

Clinical Presentation and Management of Five Dogs with Apocrine Gland Adenocarcinoma of Anal Sac

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Abstract : Five dogs diagnosed as apocrine gland adenocarcinoma (AGAC) of the anal sac based on cytology and/or histology. Mean age of these dogs was 11 years old. One dog treated with supportive care without other medical interventions for hypercalcemia was died one month after diagnosis. Other four dogs were treated with chemotherapy and one of these dogs was intervened with complete surgical resection. Two months after the diagnosis, one of the dogs treated with chemotherapy died. The survival time of other survived three dogs from the time of diagnosis was 19, 9, and 13 months respectively and they are still alive at this time. After chemotherapy, three dogs were managed generally in good body condition and maintained as similar in size as time of diagnosis. The results are suggested that it is worthwhile to try chemotherapy for managing AGAC in dogs especially complicated or metastasized to regional lymph nodes.

Key words : Anal sac, apocrine gland adenocarcinoma, chemotherapy, dog.

Introduction

Apocrine gland adenocarcinoma (AGAC) of the anal sac occurs at relatively low frequency in the dog, representing 17% of perianal tumors and 2% of all skin tumors. The average age of dogs diagnosed with this disease is 10 to 11 years. Once thought to be primarily a disease of female dogs, AGAC has since been shown to occur with approximately equal sex distribution (1-4).

AGAC in the dog are commonly reported to be malignant tumors with a high incidence of metastases and hypercalcemia. Approximately 51% dogs have metastases at the time of initial presentation. At presentation metastases to the regional lymph nodes (especially sublumbar lymph nodes) may be significantly larger than the primary tumor. The reported incidence of hypercalcemia ranges from 25% to 51% (7). The association between AGAC and paraneoplastic hypercalcemia of malignancy, mediated by tumor secretion of parathyroid hormone-related peptide (5,6), has been well documented. Clinical signs of AGAC can be related to space occupation by the primary or metastatic tumor (tenesmus, constipation, perineal discomfort and swelling, and change in shape of the bowel movement) and hypercalcemia (polyuria and polydipsia).

Workup for diagnosis includes complete physical examination, complete blood count, serum chemistry, urinalysis, x-ray,

ultrasonography, computed tomography (CT), fine needle aspiration (FNA), and biopsy.

Surgery and radiation therapy are the mainstays of treatment for this disease. If excision would compromise sphincter function or if the tumor is large, combined modality therapy including radiation and chemotherapy are recommended.

Five dogs were diagnosed with AGAC and were referred to the Veterinary Medical Teaching Hospital of Seoul National University between 2006 and 2008. This report is to describe five case studies of AGAC treated with carboplatin alone or combination with doxorubicin with or without surgical intervention.

Cases

In this report, survival time was defined as the time from diagnosis of the tumor to either the time of death or the date on which the dog was last known to be alive. Diagnostic work-up included complete physical examination, blood test (CBC, serum-chemistry), urinalysis, x-ray, ultrasonography, CT scan, FNA and biopsy.

Case 1

An eleven-year-old, neutered male English cocker spaniel was presented with a history of anorexia, weight loss, diarrhea, decreased frequency of defecation, and mass on the neck region.

Physical examination, radiography and ultrasonography demonstrated masses on the prescapular, anterior mediastinal, tracheobronchial, sternal and perineal region and multiple

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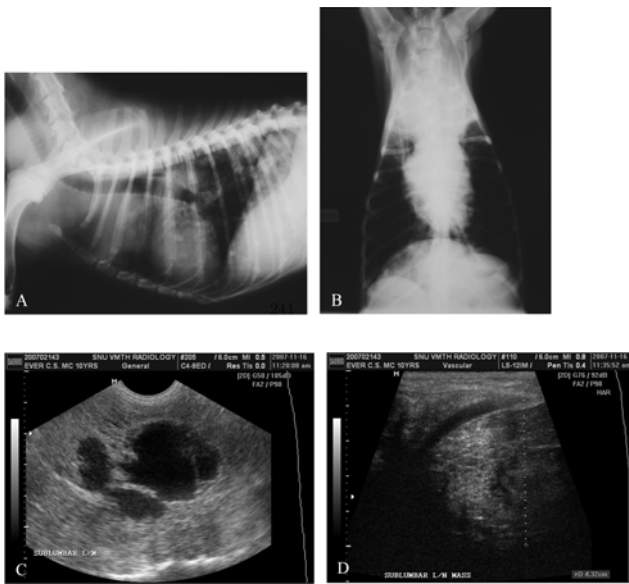


Fig 1. Lateral (A) and ventrodorsal (B) thoracic radiographs of case 1 showing multifocal pulmonary nodules, cranial mediastinal mass, cervical (prescapular) region mass, tracheobronchial and sternal lymphadenopathy. Ultrasonographic images (C, D) of case 1 showing extremely enlarged sublumbar lymph node with various cavitory lesions and irregular margination.

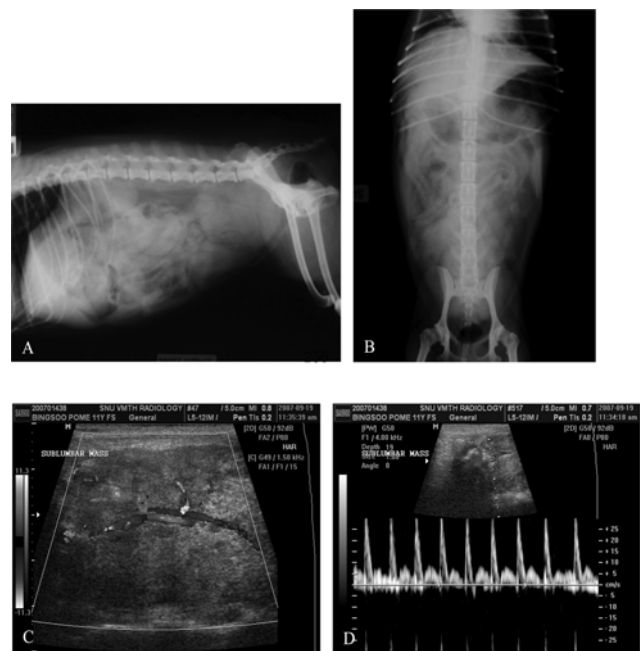


Fig 2. Lateral (A) and ventrodorsal (B) abdominal radiographs of case 2 showing a large, round soft tissue mass in the sublumbar lymph node region with ventral displacement of descending colon and urinary bladder. Ultrasonographic images (C, D) of case 2 showing a large, heterogeneous and irregularly-margined sublumbar mass surrounding the iliac vessels.

Table 4. The staging scheme proposed by Polton *et al.*

Clinical stage	T	N	M
1	< 2.5 cm	None	None
2	> 2.5 cm	None	None
3a	Any T	Present; < 4.5 cm	None
3b	Any T	Present; > 4.5 cm	None
4	Any T	Any N	Present

pulmonary nodules and urinary retention due to a large soft tissue mass in the retroperitoneal space (Fig 1). Laboratory findings revealed paraneoplastic hypercalcemia (14.4 mg/dl, reference range: 9.0~12.0 mg/dl). Cytology of the masses on the neck, sublumbar and perineal region by FNA suggested an apocrine gland adenocarcinoma (stage IV) by Polton, *et al.*, (Table 4) and metastases to lymph nodes. However, this dog was excluded by his owner from recommended treatment.

After one week, this patient came to the hospital emergency with anorexia, fecal incontinence, urine dribbling. At that time this dog hospitalized for a severe hypercalcemia (> 16 mg/dl) and was treated with furosemide and fluid therapy. Despite transient improvement of the clinical signs, the dog died 1 week after discharging from the hospital.

Case 2

A twelve-year-old, neutered female Pomeranian was referred to our hospital because of intermittent vomiting, soft stool and fecal incontinence. Physical examination revealed firm masses on the perineal and retroperitoneal region. Blood test demon-

strated severe hypercalcemia (> 16 mg/dl).

Radiography, ultrasonography, CT revealed enlargement of sublumbar lymph node. The mass includes part of right common iliac artery and vein, and ventral deviation of descending colon (Fig 2). Cytology of the masses on the sublumbar, perineal region by FNA suggested an apocrine gland adenocarcinoma (stage IIIb) and metastases to lymph nodes.

At the time of initial presentation, the patient was received supportive care (furosemide, prednisolone, fluid therapy) for severe hypercalcemia. This patient received chemotherapy alone due to the progressed course of the cancer was not feasible for surgical remove. The patient was responsive to a systemic chemotherapy regimen consisting of a combination of doxorubicin (30 mg/m² every 3 weeks, 3 treatments in total) and carboplatin (300 mg/m² every 3 weeks, 3 treatments in total) and achieved long-term progression-free survival.

Case 3

A twelve-year-old, neutered female Maltese was presented for an overhaul of perineal mass. Physical examination revealed a firm mass on the perineal region. Blood test demonstrated mild leukocytosis (26700/ul, reference range: 5,000~17,000/ul). Enlargement of sublumbar lymph node and ventral deviation of descending colon were observed on radiographic and ultrasonographic examination (Fig 3). This patient had no invasion into anal sphincter muscle. Thus the patient was undergone by surgical cytoreduction. Following surgery and

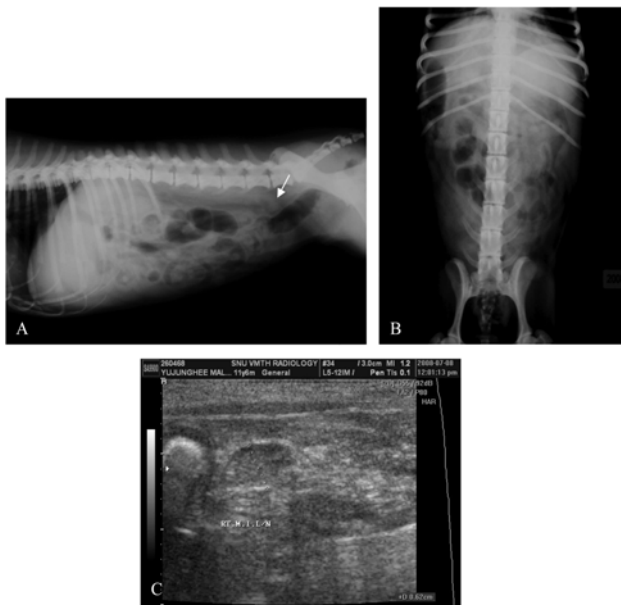


Fig 3. Lateral (A) and ventrodorsal (B) abdominal radiographs of case 3 showing a soft tissue mass (arrow) ventral to the 6th ~ 7th lumbar vertebrae with mild ventral displacement of descending colon. Ultrasonographic image (C) of case 3 showing mild enlarged, oval-shaped medial iliac lymph node with heterogeneous echotexture.



Fig 4. Lateral (A) and ventrodorsal (B) abdominal radiographs of case 4 showing ill-defined, soft tissue mass in the sublumber lymph node region (at 5th ~ 7th lumbar vertebrae level) with severe ventral displacement of descending colon. Ultrasonographic images (C, D) of case 4 showing severely enlarged, heterogeneous mass with irregular margination in the medial iliac lymph node region.

biopsy, the histopathological diagnosis of the perineal mass was a stage IIIa of apocrine gland adenocarcinoma.

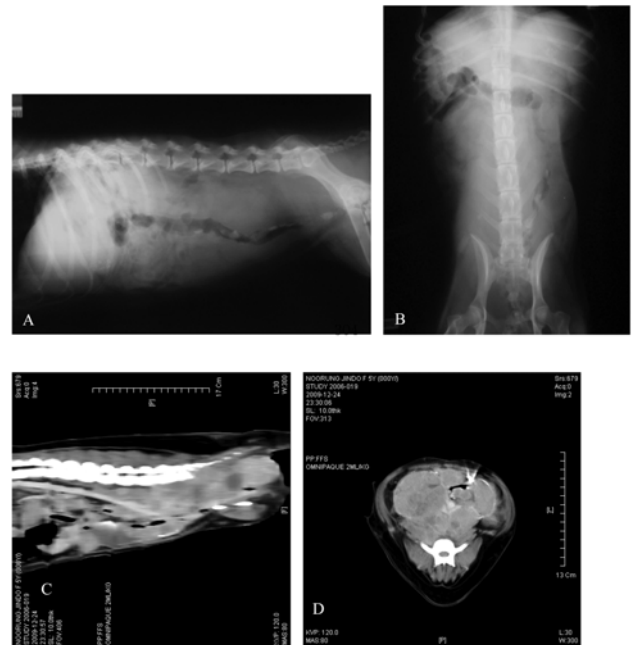


Fig 5. Lateral (A) and ventrodorsal (B) abdominal radiographs of case 5 showing ill-defined, extensive soft tissue masses in the retroperitoneal space and perianal region with severe ventral displacement of descending colon. Sagittal (C) and axial (D) planes of post-contrast computed tomographic reformatted images of case 5 showing extremely large, hypoattenuated and heterogeneous masses in the retroperitoneal space and perianal region. The masses surround the abdominal aorta, iliac arteries and veins, causing to displace ventrally.

This dog was received carboplatin (300 mg/m² every 3 weeks, 4 treatments in total) and had no side-effect thereafter. This patient remained in complete remission after 9 months from her last treatment.

Case 4

A fourteen-year-old, neutered male Poodle was presented for ribbon-like feces. Physical examination revealed masses on the perineal region. Radiography, ultrasonography demonstrated severely enlarged sublumber lymph node and ventral deviation of descending colon (Fig 4). Cytology of the masses on the perineal region by FNA suggested an apocrine gland adenocarcinoma (stage IIIa).

This patient was performed chemotherapy using carboplatin (300 mg/m² every 3 weeks, 4 treatments in total). After chemotherapeutic agents administered, often the dog had mild leukopenia and recovered in a few days. Since then this patient was monitored periodically following drug initiation.

Case 5

A six-year-old, intact female mixed breed dog was referred to our hospital because of anorexia, depression, vomiting, tenesmus, melena, abdominal mass.

Physical examination revealed firm masses on the perineal and retroperitoneal region and abdominal pain. Blood test

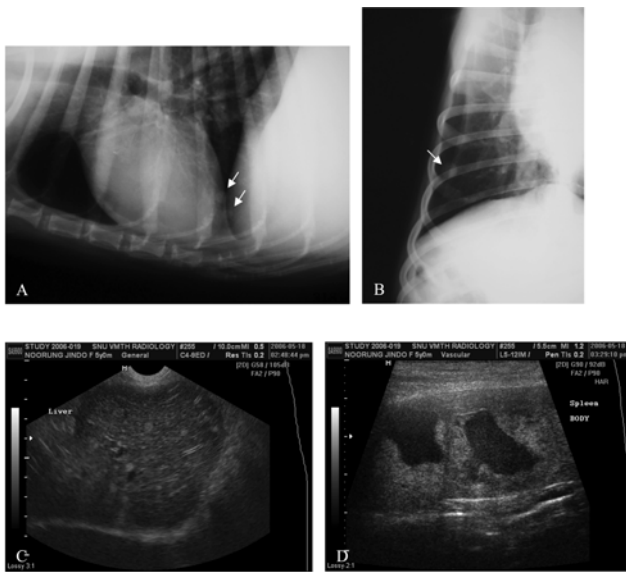


Fig 6. Close-up lateral (A) and ventrodorsal (B) thoracic radiographs of case 5 showing multiple pulmonary nodules (arrows), indicating metastasis. Ultrasonographic images (C, D) of case 5 showing metastatic changes in the hepatic and splenic parenchyma.

Table 1. The signalments of apocrine gland adenocarcinoma patients

Case No.	Age	Breed	Sex
1	11 y	Cocker spaniel	MC
2	12 y	Pomeranian	FS
3	12 y	Maltese	FS
4	14 y	Poodle	MC
5	6y	Mixed	F

demonstrated leukocytosis (29000/ul), mild hypercalcemia (13.2 mg/dl). Radiography, ultrasonography, CT revealed metastases to lung, liver, spleen, and enlargement of sublumbar lymph node (Fig 5,6). Following FNA and biopsy (Fig 7), the histopathological diagnosis of the perineal mass was an apocrine gland adenocarcinoma (stage IV).

This patient was received only chemotherapy for tumor because of too large size of mass and pulmonary metastases. The patient was responsive to a systemic chemotherapy regimen consisting of a combination of doxorubicin (30 mg/m² every 3 weeks for total of 2 treatments) and carboplatin (300 mg/m² every 3 weeks for total 1 treatment) and achieved stable disease for 2 months and since then died.

After pain management with fentanyl patch (Fentanyl transdermal system, Mylan) with chemotherapy, the patient alleviated abdominal pain and increased activity and appetite and relief of dyspnea.

Discussion

Apocrine gland adenocarcinomas (AGAC) were found in 5

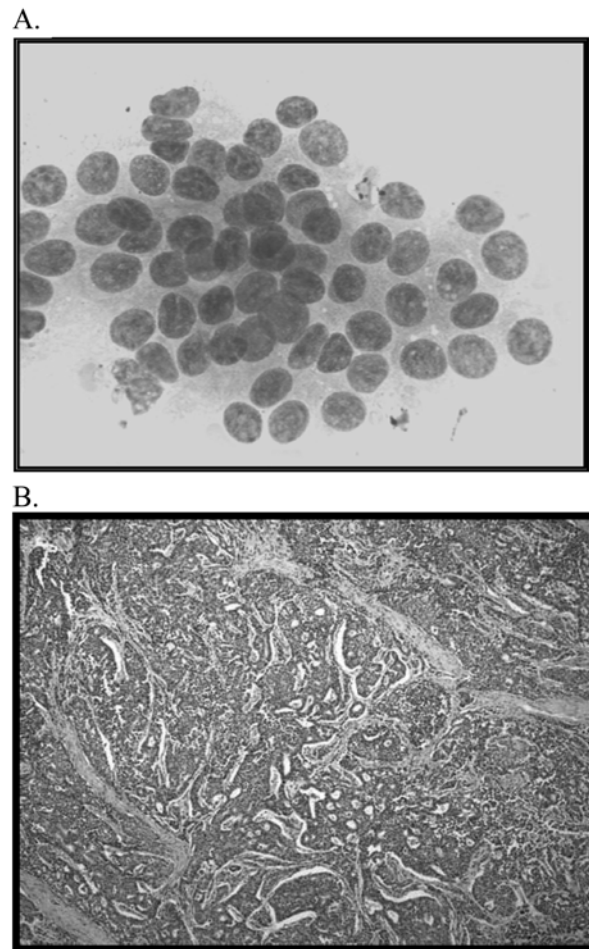


Fig 7. Case 5 dog. (A) Fine needle aspiration cytology from AGAC of anal sac. The smears are highly cellular with densely packed cells in clusters characterized by lightly basophilic poorly defined cytoplasmic borders, occasional cytoplasmic clear vacuoles, naked nuclei, mild to moderate anisocytosis, anisokaryosis, and fine to reticular chromatin pattern, high N:C ratio. (B) Histopathology from AGAC of anal sac. Acinar pattern, illustrating the invasive proliferation with simple or stratified tumor cells to adjacent tissue.

different breed dogs. The cases were composed of 2 castrated male, and 2 spayed and 1 intact female, with a mean age of 11 years (Table 1). At the time of presentation, 3 (60%) dogs had hypercalcemia and all (100%) had metastases, with the regional lymph nodes being the most common site of metastases. Pulmonary metastases was detected in two dogs. Fifty-one percent of dogs with AGAC had hypercalcemia at presentation (12.7-21.7 mg/dl) (8). Hypercalcemia was not related to the size of the primary tumor and can result in significant renal damage, which may modify prognosis and anesthetic risk. Therefore depending on the level of hypercalcemia and renal function, aggressive medical management may be needed. In these cases, case no.1 and no.2 patients with hypercalcemia (> 16 mg/dl) were managed by supportive care including fluid therapy, furosemide, and prednisolone.

Table 2. The treatment and status of apocrine gland adenocarcinoma patients

Case	Survival time (month)		Treatment	State of patient
1	Dead	1	Supportive care	-
2	Alive	19	Chemotherapy	Stable disease
3	Alive	9	Surgery + Chemotherapy	Complete remission
4	Alive	13	Chemotherapy for other tumor	Stable disease
5	Dead	2	Chemotherapy	Stable disease

Table 3. The side effects after systemic chemotherapy of apocrine gland adenocarcinoma patients

Case	Side effects	Treatment	Progress
2	Mild leukopenia, Alopecia	No treatment	Recovery Maintenance
4	Leukopenia	G-CSF (5 ug/kg, SID SC for 3 days)	Recovery

Surgical resection of primary tumor was performed in one dog, and tissue was submitted for histopathology. None of the dogs underwent radiation treatment. Adjuvant chemotherapy was administered in 4 cases (Table 2).

Side effects related to chemotherapy were recorded in 2 dogs (Table 3). One dog without treatment for tumor was dead shortly after AGAC diagnosis due to paraneoplastic hypercalcemia and the remaining three dogs were alive and healthy without any AGAC-related problems at the time of survey.

Three dogs are currently alive, the dog 3 (surgery and chemotherapy) still in complete remission, the dog 2 (only chemotherapy) and the dog 4 (chemotherapy for mast cell tumor) in stable disease (Table 2). The dog 5 was in stable disease for 2 months and since then died. Responses to treatment were assessed every 4 weeks after the therapy; 100% of all tumors treated with chemotherapy responded with objective response. 1 dog was achieved complete remission (CR) and 3 dogs were maintained stable disease (SD). The dog 5 had severe pain and anorexia, decreased activity, and dyspnea. These problems were alleviated with fentanyl patch. Opioids can be an effective part of the management of cancer pain and are used most often for the alleviation of chronic cancer pain (16-17).

AGAC is generally locally invasive, and wide surgical excision with complete removal of the neoplasm and radiation are the standard therapy and this appears to offer the best chance of cure. If radiation therapy was limited, systemic chemotherapy is worth a try. Systemic chemotherapeutic agent does not proved to be effective (complete remission) in the treatment of this tumor. But it is reported that several chemotherapeutic agents used in the treatment of AGAC (8,10,12). Among them, when cisplatin and carboplatin were used as monotherapy, rate of partial remission was reported as 31%, 33%, respectively and median survival time is 6 months (8,12).

In this paper, we described the successful treatment of AGACs by chemotherapeutic agents (doxorubicin, carbopl-

atin) with or without surgical intervention. Neither severe systemic nor local side effects were detected during the whole course of therapy. Systemic chemotherapy is a safe and efficacious adjuvant therapy for AGAC and warrants further investigation in order to standardize its protocols.

Conclusion

In this report, five dogs were diagnosed as apocrine gland adenocarcinoma (AGAC) of anal sac and four of these treated by chemotherapy with or without surgery. They were achieved status of CR (Complete remission) or SD (Stable disease).

This report is suggested there is a role for chemotherapy in the treatment of dogs with AGAC when radiation therapy is limited and research into the responses of AGAC to various chemotherapeutic agents is needed.

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다섯 마리의 개에서 발생한 아포크린샘암종 증례

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요 약 : 2006-2008년에 5마리의 환자가 아포크린샘암종으로 진단받았다. 품종은 다양하였으며 진단 당시 평균 연령은 11세이었다. 이들 중 3마리에서 종양으로 인한 고칼슘혈증이 발생하였으며, 한 마리는 화학요법(chemotherapy) 받지 않고 진단 1달 후 사망하였다. 나머지 네 마리의 환자들은 항암제 투여, 수술 등의 방법으로 치료를 받았으며 수술과 화학요법을 병행한 환자는 치료 종료 후 9개월째 완전완화(complete remission) 상태를 유지하고 있다. 화학요법만 받은 3마리의 환자들은 질병지속(stable disease) 상태로 유지되고 있으며 이 중 한 마리는 진단 후 2개월째에 사망하였다. 따라서 개의 아포크린샘암종의 치료법으로 수술 및 방사선 치료를 적용할 수 없는 경우에, 항종양제 단독 투여는 보조적으로 효과가 있는 것으로 사료된다.

주요어 : 아포크린샘암종, 화학요법, 개.