A Dollop of Daisy

Avery Smith

Class of 2019

Clinicopathologic Conference (CPC)

June 29, 2018

CPC Advisor

Hayley Gallaher, DVM

Introduction

Considering all tumors identified in canines, thyroid tumors are quite common. Studies reveal that thyroid tumors make up approximately 1.2-3.8% of all tumors found in the canine.[6] Not only are canine thyroid tumors common compared to other tumors, but specifically malignant thyroid tumors prevail over benign thyroid tumors with 88% of all thyroid masses being classified as malignant.[1] Two broad categories are recognized to characterize malignant tumors based on the cell lineage origination.[6] These categories include follicular or parafollicular cell lineage origin, both of which have different histological appearance but comparable outcome after treatment.[2] Malignant canine thyroid tumors often metastasize and it has been shown that at the time of presentation, 33-38% of dogs already had identifiable metastasis present. Metastasis is often found in the regional lymph nodes or lung tissue. When left untreated, 65-90% of dogs with malignant thyroid tumors at necropsy revealed gross evidence of metastasis.[6] As with many other types of neoplasia, a specific cause of malignant thyroid tumors has not been identified. Contributing factors to this disease process that have been suggested includes iodine deficiency, prolonged lymphocytic thyroiditis, hypothyroidism, and exposure to radiation.[6,10]

History and Presentation

An approximately 10-year-old female spayed Dachshund originally presented to the MSU-CVM Internal Medicine department on March 5, 2018 for evaluation of a thyroid mass, polyuria, and polydipsia. The thyroid mass was detected during a routine physical exam by her referring veterinarian. At the time of discovery, the patient was not showing any clinical signs of coughing or difficulty swallowing that would indicate that the mass was obstructing important anatomical structures. Daisy had a chronic history of increased thirst and urination, and previous diagnostic work-up revealed bilaterally enlarged adrenal glands, hepatomegaly, and an elevated ALP.

Ultrasound also revealed mottled kidneys and evidence of chronic kidney changes. A subsequent SDMA was normal at that time. A low dose dexamethasone suppression test was performed based on the suspicion of hyperadrenocorticism, but was inconclusive for Cushing's disease in September of 2017. Historically, the patient was diagnosed with suspected progressive retinal atrophy and was determined to be bilaterally blind. She also had a history of type I intervertebral disc disease at the T12-T13 disc space and underwent a hemilaminectomy surgery in August of 2011. While the patient was being evaluated for chronic PU/PD, the owners also wanted her thyroid mass to be evaluated as well. A fine needle aspirate was performed on the patient's thyroid mass which revealed clusters of thyroid epithelial cells with moderate numbers of erythrocytes. Based on the FNA, a biopsy was recommended for a definitive diagnosis.

The patient presented to the MSU-CVM Small Animal Surgery Department on March 14, 2018 for further diagnostics and possible removal of her thyroid mass. Upon presentation, the patient was bright, alert, and responsive. She weighed 6.0 kg and had a body condition score of 5/9 which is ideal. Her vital parameters were within normal limits with a temperature of 100F, pulse of 160 beats per minute, and a respiratory rate of 32 breaths per minute. Her hydration was adequate with pink and moist mucous membranes and a capillary refill time of less than two seconds. A grade II/VI left systolic heart murmur was detected upon auscultation. Lung auscultation did not reveal any abnormalities. The patient's skin appeared thin and she had a pendulous abdomen. She had a palpable mass that was firm, partly fixed, and spanned across the area of the left and right thyroid glands. The mass palpated larger on the left side. The patient's submandibular lymph nodes were enlarged. All other physical exam findings were unremarkable. At this time, it was suspected that Daisy's had possible thyroid carcinoma.

Physiology

The thyroid gland is an intricate endocrine organ important in many cellular functions, one of the most telling being metabolism. The thyroid gland is a bi-lobed structure located in the neck region ventral to the larynx and overlying the trachea. Histologically, the functional portion of the thyroid gland is known as the follicle which is filled with colloid that serves as a storage pool for thyroid hormones. In between the thyroid follicles are parafollicular cells or "C" cells which serve as the source of calcitonin, important in keeping serum calcium from becoming elevated. Finally, the parathyroid glands can be found located within or near the thyroid gland and serve as the reservoir of parathyroid hormone which serves to increase calcium when it becomes too low. The major functions that the thyroid gland must perform are iodide trapping and synthesis, storage, and release of thyroid hormones. The main hormones that the thyroid gland produces are tetraiodothyronine (T4), triiodothyronine (T3), and reverse triiodothyronine (rT3).[4]

For the thyroid gland to synthesize hormones, it must first trap iodide. This occurs when iodide is absorbed by the follicular cells from the general circulation present from dietary intake. This is facilitated against a high concentration gradient across the thyroid cell membrane and must be stimulated by thyroid stimulating hormone (TSH) which is released from the pituitary gland. Iodide trapping in this manner acts as an active transport pump. The trapping "pump" process is mediated by proteins found on the cell membrane. Altogether, this process is extremely efficient and is responsible for concentrating the majority of iodine in the entire body.[4]

Once the thyroid gland has successfully trapped iodide, synthesis of thyroid hormones can begin. Iodide undergoes oxidation and binds to phenyl groups of thyroglobulin which creates monoiodotyrosine (MIT) or diiodotyrosine (DIT). These iodinated phenyl groups are coupled to form T4 (DIT to another DIT) and T3 (DIT to a MIT). These hormones are then stored in the

lumen of the follicle, bound to thyroglobulin. The stored hormones are regulated by the hypothalamic-pituitary-thyroid axis. The hypothalamus releases thyrotropin releasing hormone (TRH) in response to signals from higher centers in the brain and body. An increase in TRH stimulates the pituitary gland to upregulate thyroid stimulation hormone (TSH). Subsequently, TSH binds receptors in the thyroid gland which then stimulates the synthesis process of T3 and T4 in the thyroid gland.[5] At the molecular level, thyroid hormones are needed for cellular protein synthesis and activation of the Na-K-ATPase pump on cellular membranes important when oxygen consumption needs to be increased. Clinically, these effects are seen as tremors, nervousness, hyperactivity, and weight loss to name a few. [4] When stored T3 and T4 is signaled to be released, vesicles are formed and taken up by follicular cells via endocytosis in the thyroid gland. The vesicles combine with lysozomes where proteases hydrolyze the colloid and MIT, DIT, T3, and T4 are released. T3 and T4 go into circulation via diffusion and MIT and DIT are recycled within the follicular cell. Approximately 90% of released hormone is T4, some of which is deiodinized to form biologically inactive rT3 during times of illness or starvation. Once these hormones are released into circulation, they instantaneously bind to transport proteins where they are carried throughout the plasma and delivered and reach target organs to facilitate different functions including, but not limited to, stimulation of growth, erythropoiesis, and increased metabolism .[4]

Pathophysiology

A single etiology of thyroid tumors has not been identified in dogs. The pathogenesis of thyroid tumors is best described in human literature which can be extrapolated to veterinary medicine. Without a specific cause determined, it is suggested that ultimately any mutation in the entire physiology and function of the thyroid gland could be responsible for thyroid tumors. The

most accepted hypothesis involves a series of mutations. In follicular carcinomas, an inactivation of the p53 gene is often seen. In humans with thyroid neoplasia, the TSH receptor is often affected with hyperfunctioning or silencing mutations. Studies in hypothyroid beagles have shown that canine thyroid tumors do keep their TSH receptors.[4] When hypothyroid dogs were left untreated an increased incidence of thyroid tumors were seen.[4] This is believed to have been caused by the TSH trophic effects without proper feedback in consequence to mutations.[4] Studies have also shown that irradiation of the thyroid increases incidence of thyroid tumors in humans.[1,7] Other factors such as decreased dietary iodine have been associated with thyroid tumors. [1] Decreased iodine causes TSH levels to increase which then encourages thyroid neoplasia development. [1] Prolonged lymphocytic thyroiditis causing hypothyroidism in a colony of 276 beagles was also associated with increased risk of thyroid tumors.[1] While these factors may contribute to thyroid tumor development, further research is warranted to determine a definite cause of canine thyroid cancer.

Diagnostic Approach

While thyroid tumors are common in the dog, it is important to differentiate a thyroid tumor from other causes of masses located in the region of the thyroid like abscesses, granulomas, salivary mucoceles, lymphoma, carotid body tumors, and sarcomas. Approaching diagnosis is like any other work-up and starts with signalment, history, physical exam, and clinical signs. Most dogs with canine thyroid carcinoma are 9-10 years of age with a predisposition found in Boxers, Beagles, and Golden Retrievers.[6,10] Most patients present with a palpable mass in the ventral neck region that the owner noticed or was found on routine physical exam. Clinical signs can be related to the obstruction of regional structures such as the trachea and esophagus, which can include coughing, gagging, retching, regurgitation, and dysphonia. If the tumor is fixed and

invasion of blood vessels or recurrent laryngeal nerve damage has occurred, the patient may experience dysphagia, Horner's syndrome, or cranial vena caval syndrome. Less commonly, dogs can experience consequences of hyperthyroidism if the thyroid mass is functional.[6]

A fine needle aspirate should then be performed on the mass to help facilitate diagnosis although cytology of thyroid masses has been reported to be diagnostic in only 50% of thyroid carcinomas due to hemodilution from increased vascular density in malignant tumors.[7] While FNA helps to confirm suspicions of thyroid tumors, diagnostic imaging should be performed to reach a more concise diagnosis. Ultrasonography is used to differentiate the origin of the mass and assess vascular density. Ultrasound can also aid in guiding FNA for more accurate samples. All other modalities considered, a computed tomography with contrast or magnetic resonance imaging can be performed to confirm the origin of the tumor and to evaluate the invasiveness of the tumor in preparation for surgery. Less conventionally, radionuclide imaging using ^{99m} technetium pertechnetate or iodine-131 (scintigraphy) can also be used for diagnosis of thyroid tumors. Scintigraphy is also useful for diagnosing malignant ectopic thyroid tissue and regional lymph node metastasis.[1] All diagnostic approaches considered, histopathology is the only way to reach a definitive diagnosis.

As with other forms of neoplasia, clinical staging for canine thyroid tumors is important. A stage is defined according to the World Health Organization's Tumor, Node, and Metastasis staging system.[1,6] Staging includes a complete blood count (CBC), blood chemistry, urinalysis, serum thyroxine, and TSH concentrations. Tumor characteristics and evaluation for metastasis in the regional lymph nodes and lungs are also a part of clinical staging, all of which helps to facilitate the best treatment option.

Surgical Treatment and Management

Treatment is divided into two categories which include surgery or management of clinical signs. If no metastasis is found at the time of diagnosis, then treatment is focused at local control of the tumor. If the tumor is mobile and has minimal tissue invasion, surgery is the treatment of choice and has a lower morbidity compared to other treatment options.[7] The prognosis for canine thyroid carcinoma is excellent with treatment and median survival times have shown to reach 3 years.[8] However, removal of the thyroid gland and parathyroid glands is not benign and does propose several complications including hemorrhage, damage to the recurrent laryngeal nerve, hypothyroidism, and hypocalcemia. Due to high risk of hemorrhage, it is recommended to perform a coagulation profile, cross-matching, and blood typing prior to surgery.

Thyroidectomy is performed under general anesthesia, with the patient in dorsal recumbency and the neck extended. A ventral midline approach is made extending from the larynx to the manubrium and the thyroid gland is reached through dissection of the sternohyoideus muscles. Once the thyroid tumor is identified, the cranial and caudal thyroid arteries and other large associated vessels should be found and ligated. Smaller vessels can be cauterized. The tumor is removed by delicate blunt and sharp dissection to release the tumor of its tracheal fascial attachments. Once the thyroid tumor is removed, routine closure is performed. Median survival time of patients with mobile tumors that underwent thyroidectomy reached 3 years. In patients with more fixed, invasive tumors the MST decreased to 6-12 months. [6,8] One case study of 15 cases revealed that even with complications seen from bilateral thyroidectomy, median survival time was 38.3 months.[9]

Non-mobile thyroid tumors or patients with metastasis at diagnosis are treated differently. If the tumor is deemed nonresectable, then radiation is the treatment of choice. Studies have shown

that radiation on canine thyroid tumors either stabilized the tumor or decreased the tumor in size. In dogs that underwent radiation, maximal tumor reduction was reached in 8-22 months and 72% of dogs survived to 3 years post radiation. Recent studies have also suggested that ^{131}I is a successful treatment for the more advanced staged thyroid tumors that are nonresectable, revealing median survival times of 12 months for patients with metastasis and 24 months without metastasis. Chemotherapy using doxyrubicin or cisplatin has also been used in these instances but responses are decreased with 30-50% of dogs demonstrating only a partial response.[6,7]

Management of secondary metabolic and endocrine disturbances from removal of the thyroid and parathyroid glands is important and can be life-long. Hypothyroidism should be expected with bilateral thyroidectomy and the patient should be supplemented with levothyroxine accordingly and monitored for clinical signs of hypothyroidism including dull hair coat, weight gain, and lethargy. Another complication that can arise after treatment includes hypocalcemia if the parathyroid glands are removed during surgery. Serum calcium levels should be monitored at least 48 hours postoperatively. If ionized calcium is low or clinical signs a of hypocalcemia are seen such as paraesthesia, cramps, facial excoriation, or convulsions then the patient should be supplemented with intravenous calcium gluconate, and later with oral calcium and calcitriol.[3]

Daisy's Outcome

Daisy was transferred to the MSU-CVM surgery department for further work up and evaluation for possible thyroidectomy. Computed tomography with contrast was performed on March 14, 2018 and the CT scan revealed a 2.5 X 6.5 cm lobulated, ill-defined, strongly contrast-enhancing mass that caused rightward tracheal deviation. The origin of the mass was suspected to be the left thyroid lobe. The mass was found to be close in proximity to structures such as left and right common carotid arteries, as well as the left and right jugular veins. The left

retropharyngeal and superficial cervical lymph nodes were suspicious for metastasis due to increased size and fluid attenuation. Based on these findings and the cytology results, the decision was made to proceed with thyroidectomy on March 16, 2018.

The patient was placed in dorsal recumbency and the ventral cervical region of the neck was clipped, aseptically prepped with 4% chlorhexidine scrub and draped for surgery. A ventral midline cervical approach was made from the larynx and extended 8 cm towards the manubrium. The sternohyoideus and sternothyroideus muscles were bluntly separated and retracted from midline. The trachea was visualized and the fascia to the left of the trachea was bluntly dissected using Metzenbaum and tenotomy scissors. The mass was visualized and the fascia around the mass was bluntly dissected. The recurrent laryngeal nerve was visualized and isolated from the dissection. Small vessels supplying the mass were cauterized with the bipolar cautery and the LigaSure and the mass and left and right thyroid glands were removed and submitted for histopathology. The parathyroids were dissected out and re-implanted into the right sternohyoideus muscle using a 15 blade scalpel. The tissues were closed routinely and a Telfa pad and Sure-site bandage were placed over the incision.

Under anesthesia, the patient was hypotensive and some hemorrhage was sustained. The patient received an intra-operative blood transfusion due to moderate amounts of blood loss. No other complications were encountered intraoperatively and recovery from anesthesia was slow but uneventful. The patient was hypocalcemic after surgery discovered by serial ionized calcium levels and received appropriate calcium supplementation including oral calcium and calcitriol. The patient was discharged on March 19, 2018 with strict instructions to monitor for signs of hypothyroidism, hypocalcemia, and hypercalcemia.

The patient returned to the MSU-CVM Small Animal Emergency Service on March 27,2018 for a possible seizure, which was concerning because due to her previous post-operative hypocalcemia. However, her ionized calcium levels were measured and within normal limits. She was normal at the time of presentation and the owners elected to take her home and continue to monitor her for any additional seizure like activity. Since then, the patient has been apparently healthy at home.

Conclusion

Overall, thyroid tumors are one of the most common of all canine tumors so it is important that pathophysiology and treatment options be understood by clinicians. Physical exam and presentation along with imaging and bloodwork help to facilitate diagnosis, but a biopsy is the only way to reach a definitive diagnosis. Surgery is often successful and post-operative complications can be medically managed. Dogs with thyroid tumors have an excellent prognosis and even though it is neoplasia, it is not a fatal diagnosis and treatment should always be considered.

References

1. Barber, G. Lisa. Thyroid Tumors in Dogs and Cats. Veterinary Clinics Small Animal Practice. 2007; 37:755-773.
2. Campos, M. et al. Clinical, Pathologic, and Immunohistochemical Prognostic Factors in Dogs with Thyroid Carcinoma. JVIM. 2014; 28: 1805-1813.
3. Grodski, Simon. Early Postoperative PTH Levels as a Predictor of Hypocalcemia and Facilitation Safe and Early Discharge After Total Thyroidectomy. Asian Journal of Surgery. 2007; 30:178-182.
4. Kaneko, J. Jerry. Thyroid Function. In: Clinical Biochemistry of Domestic Animals. 6th edition. Elsevier, 2009: 623-634.
5. Lathan, Patty. Thyroid Physiology. Mississippi State University, College of Veterinary Medicine. 2015.
6. Liptak, M. Julius. Canine Thyroid Carcinoma. Clinical Techniques in Small Animal Practice. 2007; 22:75-81.
7. Lunn, Katherine and Page, L. Rodney. Tumors of the Endocrine System. In: Witrow and MacEwen's Small Animal Clinical Oncology. 5th edition. Saunders, 2012: 504-531.
8. Tobias, M. Karen. Veterinary Surgery: Small Animal. Elsevier Saunders, 2012.
9. Tuohy, L. Joanne. Outcome following simultaneous bilateral thyroid lobectomy for treatment of thyroid gland carcinoma in dog: 15 cases (1994-2010). JAVMA. 2012; 241:95-103.
10. Wucherer, L, Katja. Thyroid Cancer in Dogs: An update Based on 638 cases (1995-2005). Journal of the American Animal Hospital Association. 2010; 46: 249-254.