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Hypothyroidism after Unilateral Thyroidectomy of a Thyroid Adenocarcinoma

Miros-Prieto R[1*], Ramírez-Serrano B[2], Márquez-Peña YC[2], Campuzano-Granados J[3], Núñez-Ochoa L[1]

[1]*Department of Pathology, Clinical Pathology Area, Faculty of Veterinary Medicine, National Autonomous University of Mexico, Mexico*

[2]*Department of Small Animal Medicine and Surgery, Faculty of Veterinary Medicine, National Autonomous University of Mexico, Mexico*

[3]*Department of Pathology, Anatomopathology Area, Faculty of Veterinary Medicine, National Autonomous University of Mexico, Mexico*

ABSTRACT

The patient was a 10-year-old female, spayed, Poodle dog with a subcutaneous mass in the ventral region of the neck. Fine needle aspiration was performed yielding a diagnosis of thyroid adenocarcinoma, which was confirmed by histopathology as solid follicular cell thyroid adenocarcinoma, after a right extracapsular thyroidectomy.

Canine Total Thyroxine and Free Thyroxine (cTT4) and (cFT4) were evaluated on 2 occasions; the first time on day 42 and the second one on day 63 of evolution. Both evaluations showed a decrease in cTT4 and cFT4 with an increase in Canine Thyroid-Stimulating Hormone (cTSH) compatible with hypothyroidism, secondary to unilateral thyroidectomy. Treatment with levothyroxine (Trioxil®; Alphachem) at a dose of 25 µg/kg orally twice a day was given.

Keywords: Thyroid adenocarcinoma; Thyroidectomy; Hypothyroidism; Thyroid profile; Levothyroxine

INTRODUCTION

Neoplasms of the thyroid gland in dogs are generally malignant [1,2]. Of all the dogs with thyroid adenocarcinoma, 60% are euthyroid, 30% hypothyroid secondary to the destruction of the thyroid parenchyma and 10% hyperthyroid associated with functional neoplasia [3]. The evaluation of thyroid hormone concentrations allows us to determine if it is a functional neoplasm or if it requires treatment before or after the surgical procedure [4].

The definitive diagnosis of thyroid adenocarcinoma is done by biopsy; however, there was an agreement between the cytological and histopathological findings in the neoplastic cells in this case.

CASE REPORT

The patient was a 10-year-old female, spayed, Poodle dog, with the presence of a subcutaneous mass in the ventral region of the neck, lateral to the trachea, firm consistency, non-mobile, well-defined borders, 2 cm in diameter.

The patient had a current vaccination and deworming schedule. During consultation, no alterations were observed at the physical examination.

It was decided to perform a cytological study of the mass using fine needle aspiration, as well as blood and urine sampling to perform a complete blood count, serum biochemistry and urinalysis.

The description of the cytological study was moderate

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Corresponding author Ruth Miros-Prieto, Department of Pathology, Clinical Pathology Area, Faculty of Veterinary Medicine, National Autonomous University of Mexico, Mexico, E-mail: ruthmiros@gmail.com

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cellularity confined to the end of the smear, represented by individual polygonal cells or grouped in small islets. The cells were characterized by having poorly defined or wave-shaped borders, abundant acidophilic, finely clumpy cytoplasm, with occasional small vacuoles, and a round hyperchromatic nucleus; some of these cells were bi-nucleated. High anisocytosis and anisokaryosis with 1 to 3 nucleoli of 2 µm in diameter were also observed. The overall mitotic index was low. In addition, some macrophages showing erythrophagia and a high number of erythrocytes were found. This description was interpreted as a malignant, glandular, epithelial neoplasia with a diagnosis of thyroid adenocarcinoma (**Figure 1**).

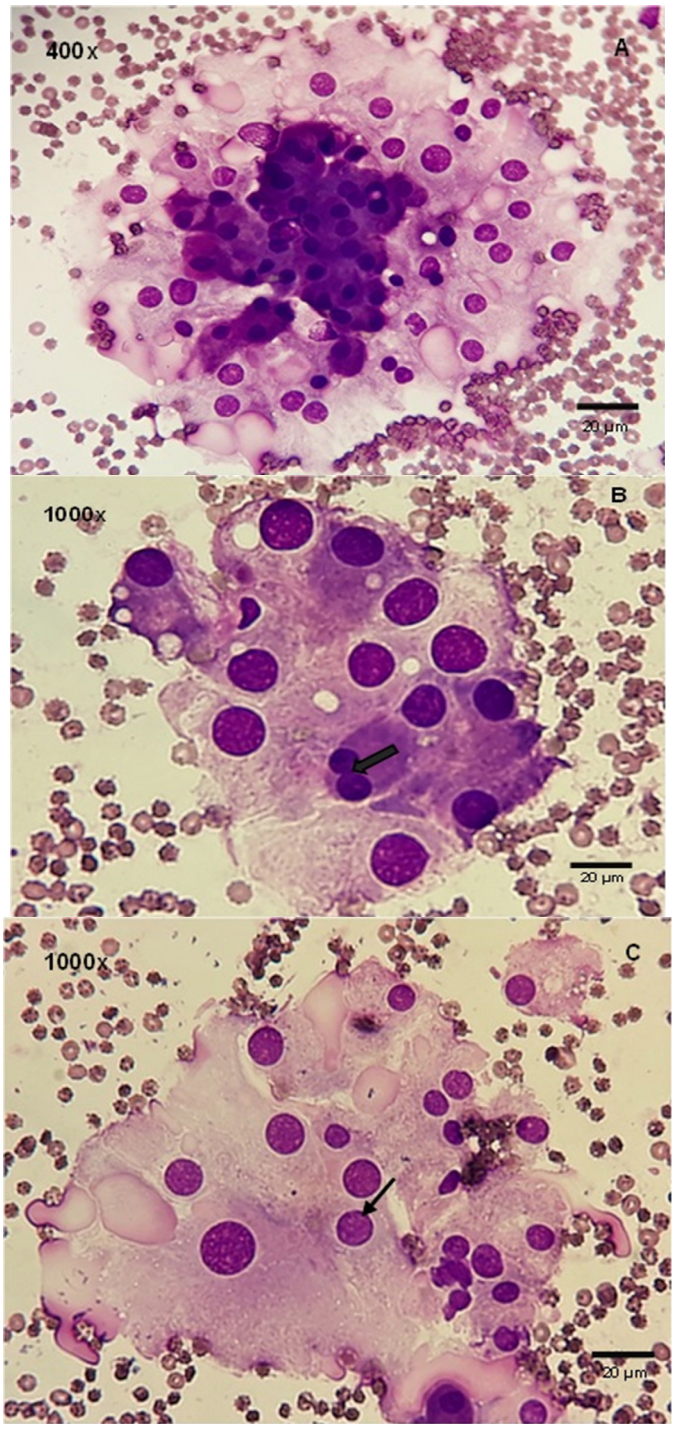

Figure 1: Cytological study of a subcutaneous mass in the ventral neck. A) Islets of polygonal cells are observed, with poorly defined or wave-shaped borders, abundant acidophilic cytoplasm, and a round euchromatic nucleus, B) The large arrow points to a binucleated cell, C) The small arrow points to a 2 µm nucleoli (Staining with Hycel Rapid Hemostain)

Complete blood count findings were relative erythrocytosis and increased Total Solids (TS) due to haemoconcentration and lymphopenia due to stress (**Table 1**). Prerenal hyperazotemia with hyperamylasemia and hyperchloremia due to haemoconcentration were observed by serum biochemistry. The slight increase in Alanine Aminotransferase (ALT) was related to an increase in hepatocellular permeability due to haemoconcentration, as well as the increase in Creatine Kinase (CK) and Aspartate Aminotransferase (AST) due to muscular effort and slight hypophosphatemia (**Table 2**). Marked proteinuria of 5.0 g/L with Urinary Specific Gravity (USG) of 1.032 was seen at the urinalysis (**Table 3**). As part of the clinical approach, a radiographic study of the lung fields was performed with left lateral-right lateral (Li-Ld), right lateral-left lateral (Ld-Li) and Ventrodorsal (VD) projections, in which no radiographic changes suggestive of lung metastasis were observed. Systemic blood pressure with Systolic Blood Pressure (SBP) of 183 mmHg (<140 mmHg), Diastolic Blood Pressure (DBP) of 110 mmHg and Mean Arterial Pressure (MAP) of 110 mmHg, were interpreted as marked arterial hypertension. Because of this situation, treatment with enalapril (Cardial®; Holliday), at a dose of 0.5 mg/kg orally, once a day, was started.

On day 27 of evolution, a right extracapsular thyroidectomy was performed. The mass was sent for histopathological examination, preserved in 10% formalin. Its macroscopic appearance was a multilobulated dark brown thyroid nodule, measuring 2.1 cm × 1.5 cm × 1.3 cm (**Figure 2**). The results of the histopathological study indicated the presence of neoplastic cells that replaced approximately 90% of the normal thyroid parenchyma, arranged in solid sheets and few follicles, poorly delimited by fine collagen trabeculae; scarce homogeneous eosinophilic material (colloid) was seen in the lumen of some follicles. The neoplastic cells were characterized by having abundant, polygonal, eosinophilic, finely granular cytoplasm and round, euchromatic nuclei. Eosinophilic pseudoinclusions were observed in some nuclei. The cells showed marked anisocytosis, anisokaryosis, nuclear pleomorphism. Numerous cells were binucleated and 3 atypical mitoses were observed in 10 fields at 400x. Extensive areas of haemorrhage and some foci of mineralization were present, without evidence of neoplastic tissue in the histological borders or blood or lymphatic vessel invasion. The morphological diagnosis was solid follicular cell thyroid adenocarcinoma (**Figure 3**). Subsequently, immunohistochemistry was performed to detect thyroglobulin, showing positive labelling within the cytoplasm of the cells (**Figure 4**).

On day 42 of evolution, a thyroid profile was performed indicating a decrease in Canine Total Thyroxine (cTT4) and Free Thyroxine (cFT4) and an increase in Canine Thyroid-Stimulating Hormone (cTSH) compatible with hypothyroidism, which was associated to the right unilateral thyroidectomy (**Table 4**).

Table 1: Results of complete blood counts during patient follow-up

COMPLETE BLOOD COUNT					
Analyte	Units	Reference	Day 1	Day 56	Day 190
Hematocrit	L/L	0.37-0.55	0.55	0.53	0.57
Haemoglobin	g/L	120-180	190	181	195
Erythrocytes	X 10^{12}/L	5.5-8.5	8.3	7.3	8.8
MCV	fL	60-77	66	73	65
MCHC	g/L	320-360	345	341	342
Platelet	X 10^{9}/L	200-600	Aggregates	384	396
Total Solids	g/L	60-75	78	78	92
Leukocytes	X 10^{9}/L	6.0-17.0	7.0	5.6	6.8
DIFFERENTIAL					
Neutrophils	X 10^{9}/L	3.0-11.5	6.7	4.8	5.9
Lymphocytes	X 10^{9}/L	1.0-4.8	0.1	0.4	0.3
Monocytes	X 10^{9}/L	0.1-1.4	0.1	0.2	0.3
Eosinophils	X 10^{9}/L	0-0.9	0.1	0.2	0.3
Basophils	X 10^{9}/L	rare	0	0	0
			Hemolysis +	Hemolysis +	Hemolysis + Lipemia +

MCV: Mean Corpuscular Volume, MGHC: Mean Corpuscular Haemoglobin Concentration

Table 2: Results of serum biochemistry during patient follow-up

SERUM BIOCHEMISTRY					
Analyte	Units	Reference	Day 1	Day 56	Day 190
Glucose	mmol/L	3.88-6.88	5	5.9	6.2
Urea	mmol/L	2.1-7.9	9.3	16.1	12.5
Creatinine	µmol/L	60-130	92	132	96
Cholesterol	mmol/L	2.85-7.76	6.45	8.56	10.54
Total Bilirubin	µmol/L	1.7-5.16	3.6	2	3.9
Conjugated	µmol/L	0-4.2	1.2	0.7	0.7
Unconjugated	µmol/L	0-2.5	2.4	1.3	3.2
ALT	U/L	<70	99	39	40
AST	U/L	<55	75	52	24
ALP	U/L	<189	189	61	95
Amylase	U/L	<1110	1502	868	975
CK	U/L	<213	705	567	139
Total Protein	g/L	56-75	71	70	76
Albumin	g/L	29-40	34	31	37
Globulin	g/L	23-39	37	39	39
A/G Ratio	-	0.78-1.46	0.92	0.79	0.95
Calcium	mmol/L	2.17-2.94	2.63	2.45	2.73
Phosphorus	mmol/L	0.80-1.80	0.74	1.17	1.12
Ca/P ratio	-	1.3-3.1	3.55	2.09	2.44
Potassium	mmol/L	3.8-5.4	4.4	4.9	4.5
Sodium	mmol/L	141-152	151	148	149
Chloride	mmol/L	108-117	118	116	118
Bicarbonate	mmol/L	17-25	19	18	21
Nonvolatile Acids	mmol/L	12-24	18	19	14
cSID	mmol/L	30-40	33	32	31
Osmolality	mOsm/kg	280-305	304	306	305
Triglycerides	mmol/L	0.6-1.2	1	1.3	4.4
-	-		Hemolysis +	-	Hemolysis + Lipemia +

ALT: Alanine Aminotransferase, A/G: Albumin/Globulin Rate, AST: Aspartate Aminotransferase, Ca/P: Calcium/Phosphorus, CK: Creatine Kinase, cSID: Clinical Strong Ion Difference, ALP: Alkaline Phosphatase

Table 3: Urinalysis results during patient follow-up

URINALYSIS		
Day 1	Day 56	Day 190
Urine collection method	Cystocentesis	Cystocentesis
PHYSICAL EXAM	**PHYSICAL EXAM**	**PHYSICAL EXAM**
Appearance: Transparent	Appearance: Transparent	Appearance: Cloudy 3+
Colour: Yellow	Colour: Yellow	Colour: Yellow
USG: 1.032	USG: 1.039	USG: 1.030
BIOCHEMICAL EXAM	**BIOCHEMICAL EXAM**	**BIOCHEMICAL EXAM**
pH: 7.5	pH: 6.5	pH: 7.0
Protein: 5.0 g/L	Protein:1.0 g/L	Protein: 1.0 g/L
Glucose: 0 mmol/L	Glucose: 0 mmol/L	Glucose: 0 mmol/L
Ketones: Negative	Ketones: Negative	Ketones: Negative
Bilirubin: Negative	Bilirubin: Negative	Bilirubin: Negative
Urobilinogen: Normal	Urobilinogen: Normal	Urobilinogen: Normal
RBC's: 0/µL	RBC's: 0/µL	RBC's: 50/µL
SEDIMENT EXAMINATION Without alterations	SEDIMENT EXAMINATION Without alterations	SEDIMENT EXAMINATION Erythrocytes 3-6 /field (400x)

USG: Urinary Specific Gravity, Hb: Haemoglobin, RBC's: Red Blood Cells

Table 4: Thyroid profile results during patient follow-up

THYROID PROFILE					
Analyte	**Units**	**Reference**	**Day 42**	**Day 63**	**Day 90**
cTT4	nmol/L	19.0 – 45.0	< 6.44	*	84.9
cFT4	pmol/L	12.5 – 50.0	5.21	8.47	29.5
cTSH	ng/ml	0.017 – 0.591	1.53	3.85	0.303

cTT4: Canine Total Thyroxine, cFT4: Canine Free Thyroxine, cTSH: Canine Thyroid Stimulating Hormone. *Below detection limit.

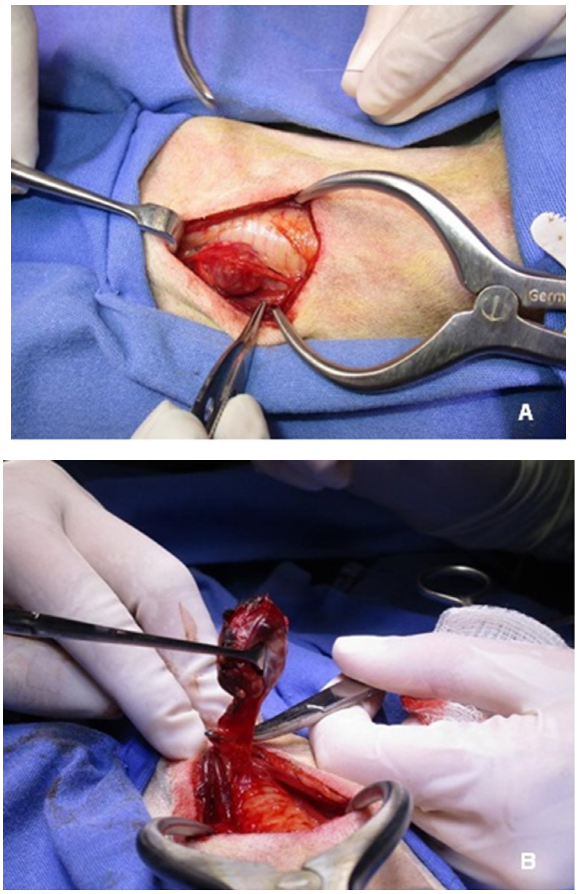

Figure 2: Right extracapsular thyroidectomy. A) Surgical procedure, B) A dark brown, multilobulated thyroid nodule is observed

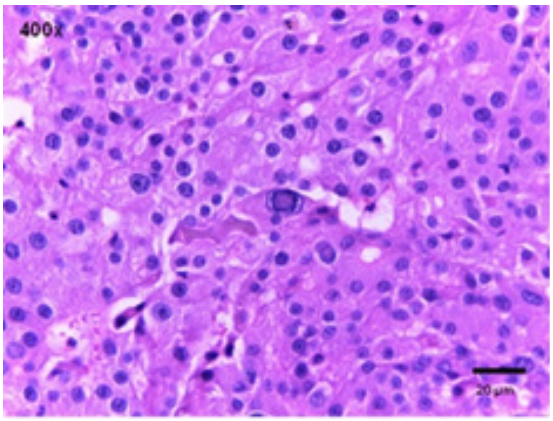

Figure 3: Histopathological study. Polygonal cells are seen with abundant eosinophilic cytoplasm and round, euchromatic nuclei, arranged in solid mantles and few follicles, poorly delimited with fine collagen trabeculae (H and E stain)

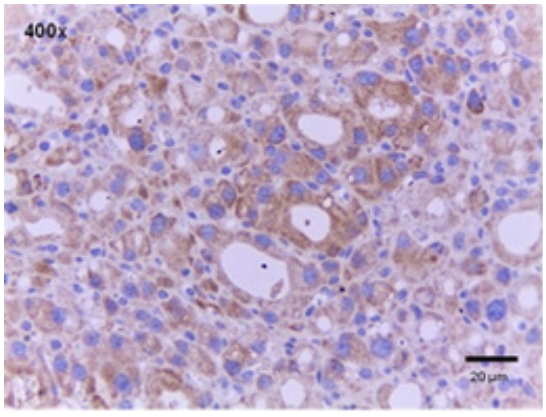

Figure 4: Positive immunohistochemistry for thyroglobulin inside the

cytoplasm of neoplastic cells

On day 56 of evolution, the ionized calcium concentration was 1.34 mmol/L (1.20-1.50), which made it possible to rule out hypoparathyroidism, given that this complication can occur when removing the parathyroid glands by thyroidectomy. On this day, a complete blood count, serum biochemistry, and urinalysis were also performed. Findings in the complete blood count were relative erythrocytosis and increased TS due to haemoconcentration. The increase in TS was partially associated with analytical interference due to hyperazotemia and hypercholesterolemia. Lymphopenia was associated with stress. Serum biochemistry showed prerenal hyperazotemia due to haemoconcentration, marginal hyperlipidemia associated with decreased thyroid hormones, as well as increase in CK due to muscular effort. The urinalysis yielded proteinuria of 1.0 g/L with USG of 1.039.

On day 63 of evolution, a thyroid profile was performed, resulting in undetectable cTT4 values, persistence of decreased cFT4 values and a greater increase in cTSH, which confirmed the diagnosis of hypothyroidism secondary to the right unilateral thyroidectomy. Due to this, treatment with levothyroxine (Trioxil®; Alphachem) was started at a dose of 25 µg/kg orally, twice a day. On day 90 of evolution, the thyroid profile was re-evaluated to adjust the treatment. An increase in cTT4 related to levothyroxine overdose was observed. Due to the proteinuria reported in the urinalysis on day 90, the protein/creatinine ratio in urine (UPC) was assessed, with a significant proteinuria of 2.1 (0.2-0.5) (**Table 5**). Based on these results, it was indicated to reduce the levothyroxine dose to 14 µg/kg orally twice a day. Treatment with amlodipine (Norvasc®; Pfizer) at a dose of 0.2 mg/kg orally, once a day, was given because of persistent proteinuria.

Table 5: Results of the urine protein/creatinine ratio during follow-up of the patient

URINE PROTEIN/CREATININE RATIO					
Analyte	**Units**	**Reference**	**Day 90**	**Day 135**	**Day 190**
Creatinine	mg/dL	-	70.8	139.7	73.4
MPT	mg/dL	-	147.9	227	227
UPCR	-	(0.2-0.5)	2.1	1.6	3.09 (Hematuria)

MPT: Microprotein, UPCR: Urine Protein/Creatinine Ratio

By day 120 of evolution, marked hypertension was observed with SBP: 187 mmHg (<140 mmHg), DBP: 107 mmHg, MAP: 140 mmHg. On day 134 of evolution, cTT4 continued to be elevated, so it was indicated to reduce the frequency of treatment to 14 µg/kg orally once a day. On day 135 of evolution, the UPC ratio was again carried out, which had decreased, however, the patient continued with significant proteinuria of 1.6 (0.2-0.5).

On day 190 of evolution a complete blood count, serum biochemistry, and urinalysis were performed again. Complete blood count reported relative erythrocytosis and an increase in TS due to haemoconcentration. The increase in TS was partially associated with analytical interference with lipemia and haemolysis; stress lymphopenia was also found. The serum biochemistry analysis yielded hyperlipidemia due to alterations in lipid metabolism, hyperproteinemia due to haemoconcentration, and partly due to analytical interference because of hyperlipidemia. Proteinuria and haematuria were observed by urinalysis. The UPC ratio increased significantly to 3.09 (0.2-0.5).

This was the last time the patient's tutors communicated with the hospital.

DISCUSSION

Thyroid adenocarcinoma occurs with a higher incidence in dogs over 9 years of age. Breeds with the highest reports are Golden Retriever, Beagle, Boxer and Siberian Husky [5]. The majority of the reported thyroid neoplasms in dogs are malignant, vascular, invasive and non-functional, of which 90% are primary neoplasms [1,2]. This neoplasia may arise from thyroid follicular cells or parafollicular cells [6]. According to histopathological classification, follicular cell adenocarcinomas can be categorized as follicular, compact, follicular-compact or papillary [1,7]. Follicular adenocarcinomas are the most common type and are usually thyroglobulin positive [8]. Parafollicular adenocarcinomas are also known as medullary or C-cell adenocarcinomas.

Biopsy remains as the reference for diagnosis however excisional biopsy in small neoplasms has the advantage of being diagnostic and therapeutic. Fine needle aspiration cytology is minimally invasive, it usually does not require sedation or general anaesthesia, however, it is mentioned that hemodilution and low cellularity might make diagnosis difficult [7,8]. The cytological study performed on the patient described a high number of polyhedral cells individually or in small islets with sufficient criteria for malignancy; the cytological diagnosis was compatible with thyroid adenocarcinoma. The diagnosis was confirmed with the histopathological study of the ventral neck mass, to our knowledge; this is the first report where both studies described similar characteristics in the neoplastic cells. Immunohistochemistry confirmed the follicular origin by revealing thyroglobulin in the cytoplasm of the cells.

Of patients with thyroid adenocarcinoma, 60% are euthyroid, 30% hypothyroid secondary to the destruction of the thyroid parenchyma, and 10% hyperthyroid associated with functional neoplasia [3]. Most thyroid neoplasms are firm, non-painful, and can be uni or bilateral; approximately 67%-75% of neoplasms are unilateral and 25%-33% are bilateral [7]. Bilateral neoplasms are generally malignant and more likely to metastasize than unilateral ones. The most common sites of metastasis are the lungs, regional lymph nodes, jugular veins, larynx, trachea, oesophagus and heart [1,2]. The radiographic studies of lung fields performed on the patient did not show changes suggestive of metastasis.

Surgical excision provides the best outcome for neoplasms

that do not have extensive invasion of deep thyroid tissue. Thyroidectomy is not recommended when the neoplasm is fixed (non-mobile) or with extensive invasion of adjacent structures [5]. The most common complications of thyroidectomy are hypocalcemia due to hypoparathyroidism if the parathyroid glands are also removed, damage to the recurrent laryngeal nerve, and hypothyroidism [6]. The survival time after thyroidectomy is approximately 3 years if the neoplasia is unattached and 6 months to 12 months if it is non-mobile or invasive [9].

Most dogs with thyroid adenocarcinoma are taken for consultation because of a palpable, ventral, cervical mass, which may be an incidental finding by the tutor, as it was in this case. Secondary clinical signs include coughing, tachypnea, dyspnea, dysphagia, dysphonia, laryngeal paralysis, and facial edema. Secondary acute haemorrhage may occur due to invasion of the cervical vessels [8]. Clinical signs may also be related to hypothyroidism or hyperthyroidism, depending on the degree of tissue destruction or functionality of the neoplasm [5]. When the thyroid neoplasia is functional, there are clinical signs associated with hyperthyroidism such as polyphagia, weight loss, muscle atrophy, polyuria and polydipsia [3].

Dogs do not usually show clinical signs of abnormal thyroid function [8]. In this case, the patient did not present any alterations at physical examination or laboratory results that suggested hypothyroidism or hyperthyroidism before performing the thyroidectomy. The only alteration in the patient was systemic hypertension which is compatible with hyperthyroidism [4,10].

It is necessary to know the concentrations of thyroid hormones in order to determine if it is a functional neoplasm and if treatment is required before or after the surgical procedure [4]. Because in this patient a cytological diagnosis of thyroid adenocarcinoma was established before performing the thyroidectomy, the concentrations of cTT4, cFT4 and cTSH had to be evaluated to determine if early levothyroxine therapy was required. The determination of thyroid hormones should be carried out when there is suspicion of thyroid neoplasia. Supplementation was started approximately one month after the thyroidectomy and after the assessment of thyroid hormones, in which a decrease in cTT4, cFT4 and an increase in cTSH were observed on 2 occasions.

In a survival analysis report of 144 dogs with thyroidectomy for thyroid neoplasia, 18 dogs (12.5%) received levothyroxine supplementation after surgery; 12 dogs (66.7%) were euthyroid before thyroidectomy [11]. In a retrospective analysis of 44 dogs treated with thyroidectomy, 28 dogs (66.6%) had differentiated follicular cell adenocarcinoma; 13 dogs (46.42%) received lifelong levothyroxine supplementation after thyroidectomy [1]. It is thought that the alterations were secondary to thyroidectomy since the cTT4 remained below the reference values and the cTSH continued to increase instead of normalizing. On day 56 of evolution, the patient showed depression, a clinical sign reported in hypothyroidism [4,12]. Systemic hypertension in this patient may have had several origins, one of them is early renal dysfunction, related to the proteinuria that was persistently found. Both changes (proteinuria and hypertension) were present before and after thyroidectomy, however, it was not possible to determine what the initial alteration was, hypertension as a consequence of early renal dysfunction or early renal dysfunction as a consequence of hypertension. Hypertension was only related to a possible thyrotoxicosis, since patients with hypothyroidism may develop hypotension [13].

Relative erythrocytosis was observed in the three complete blood counts performed, as evidence of hemoconcentration, which partially correlates with the increase in TS; This is also it is explained by hyperazotemia, hyperamylasemia, hyperchloremia and hyperproteinemia evidenced by serum biochemistry.

Persistent hyperlipidemia was related to hypothyroidism. This alteration is associated with a decrease in lipid metabolism due to a decrease or absence of thyroid hormones, which favors the accumulation of lipids in blood plasma [14]. Hyperlipidemia persisted from day 56 of evolution until day 190. On this last day, hyperlipidemia could not be resolved even with the levothyroxine treatment.

Overdose of levothyroxine has been seen most frequently in patients receiving treatment twice a day, as in this case [15]. The diagnosis of thyrotoxicosis is mainly based on the presence of clinical signs, including nervousness, panting, tachypnea, tachycardia, aggressiveness, polyuria, polydipsia, polyphagia, and weight loss [15]. Elevated serum concentrations of cTT4 and cFT4, with undetectable cTSH, support the diagnosis. The patient presented an increase in cTT4 and systemic hypertension with values higher than the first measurement. Hypertension was probably related to the increase in thyroid hormones secondary to the overdose with levothyroxine.

The most important risk factors reported in humans regarding the development of unilateral post-thyroidectomy hypothyroidism are thyroiditis, presurgical TSH concentration, and the presence of anti-thyroid antibodies. High pre-surgical TSH concentration, in the case of thyroid lobectomy in humans, represents a high probability of developing hypothyroidism and requiring thyroid hormones after surgery to maintain an euthyroid state [16].

In humans, normalization of TSH after total thyroidectomy can be prolonged, which is why TSH is considered relevant in order to determine the appropriate thyroid hormone replacement therapy [17].

CONCLUSION

Neoplasms detected in the thyroid glands in dogs are generally malignant. Determination of thyroid hormones should be performed in suspected thyroid neoplasia. Once the diagnostic is established, clinical and treatment approaches allow improving survival and evolution time. In this patient, the cytological and histopathological study had a precise correlation, unlike what is mentioned by other authors. In this report, it was not possible to conclude whether the right unilateral thyroidectomy was the only cause of hypothyroidism or was it a factor that added to the decrease in thyroid hormones as a consequence of thyroid adenocarcinoma.

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CONFLICT OF INTEREST

No conflicts of interest have been declared.

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