercalcemia (corrected for abnormalities in albumin) ranged from 12.7 to 21.7 mg/dL (reference range, 8.9–12.6 mg/dL), with a mean of 15.0 mg/dL. Three of the dogs with hypercalcemia, but none of the dogs with normocalcemia, had azotemia at the time of initial presentation. None of the azotemic dogs were previously known to have renal disease, and the azotemia did not resolve with resolution of the hypercalcemia. Hypercalcemia resolved in all dogs after medical management or removal of all the tumor. In dogs whose tumor was completely removed (n = 4), there was no continuing therapy given, and these dogs remained normocalcemic. In 3 dogs, recurrence of hypercalcemia was documented at the time of relapse of ASAC.

Table 1. Presenting complaint by owner at the referring veterinarian in 43 cases of ASAC.

Presenting Complaint	No. Cases (%)
Rectal mass	11 (26)
Tenesmus	11 (26)
Anorexia or inappetence	9 (21)
Polyuria/polydipsia	7 (16)
Lethargy	5 (12)
Weight loss	4 (9)
Urinary incontinence	4 (9)
Constipation	4 (9)
Posterior weakness	4 (9)
Presented for routine examination	3 (7)
Stranguria	2 (5)
Abnormal stool shape	2 (5)
Not feeling well	2 (5)
Fresh blood on stool	2 (5)
Vomiting	1 (2)
Lameness	1 (2)
Scooting	1 (2)
Dyspnea	1 (2)

ASAC, anal sac adenocarcinoma.

Metastases were found by clinical staging or postmortem examination on initial presentation in 34 dogs (79%). The sites of confirmed and presumptive metastases were regional lymph nodes in 31 dogs (this was the only site in 13 dogs), lungs in 8 dogs, liver in 7 dogs, spleen in 6 dogs, bone-lumbar vertebrae in 1 dog, femur in 2 dogs, inguinal lymph node in 2 dogs, and pancreas, heart, and mediastinum (in 1 dog each). These sites were confirmed histopathologically or cytopathologically in 24 dogs.

Fifteen dogs underwent surgery. In 11 dogs, resection of the primary tumor was performed. Recurrence at the surgical site occurred in 5 of these 11 dogs (45%), with a median time to recurrence of 10 months. In 5 of the 11 dogs with primary tumor resection, surgery was palliative in intent, as metastases were present at the time of the surgery. The regional lymph nodes alone were debulked in 4 dogs, and they were debulked in conjunction with removal of the primary tumor in 1 dog.

Chemotherapy was administered to 20 dogs (Table 2). Eleven dogs received more than 1 drug. No animals achieved a complete response. In all of the dogs receiving chemotherapy, mild gastrointestinal adverse effects were reported in 5 (25%), but this did not lead to dose reduction. Azotemia developed in 5 dogs receiving cisplatin[b] and in 1 dog receiving carboplatin.[c] Clinically evident renal failure was not seen in any dog. Azotemia was seen in 4 of the 5 dogs that achieved a PR. One of the 2 dogs receiving 5-fluorouracil[d] had seizures and died, but on postmortem examination, a meningioma and meningitis were found. In the dogs receiving chemotherapy alone, 11 received at some time a platinum agent, with 1 dog receiving only nonconventional agents such as mithramycin and vincristine. The other drugs were administered mostly after there was a fail-

Table 2. Responses to chemotherapy in dogs with ASAC.

Drug	No. Dogs (%)	Response to Treatment[a]
Cisplatin	13 (30)	PR 4 (31%)
		SD 1 (8%)
		PD 8 (61%)
Carboplatin	3 (7)	PR 1 (33%)
		SD 2 (67%)
Doxorubicin[h]	4 (9)	SD 2 (50%)
		PD 2 (50%)
Actinomycin D[i]	4 (9)	PD 4 (100%)
5-Fluorouracil	2 (5)	PD 2 (100%)
Mithramycin[j]	1 (2)	PD 1 (100%)
Vincristine[k] and cyclophosphamide[l]	1 (2)	PD 1 (100%)
Melphelan[m]	1 (2)	PD 1 (100%)
Epirubicin[n]	1 (2)	PD 1 (100%)
Mitoxantrone[o]	1 (2)	PD 1 (100%)

ASAC, anal sac adenocarcinoma.

[a] PR, partial remission (≥50% reduction in tumor size); SD, stable disease (<50% change in size of tumor within a 1-month period); PD, progressive disease (≥50% increase in tumor size within 1 treatment period or any new tumor lesions).

ure of response to a platinum agent, and 1 dog received both cisplatin and carboplatin. The dogs that achieved a partial response to chemotherapy had a median survival of 13 months, compared to a median survival of 8 months in those dogs that received chemotherapy and failed to have a response. This difference was not statistically significant.

Palliative medical care alone was used in 10 dogs. This consisted of piroxicam[e] in 7 dogs and a combination of short-term IV fluids, prednisone,[f] and furosemide[g] for hypercalcemia in the 3 remaining dogs. All dogs that were hypercalcemic received medical treatment for this in addition to other therapies, which most often consisted of a combination of IV fluids and furosemide. Piroxicam was also used as a palliation after the failure of chemotherapy in 2 dogs and the failure of surgery and chemotherapy in 1 dog.

Survival data were available for 34 dogs (Table 3; Figs 1, 2). There were no statistically significant differences in survival between the different treatment groups or between the dogs with normocalcemia and hypercalcemia. There were insufficient numbers of animals within a treatment group to assess the effects of hypercalcemia within the group. Hypercalcemia did not appear to be related to tumor volume or stage.

In the 20 dogs for which the cause of death was known, euthanasia was the most common cause (11 dogs, 55%). This was most often because of debilitation or an inability to defecate or urinate. Other causes of euthanasia included relapse and renal failure. In all dogs, the cause of death was tumor related.

Discussion

In this study, a gender predisposition was not observed, and clinical presentation was similar to that previously reported.[3–5] There was a wide diversity of historical and clinical signs associated with ASAC. Approximately half of the dogs were presented to the referring veterinarian with no historical signs that suggested anal sac disease. In a large number of dogs, the clinical and historical signs were related to metastases in the regional lymph nodes or to paraneoplastic hypercalcemia. Clinical signs were present for approximately 2–3 weeks in the majority of patients. The exception to this was that 2 dogs had a palpable mass that was present for up to 1 year before presentation. When a mass was known to be present and not surgically removed, the reason was usually owner reluctance for surgery in an older patient.

Hypercalcemia was found in 51% of the dogs in this series. This is in contrast to the only other study in which data on the presence of hypercalcemia were included (25% of dogs).[5] In this series, only 7 of the 22 dogs with hypercalcemia had detectable polyuria and polydipsia. The 4 dogs that were incontinent had concurrent polyuria and hypercalcemia, which were probably contributing factors. It is important to determine if a serum calcium concentration as hypercalcemia poses a risk for renal failure and soft tissue calcification.[11]

In 16 of the dogs (37%), enlargement of the iliac lymph nodes caused the presenting clinical signs. The degree of enlargement of the sublumbar lymph nodes can be massive. Small, less invasive primary tumors were unlikely to cause clinical signs. Larger, more invasive primary tumors resulted in clinical signs.

Surgery has been considered the most appropriate therapy for ASAC with no evidence of metastatic disease at the time of presentation.[3–5] There is information that surgery can still be helpful when the metastases are confined to regional lymph nodes. Surgery can be palliative, al-

Table 3. Survival data for dogs with ASAC and follow-up available.

Group	No. Dogs (% dogs with data)	Median Survival (months) (95% CI)	Range of Survival
All dogs	34 (100)	8.7 (7.0–11.6)	2 days–41 months
Palliative care[a]	10 (29)	8.7 (3.6–9.6)	2 days–9 months
Chemotherapy alone	12 (35)	8.7 (1.2–13.5)	1–14 months
Surgery alone	8 (24)	7.9 (1.4–41.7)	2 days–41 months
Surgery and chemotherapy	4 (12)	14.4 (11.4–22.7)	9 months–22 months
Dogs with hypercalcemia	18 (53)	7.7 (1.4–11.6)	2 days–14 months
Dogs with normocalcemia	16 (47)	11.4 (8.7–17.3)	2 days–41 months

ASAC, anal sac adenocarcinoma; CI, confidence interval.

[a] Palliative care = piroxicam in 7 dogs and short-term IV fluids followed by furosemide and prednisone in 3 dogs.

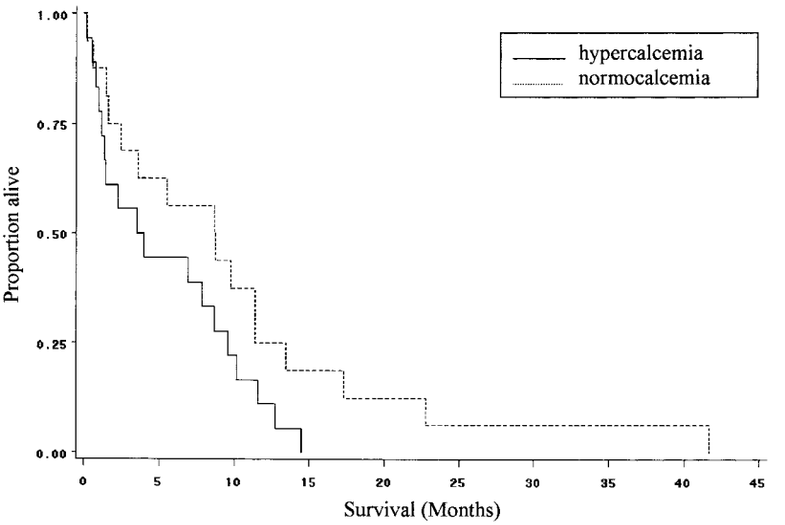

Fig 1. Kaplan-Meier survival curves for dogs with hypercalcemia (n = 18) and normocalcemia (n = 16).

though there is a fairly high morbidity and mortality, with hemorrhage being the major complication. The only surgery-related death in this study was in a dog that had debulking of the iliac lymph nodes. Radiation therapy has also been reported to control local disease and regional lymph node metastases.[12] In patients with the spread of ASAC beyond regional lymph nodes, chemotherapy is of most potential benefit. The platinum drugs had antitumor activity in this study. Because ASAC may progress slowly in some patients, it is not possible to know if SD with chemotherapy was truly a drug effect or simply a reflection of slow tumor progression in the follow-up interval.

There was no marked decrease in survival in dogs that had hypercalcemia. As mentioned in Materials and Methods, there was a low power in this study, and therefore, an increased chance of a type II error (ie, missing a clinically significant difference). This was because of the small number of dogs in the study and the wide variance seen in the survival. The median survival of 7.9 months in the dogs with hypercalcemia appears less than the median survival of 11.4 months in the dogs without hypercalcemia, but this did not reach statistical significance. All dogs became normocalcemic with either specific therapy or therapy of the primary tumor.

The dogs that had surgery alone had the shortest median survival time, which was even less than that of the dogs treated with palliative care only. This may be because the dogs that had only palliative care had less severe disease than those that had surgery, or it may be because the palliative care prolonged survival. It did appear from the medical records that the dogs treated with palliation had more advanced disease than the dogs treated with surgery alone. A number of dogs in this study that had palliative care received the nonsteroidal drug piroxicam, which may have

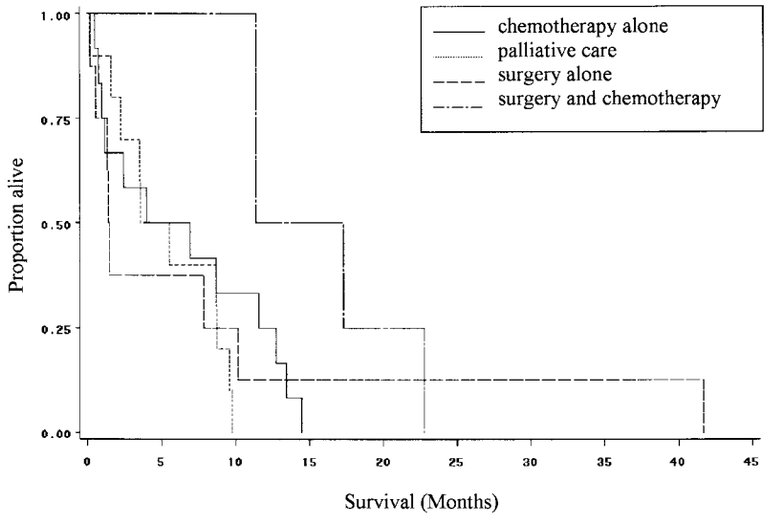

Fig 2. Kaplan-Meier survival curves for dogs treated with chemotherapy alone (n = 12), palliative care alone (n = 10), surgery alone (n = 8), and combined surgery and chemotherapy (n = 4).

some antitumor effects. There was no tumor response seen in any of the dogs treated, but tumor responses have been noted in other canine tumors. Piroxicam can also act as a modulator of the immune response or can potentially have an antiangiogenic effect, and this may also have played a role in the survival of the dogs treated with this agent.[13] The dogs that received the combination of chemotherapy and surgery appeared to have a longer survival time. Statistical analysis did not show a significant difference in survival between the various treatment groups. However, once again, the small numbers of dogs in each group and the wide range of the survival times would require large differences in survival to be detected by this small study.

The retrospective nature of this study leads to limitations, including the lack of a specific systematic protocol for treatment and evaluation. Also, supportive care has become more available for cancer-bearing dogs over the time that this study covered, which could alter the survival time. It was not possible to stratify the dogs with varying stages of disease into the various treatment groups, but it was determined that the distribution of dogs with hypercalcemia was similar in those treated with chemotherapy and those not.

The clinically important findings from this study suggest that there is a role for platinum chemotherapy in dogs with ASAC, especially when surgery or radiation therapy is declined or is not an option. This study did not show that there was a statistical survival benefit in those dogs that achieved a response to these drugs, but again, this may reflect the low power of the study to detect a difference. The findings in this retrospective study justify further prospective studies of platinum chemotherapy in ASAC. Information from further studies is needed before platinum chemotherapy can be recommended for dogs with ASAC, given the cost of treatment and the toxicity that was seen in this study. A benefit in either survival or quality of life would be needed.

Footnotes

[a] SAS/STAT User's Guide, Version 8, Vol 2, SAS Institute Inc, Cary, NC
[b] Platinol—AQ®, Bristol-Myers Squibb, Princeton, NJ
[c] Paraplatin®, Bristol-Myers Squibb, Princeton, NJ
[d] Adrucil®, Pharmacia & Upjohn, Kalamazoo, MI
[e] Feldene®, Pfizer, New York, NY
[f] Prednisone tablets, Roxane Labs, Columbus, OH
[g] Lasix®, Hoechst Marion Roussel, Kansas City, MO
[h] Adriamycin PFS®, Pharmacia & Upjohn, Kalamazoo, MI
[i] Cosmogen®, MSD, Iselin, NJ
[j] Plicamycin®, Bayer Corporation, West Haven, CT
[k] Oncovin®, Eli Lilly & Corporation, Indianapolis, IN
[l] Cytoxan®, Mead Johnson Oncology, Princeton, NJ
[m] Alkeran®, Glaxo Wellcome, Research Triangle Park, NC
[n] Ellence®, Pharmacia & Upjohn, Kalamazoo, MI
[o] Novantrone®, Immunex, Seattle, WA

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