

Principles of Wound Healing Applied to Tumors and Interventions in the Perianal Region

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History and Presentation:

Approximately 2% of canine skin tumors are apocrine gland anal sac adenocarcinomas (AGSACA). They comprise 17% of total perianal tumors.¹ AGASACAs are malignant and can have distant metastasis to other organs in the body, most commonly the lymph nodes, liver, spleen and lungs.¹ The mean age of a canine presenting with AGASCA is 10 years of age, with no breed predilection.² Both intact and fixed animals can be affected, with a predilection for older female dogs.² However, studies reporting a higher incidence in females were considered underpowered. In a study of 238 dogs, a more equal gender distribution of AGASCA was noted with 56% being female and 44% being male.¹ No studies exist that support that evidence of hormonal influence.³

Frequent owner complaints in animals presented with perianal tumors include licking, scooting or 'dragging' of the perineum.⁴ Polyuria, polydipsia, lethargy or weakness, often attributed hypercalcemia due to elevations in parathyroid hormone - related to polypeptide produced by the tumor cells (or PTHrp.)¹ Often, perineal mass lesions are encountered incidentally during routine annual examination by way of visual inspection of the anal/perianal region, during rectal exams in intact males for prostatic evaluation, or during routine anal gland expression.^{1,5} Thirty-nine percent of cases reported in one study were diagnosed as incidental findings.³ In some instances, enlarged sublumbar lymph nodes can lead to difficulty defecating. Owners may observe straining during defecation (tenesmus), and a ribbon-like appearance to the stools.¹ In addition patients may have concurrent tenesmus, constipation and obstipation.¹

Pathophysiology (Including Anatomical Considerations)

Anal sacs, also known as perineal sinuses, are paired structures located in the perineal region in carnivores and most rodents.⁶ In dogs, these glands are thought to be nonsecretory

forms of sebaceous glands.⁶ While the exact cause of AGASACA is unknown the disease is often complicated by secondary hypercalcemia of malignancy.²

In a study of 113 dogs, 27% exhibited hypercalcemia.³ A more recent study, reported hypercalcemia of malignancy in 90% of the dogs with AGASCA.⁷ Of these, 96% had metastasis to the sublumbar lymph nodes (a nodal system consisting of the medial iliac, hypogastric and sacral lymph nodes). Forty-six percent of these dogs had metastasis to other parts of the body.^{7,8}

Patients with elevated calcium should be evaluated for evidence of bone metastases and other underlying comorbidities such as parathyroid hyperactivity.⁷ Adenocarcinomas are thought to produce bone-resorbing compounds such as parathyroid hormone, parathyroid hormone-like peptides, prostaglandin E, vitamin D sterols and osteoclast-activating factor.⁷ Ultrastructural studies have demonstrated that neoplastic cells can synthesize and produce organelles that produce polypeptide hormones.⁷ Numerous studies report normalization of serum calcium levels with surgical removal of AGASCAs.⁷ Tumor regrowth however, often leads to a recurrence of Hypercalcemia.⁷

Differential Diagnosis:

Differentials for masses of the perineum and anal sac region include anal sac impactions and infections. Neoplasia is less common than general anal sac disease.¹ Anal sac squamous cell carcinoma is uncommon, but reported based histological evidence of tissue biopsy of the stratified squamous epithelial lining of the anal sac.⁶ Intact male dogs are more likely to develop testosterone dependent, perianal adenomas (benign tumors, until proven otherwise.)¹ Although the perianal region may be affected by almost any tumor, 80% of perineal tumors are reported to be perineal adenomas.⁶

Diagnostic Approach/Considerations:

Tumors that originate from the internal lining of the anal sac are often not detected early on.⁶ Often these tumors do not contact the colon, rectum or merocrine anal glands directly. Rather, they extend ventrally and laterally from their primary site and eventually move into the pelvic canal.^{6,7} Thus, definitive diagnosis of an AGASCA may include a fine needle aspirate or biopsy of pelvic lymph nodes if lymphadenopathy is present.⁹ Cytologically, AGASCAs have round nuclei that contain coarse chromatin. In some cases, glandular acinar structures can be observed with central lumens and microacini, but for the most part, the cell margins are indistinguishable and nuclei appear to be free floating in a large amount of cytoplasm.¹⁰

As with any general work up, complete blood count, serum biochemistry to include albumin bound calcium levels should be performed. Concurrently, ionized calcium levels should also be performed and interpreted in the face of circulating PTHrp.⁹ Abdominal and thoracic radiographs should be performed, for metastatic screening as metastasis to the sublumbar lymph nodes is common (metastatic rates have been reported to be between 36 – 96 % of cases).³ Rarely, metastatic nodular pulmonary metastasis is reported, although this generally occurs late in the disease.^{3,9} Abdominal ultrasound can additionally be used to evaluate the size and number of the lymph node involvement and can provide a window of opportunity for lymph node sampling with fine needle aspiration in the sedated patient.⁹ Fine needle aspiration aids in determining whether or not the lymphadenopathy is of reactive or metastatic etiology.⁹ Although there is a lack of evidence that supports lymph node involvement as a poor prognostic indicator, accurate knowledge of metastases aids presurgical planning.⁹ It is also helpful in determining which patients will require adjuvant chemotherapy.⁹ On ultrasound, lymph nodes affected by

AGASCA are much larger than normal, have a more rounded shape and have a reduced heterogeneous echogenicity⁹

Tomographic imaging may also be considered. Computed tomography is especially for evaluation of the pelvic canal and in metastatic evaluation of the abdomen's of large and giant breed dogs, whose size may preclude full evaluation of the abdomen with ultrasonography. In addition, CT is often used for surgical planning with contrast enhancement being useful for the evaluation of tumor margins. AGASACA tumors are often locally invasive and although achieving removal with complete margins is important, the surrounding soft tissue morbidity and proximity to the rectum and anus makes removal with complete margins difficult.^{3,9} Magnetic resonance imaging (MRI) is more sensitive than ultrasound in determining lymph node involvement.⁹ On MRI, lymph nodes with metastatic involvement will have T2 and T1 heterogeneity with moderate STIR hyperintensity and avid enhancement following the administration of a gadolinium based contrast agent. hypointensity with similar changes as seen with ultrasound.^{9,10}

Treatment and Management Options:

Due to the highly metastatic nature of AGASCA tumors (metastatic rates to the sublumbar lymph nodes are reported to be 50 – 90 %), therapy is often multimodal, meaning, surgery, radiation and chemotherapy are needed for disease control.^{4,9}

As part of effective presurgical management, clipping of the hair around the mass should be performed¹² This aids in inspection of the extent of the mass and prevents contamination during removal.¹² Purse string sutures can be used to prevent fecal contamination; however, some clinicians prefer to leave the anus open as digital manipulation can be performed and used

to assess the depth as well as for tissue manipulation.⁸ Basic surgical principles dictate doing procedures in an order moving from clean to contaminated regions. As the tumor is adjacent to the anus, the risk of fecal contamination is high and every effort should be made to avoid fecal contamination on equipment and the surgical field, which may be allowed to enter the abdomen if the lymph nodes are removed after the primary tumor. As such the sublumbar lymph nodes are often removed prior to surgical removal of the neoplasm near the anus.

Sublumbar lymph nodes are generally removed via a caudal ventral midline celiotomy. Due to the association with the surrounding vasculature, blunt dissection is preferred for removal of the lymph nodes. The pelvic canal should also be thoroughly explored as frequently enlarged lymph nodes can extend caudally into this region.⁸

The principles of surgical removal are different for neoplastic malignant tissue.¹² Ideally the tumor would be removed en bloc.¹² The incision is made in tissue that is healthy and surrounds the mass. The aim is to not enter the mass and seed cancerous cells throughout a healthy bed of tissue. This is an important post operative consideration with regard to the use of indwelling drains, which can lead to further seeding of cancer cells.¹² If removal of the anal sphincter is necessary, preservation of the rectal wall and pudendal nerve are pertinent to the prevention of fecal incontinence. For closure, external sphincter muscles are reapposed and subcutaneous and skin closure is then performed.⁸ In some cases incontinence can be temporary and just the result of inflammation.⁸

Post operative care should include proper pain management, this may be achieved by physical methods such as ice pack application to reduce swelling or with medications such as opioids and NSAIDS.^{12,13} Stool softeners may also be required to reduce straining which can lead to dehiscence. While stool softeners may be required post operatively, their use should be

determined on a case-by-case basis.⁸ In general the perineal region should be kept free of feces, to prevent further contamination.⁸ Stool softeners in some patients may exacerbate fecal contamination, but in others with severe swelling they may be needed in order to allow the passage of feces without excessive straining that can lead to torn sutures.⁸ The perineal area can also be cleaned with baby wipes or post operatively wounds with large amounts of fecal material water may be cleaned with tap water.¹² Many patients may mutilate the incision site post operatively so basket muzzles and Elizabethan collars may be used to restrict access to the surgical site.¹⁵ The incision site should be checked regularly for signs of infection or dehiscence.

The major causes of incisional dehiscence in perineal and perianal incisions include self-mutilation (licking the incision), infection, and excessive tension at the incision site if a large area of skin was resected. In general, neoplasia causes extensive tissue damage and incomplete resection can leave behind tumor cells which, may lead to a high probability of wound dehiscence.¹² Wounds that dehisce due to tension should only be closed if methods such as tension relieving sutures can be applied to overcome tension.¹² Wounds contaminated with $>10^5$ colony forming units per gram have a greater chance of becoming infected.¹³ Open wounds may lead to the formation of biofilms (a collection of sessile aggregates that essentially form a slime layer), which may lead to antibiotic resistance.^{13,14} Visually, clinicians may notice that infected wounds have increased exudates, poor granulation that may be pale and friable and the patients may show more clinical signs of pain.^{13,15} Infected wounds may require antibiotics, and antibiotic selection should be based on appropriate culture results.¹⁵ Culture and sensitivity can guide antibiotic therapy. Tissue cultures for microbes are an important part of perineal wound management, especially in those that display signs of delayed healing. When performing perineal wound tissue cultures it is imperative during initial treatment to sample from the center

and edge of the wound.¹⁶ Proper culture will yield a more representative sample of the bacterial load, as normal fecal flora and surface contaminants in the perianal region can lead to improper antibiotic selection and further delay healing.^{12,16}

If infection is suspected and culture is necessary then the skin adjacent to the wound or incision should be scrubbed prior to obtaining the culture swab to decrease the likelihood of contamination from commensal skin or fecal organisms, cultures of open wounds should be for aerobic organisms.¹⁵ Care should be taken to avoid getting the scrub solution into the wound as many scrubs are also damaging to tissues and will interfere with the culture results.^{12,15} Gram stains can be useful in identifying bacterial populations when waiting on culture results.¹²

Infected perineal wounds may require other forms of topical treatment, even if the sole purpose is to provide a preventative barrier for fecal contamination.¹⁶ Topical antimicrobials such as gentamicin sulfate, nitrofurazone, SSD and triple antibiotic ointment (that contains neomycin sulfate, polymixin B and bacitracin zinc) are often used to aid in prevention of further colonization of the wound with bacteria.¹³ Antibiotic therapy may be empirical, and based on the expected knowledge of flora, suspected ability of the antimicrobial to reach the site of a wound and established resistance patterns for a given environment.¹³ Discontinuation of an antimicrobial is often considered once a healthy granulation bed forms, as most antibiotics are not able to achieve sufficient concentrations within granulation tissue.¹³

Clinical knowledge of the 3 stages of repair (inflammatory, repair and maturation) and the wound healing principles at a macroscopic level can aid clinicians in management and postoperative decision making.^{13,16} Continuous wound assessment, especially for perineal lesions, is essential.¹² The response of the tissue and the patient's comprehensive clinical picture should guide the therapy.¹²

Expected Outcome and Prognosis:

Even with the variety of available treatment options for anal sac adenocarcinomas, surgery combined with chemotherapy is considered the only method that has a proven influence on survival times.⁸ Local recurrence of the tumors is considered low when complete excision is performed and chemotherapy is also instituted.¹⁸ Studies have found there is no difference in median survival times of dogs with or without sublumbar metastasis.¹⁶ Negative prognostic indicators include tumor stage, lymph node involvement, metastasis and concurrent hypercalcemia.³ When uncomplicated by metastases, surgery combined with chemotherapy can increase median survival time to 29.3 months (n = 7), compared to patients undergoing surgery alone which had a median survival time of 15.5 months (n=10.)¹⁸

Conclusion:

From a clinician's standpoint the perianal region presents numerous challenges relative to wound healing. The anatomic location (ventral to the anus) can lead to fecal contamination and introduction of numerous strains of bacteria and promotion of biofilm in the moist environment. Advanced imaging can be critical to determining the full extent of disease and can be especially useful in surgical planning. Most perineal wounds will heal in a similar fashion. In short, assessment of the wound should determine the feasibility of management of the wound as open or closed and which treatments to employ. Management methods such as surgical drains, antibiotics, bandages, drains and antiseptics should be applied when necessary. Reassessment of the wounds will aid adaptation of planning and implementation of successful wound closure in the majority of clinical situations.

While the location of an anal sac adenocarcinoma may be less than ideal, medical and surgical interventions can prolong mean survival time and improve patient quality of life. A discussion with owners regarding potential surgical complications is imperative (early on) due to intensive postoperative management commitments and financial investment in a patient that will eventually succumb to the disease.

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