Case Report

Metastasis of Thyroid Gland Carcinoma to Mandibular Lymph Node

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Abstract

Thyroid neoplasms encompass a range of abnormal growths of the neoplastic cells ranging from benign adenomas to malignant carcinomas and are one of the lists for the differential diagnoses from the thyroid gland or parathyroid neoplasm. These tumors cause various clinical signs in dogs, including breathing difficulties, swallowing issues, and compressing the surrounding tissues. Diagnosis involves a combination of physical examinations, radiography, ultrasound, hematology, clinical pathology investigation, and histopathological analyses. Treatment options depend on tumor types and stages, with surgical resection being common for benign tumors and more aggressive approaches such as surgery, radiation, and chemotherapy for malignancies. Even if the metastasis occurs to the regional lymph nodes, the mandibular lymph node metastasis is uncommon. The prognosis varies, with carcinomas posing greater challenges, particularly if they metastasize. Continuous monitoring and follow-up are crucial to assess treatment outcomes and tumor recurrences. Early detection and comprehensive veterinary management are essential in addressing thyroid neoplasms in dogs effectively.

Keywords: Thyroid gland carcinoma, Metastasis, Mandibular lymph node

การแพร่กระจายของมะเร็งของต่อมไทรอยด์ไปสู่ต่อมน้ำเหลืองที่บริเวณกราม

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บทคัดย่อ

เนื้องอกของต่อมไทรอยด์เป็นเนื้องอกที่เกิดจากความผิดปกติในการเจริญเติบโตของเซลล์ที่บริเวณตำแหน่งของไทรอยด์และพาราไทรอยด์ซึ่งสามารถพบได้ทั้งเนื้องอกที่ไม่ใช่มะเร็งและเนื้องอกที่เป็นมะเร็ง โดยเนื้องอกดังกล่าวมักได้รับการวินิจฉัยแยกจากเนื้องอกของเนื้อเยื่อข้างเคียง เช่น พยาธิสภาพการโตของต่อมไทรอยด์และพาราไทรอยด์เนื่องจากการแบ่งตัวเพิ่มจำนวนของเซลล์ เนื้องอกของต่อมไทรอยด์ ต่อมพาราไทรอยด์ มะเร็งของต่อมไทรอยด์และพาราไทรอยด์ อย่างไรก็ตามเนื้องอกในตำแหน่งดังกล่าวมักส่งผลให้เกิดอาการทางคลินิกในเรื่องของการหายใจลำบาก การกินได้ลำบากและการกดทับของเนื้องอกสู่เนื้อเยื่อข้างเคียง ซึ่งโดยทั่วไปแล้วการวินิจฉัยเนื้องอกดังกล่าวจำเป็นต้องได้รับการตรวจร่างกาย การฉายภายรังสี การทำอัลตราซาวนด์ การตรวจทางพยาธิวิทยาคลินิกและการตรวจทางจุลพยาธิวิทยา ในส่วนของการรักษาขึ้นอยู่กับลักษณะชนิดของเนื้องอกและระยะ โดยการทำการผ่าตัด การฉายรังสีและการทำเคมีบำบัด นอกจากนั้นเนื้องอกดังกล่าวสามารถแพร่กระจายไปสู่ต่อมน้ำเหลืองข้างเคียงแต่มีรายงานการพบที่ไม่บ่อยหนัก ดังนั้นการพยากรณ์โรคจึงอาจขึ้นอยู่กับการแพร่กระจายของเนื้องอกไปยังต่อมน้ำเหลือง การเฝ้าระวังการแพร่กระจายจึงมีความสำคัญต่อการรักษาและการจัดการ โดยการตรวจพบมะเร็งในระยะเริ่มต้นจึงส่งผลต่อประสิทธิภาพในการรักษา

คำสำคัญ : มะเร็งต่อมไทรอยด์ การแพร่กระจายไปยังต่อมน้ำเหลือง ต่อมน้ำเหลืองบริเวณกราม

Introduction

Thyroid gland carcinoma in dogs is a rare and aggressive tumor that originates in the thyroid glands (Meuten 2020). The thyroid glands are small endocrine glands, and play a particularly crucial role in producing the thyroxine for metabolism and regulating the calcium level in the body together with the parathyroid gland (Stanley and Martin 2023). Thyroid carcinoma originates from uncontrolled growth of the neoplastic cells and might cause abnormal levels of hormone from thyroid gland cells, especially thyroxine, calcitonin, and also other hormones from the parathyroid gland such as parathyroid hormone (Worley 2023). The clinical signs might be associated with hypercalcemia, including polyuria and polydipsia, weakness, loss of appetite, vomiting, constipation, muscle tremors, and renal failure. The diagnosis involves to hematological, serum biochemistry test, and serum hormonal level for identifying the clinical disorders. Moreover, the imaging analysis such as radiography or CT-scan for locating the tumor, histopathological examination, and/or immunohistochemistry for confirming the presence of carcinoma (Morris and Dobson 2008; Dobson and Lascelles 2011).

For the specific treatment, the complete surgical removal of the affected thyroid gland, parathyroid gland, and metastatic tissues is undeniable, and clinicians might need to consider additional therapy such as radiation therapy or chemotherapy (Dobson and Lascelles 2011). The prognosis is usually guarded as a malignant and aggressive tumor because the tumor behavior can cause metastasis to regional lymph nodes and lungs with abnormal levels of the hormone level for metabolism and calcium level regulation. Most dogs usually develop clinical signs related to hypothyroidism and abnormal calcium levels after surgical removal, especially, hypocalcemia. Therefore, tumor monitoring and clinical follow-up are necessary.

In this case report, we introduce the clinical case of the dog which was diagnosed with the neoplasm of the thyroid carcinoma, which is a rage and aggressive neoplasm, and metastasis to the mandibular lymph nodes. Moreover, the Immunohistochemistry panels (chromogranin A, calcitonin, parathyroid hormone, thyroglobulin, thyroid transcription factor-1; TTF-1) have been used for differentiating the thyroid carcinoma from other neoplasms (Doss et al., 1998; Meuten 2020).

Case description

A 10-year-old female beagle dog, 4.1 kilograms in body weight was presented at the Prasuarthorn Animal Hospital, Faculty of Veterinary Science, Mahidol University. The dog had a history of enlargement of tissues around the thyroid and parathyroid glands. The vaccination and parasitic prevention program were complete, and there were no other abnormal medical conditions.

On initial physical examination, the dog was bright, alert, and responsive. The heart and lung sounds were normal, the thoracic radiography illustrated the interstitial lung pattern, and the vertebral heart score was 10.0. (Figure 1). The metastatic nodules and abdominal masses were not found from radiography.

For clinical diagnosis, a clinical pathology examination was performed to rule out other systemic diseases when the first visit to our animal hospital. The complete blood count presented mild normocytic normochromic anemia, and there were no other remarkable abnormalities from hematology. The ALT (four times from the upper reference range) and ALP

(three times from the upper reference ranges) were highly elevated from the serum biochemistry investigation. The total T4 hormone level was elevated when compared to the reference range. The full results of the blood examination are shown in Table 1.

The computed tomography suggested that there were heterogeneously contrasted enhancing with 150 HU of the left thyroid gland which illustrated the irregular shape with approximately dimension 2.0 x 1.5 x 2.0 cm, and non-presence of iodine uptake within gland parenchyma with 45 HU. The right thyroid is normal size with non-presence of iodine uptake within the gland. The post-contrast images illustrate the left thyroid gland with heterogeneous contrast-enhancing its 150 HU, and no evidence of vessels invasive. The regional lymphadenopathy was observed from both the mandibular lymph nodes and the right superficial cervical lymph nodes. The multiple mediastinal lymphadenopathies were observed; however, there was no evidence of pulmonary metastasis. The multiple masses vary in size and were located from the right liver lobes.

Based on the suggestion from computed tomography and ultrasonography, the cytology was performed at the left thyroid and parathyroid glands. Then, the cytological findings found a cluster of neoplastic cells and mixed inflammatory cells. The cluster of neoplastic cells is a polyhedral cell with basophilic cytoplasm and hyperchromatic round to oval nuclei indicating a tumor of epithelial origin such as adenoma or adenocarcinoma (Figure 2). Therefore, complete surgical removal and histopathological examination of the thyroid and parathyroid were recommended. The gross appearance of the neoplasm was not described in the clinical record. After the surgical removal of the parathyroid and thyroid glands, the samples were sent to the Center for Veterinary Diagnosis, Faculty of Veterinary Science, Mahidol University for histopathological diagnosis. The samples were trimmed, embedded as paraffin-embedded tissues, and sectioned at 3 μm. The sections were stained for routine hematoxylin and eosin staining for histopathological diagnosis. The histopathological findings (Figure 3) showed the location of the neoplasm was closed to the thyroid glands and parathyroid gland, and the neoplasm was well-circumscribed, well-differentiated, encapsulated, and the neoplastic cells formed as sheets of densely packed polygonal cells. The neoplasm was separated by a thin fibrovascular stroma. Each neoplastic cell showed moderate pleomorphism, anisocytosis, and anisokaryosis. The cells varied from round to polygonal and have round nuclei with hyperchromatic nuclei. The cytoplasm was eosinophilic cytoplasm. Moreover, the neoplastic cells also infiltrated the subcapsular sinus of the mandibular lymph nodes. The histopathological diagnosis suggests for thyroid carcinoma or parathyroid carcinoma. Therefore, immunohistochemistry was performed for differentiating diagnosis. Briefly, the samples were sectioned at 6 μm coated on the positively charged glass slides and sent to the Institute of Pathology, Ministry of Public Health, Thailand. The sets of the mouse monoclonal antibodies were used as primary antibodies (TTF-1, thyroxine, calcitonin, PTH receptor, chromogranin A) for differentiating thyroid carcinoma and parathyroid carcinoma (Table 2). The neoplasm was strongly positive for chromogranin A (Figure 4) and TTF-1 (Figure 5) indicating the thyroid origin of the neoplastic cells.

After the total thyroid and parathyroid surgical removal operation, the dog was routinely followed up by clinicians for monitoring the hematological results, serum biochemistry, blood gas, and electrolytes in Table 3.

The hematological results, serum biochemistry, and total T4 level were returned to be within the reference ranges after the operation. Although the acid-base balance is slightly metabolic alkalosis with physiological compensation (normal bicarbonate, but increased base excess). The serum electrolyte was slightly changed. For example, the ionized calcium was slightly low level but still was within the lower limit of the reference range and mild hyperkalemia in Table 3. Therefore, routinely followed up of the electrolytes should be intensively monitored. After the complete surgical removal of the tumors, the chemotherapy was performed according to the 2016 American Hospital Association Oncology guidelines for dogs and cats (Biller et al., 2016). The carboplatin was intravenously administered as chemotherapy once every three weeks for a total of four treatments after surgical removal of the thyroid carcinoma.

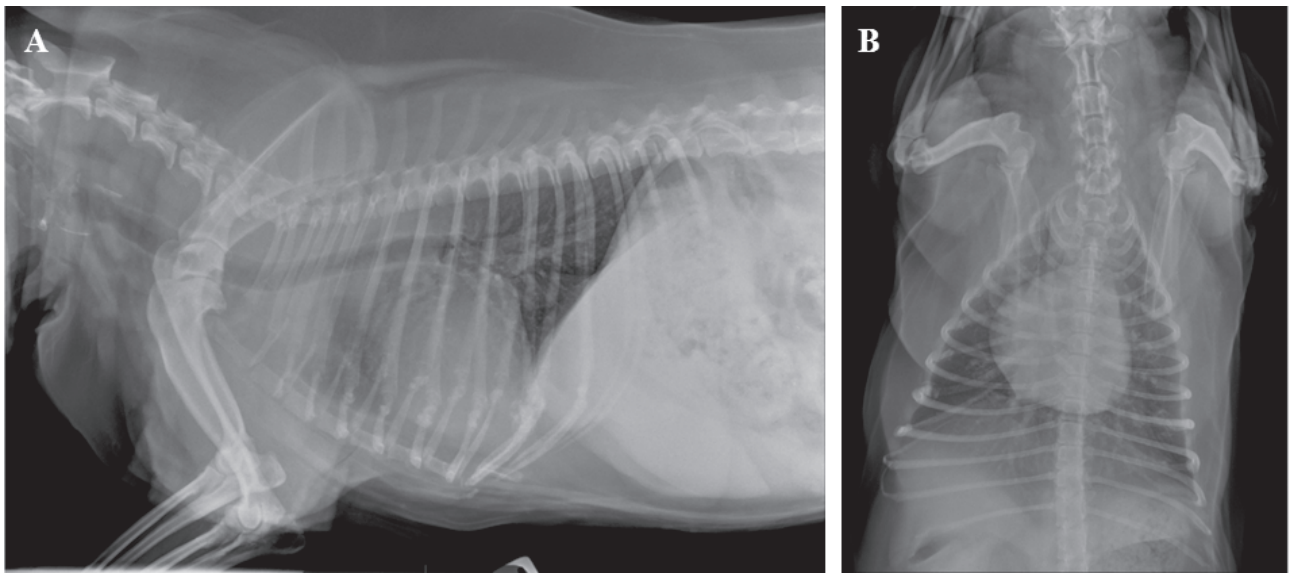

Figure 1. Right lateral recumbency (A) and ventrodorsal (B) view of thoracic radiography.

Table 1. Results of blood examination on 21 June 2023, the first day of the visit before surgical removal of thyroid and parathyroid gland.

Complete blood count			
Parameters	**21/06/23**	**Reference**	**Unit**
Total white blood cells	14.48	6.0-17.0	$10^3/\mu L$
Monocytes	1.16	0.15-1.35	$10^3/\mu L$
Neutrophils	11.29	3.00-11.50	$10^3/\mu L$
Band neutrophils	0	0-3	%
Lymphocytes	2.03	1.00-4.80	$10^3/\mu L$
Eosinophils	0.14	0.10-1.25	$10^3/\mu L$
Basophils	0	0.00-0.10	$10^3/\mu L$
Red blood cells (RBC)	4.91	5.0-9.0	$10^6/\mu L$
Hemoglobin (Hb)	10.7	10.0-18.0	g/dL
Hematocrit (Hct)	32.6	35-55	%
MCV	66.5	60-77	fL
MCH	21.8	20-25	pg
MCHC	32.8	32-36	g/dL
Platelet count (PLT)	482	200-500	$10^3/\mu L$
RDW	15.1	12-15	%
Plasma protein	7.6	6.0-7.5	g/dL
Platelet smear	Aequate		
Blood morphology			
Polychromasia	Few		
Anisocytosis	Few		
Macrocyte	Few		
Blood chemistry			
Parameters	**21/06/2023**	**Reference**	**Unit**
BUN	11	7-27	mg/dL
Creatinine	0.96	0.5-1.8	mg/dL
ALT	488	10-100	U/L
ALP	781	23-212	U/L
Total protein	7.0	5.2-8.2	g/dL
Albumin	3.1	2.7-3.8	g/dL
Glucose	100		
Total T4	6.48	1.0-4.0	µg/dL

Abbreviation: Mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC), Red blood cell distribution width Blood urea nitrogen (BUN), Alanine aminotransferase (ALT), Alkaline phosphatase (ALP), Total T4 (Total thyroxine 4).

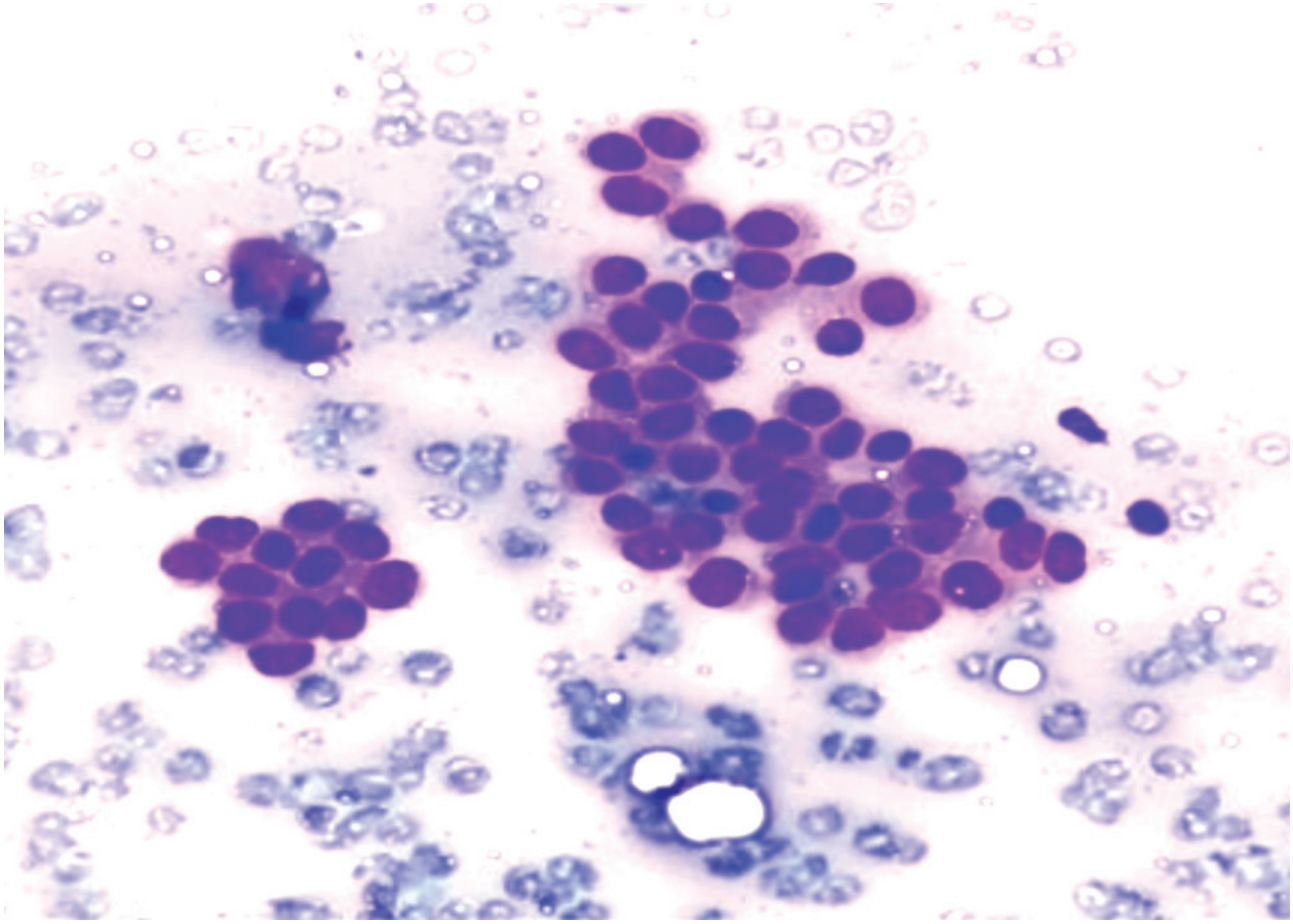

Figure 2. The cytological finding shows a cluster of epithelial-origin neoplastic cells showing pleomorphism, anisocytosis, and anisokaryosis. The cells are polygonal, and the nucleus is round with hyperchromatic nuclei (40x).

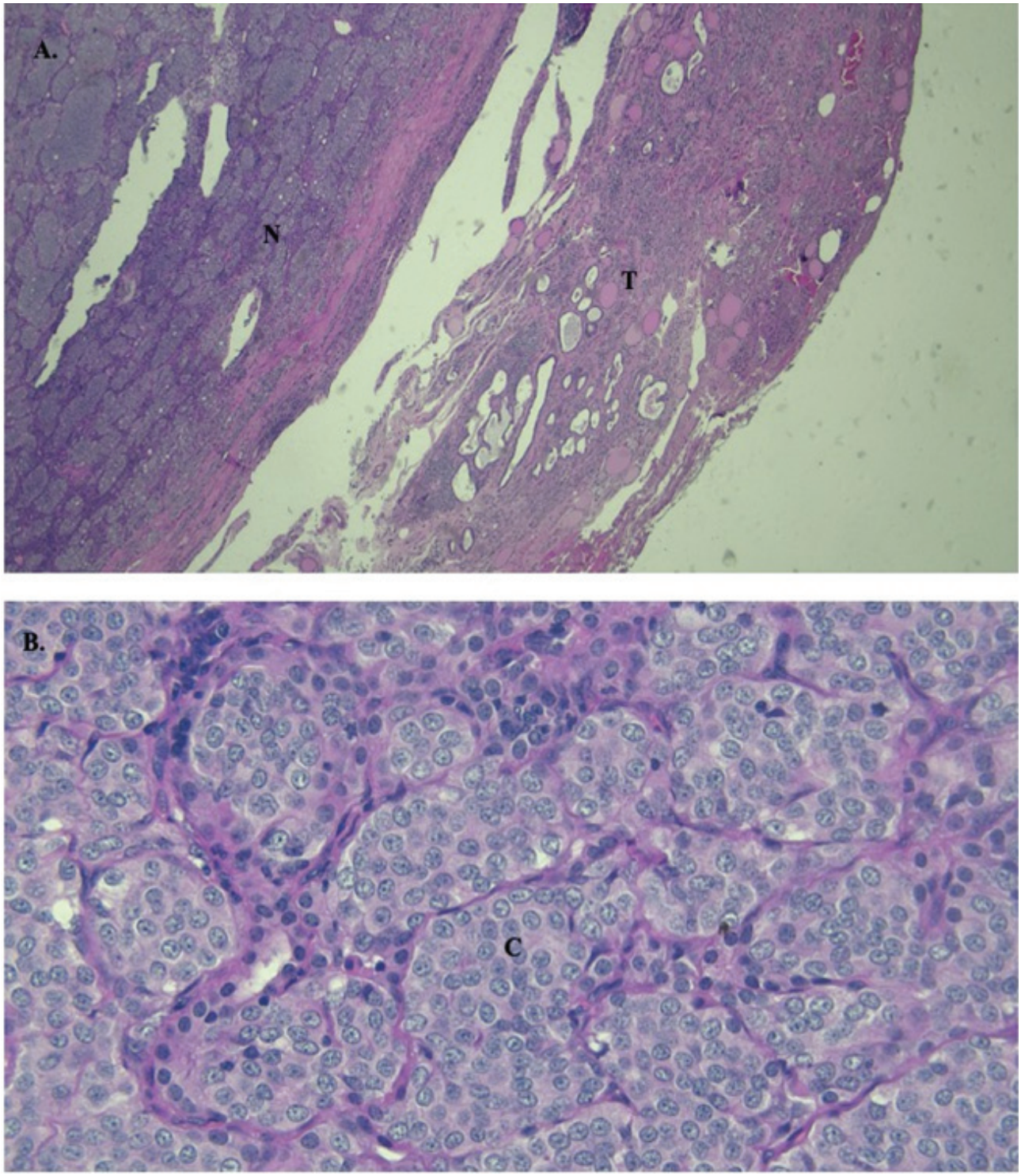

Figure 3. Thuroid carcinoma with H&E stain 4x and 40x respectively. A. Neoplasm (N) and thyroid gland (T) 4x. B. Thyroid carcinoma (C) proliferated as a lobular pattern, and the cells showed moderate pleomorphism anisocytosis, and anisokaryosis 40x.

Table 2. Immunohistochemistry for differentiating the thyroid carcinoma from other neoplasms.

Immunohistochemistry	Results
Chromogranin A	Positive
Calcitonin	Negative
Parathyroid hormone	Negative
Thyroglobulin	Negative
TTF-1	Positive

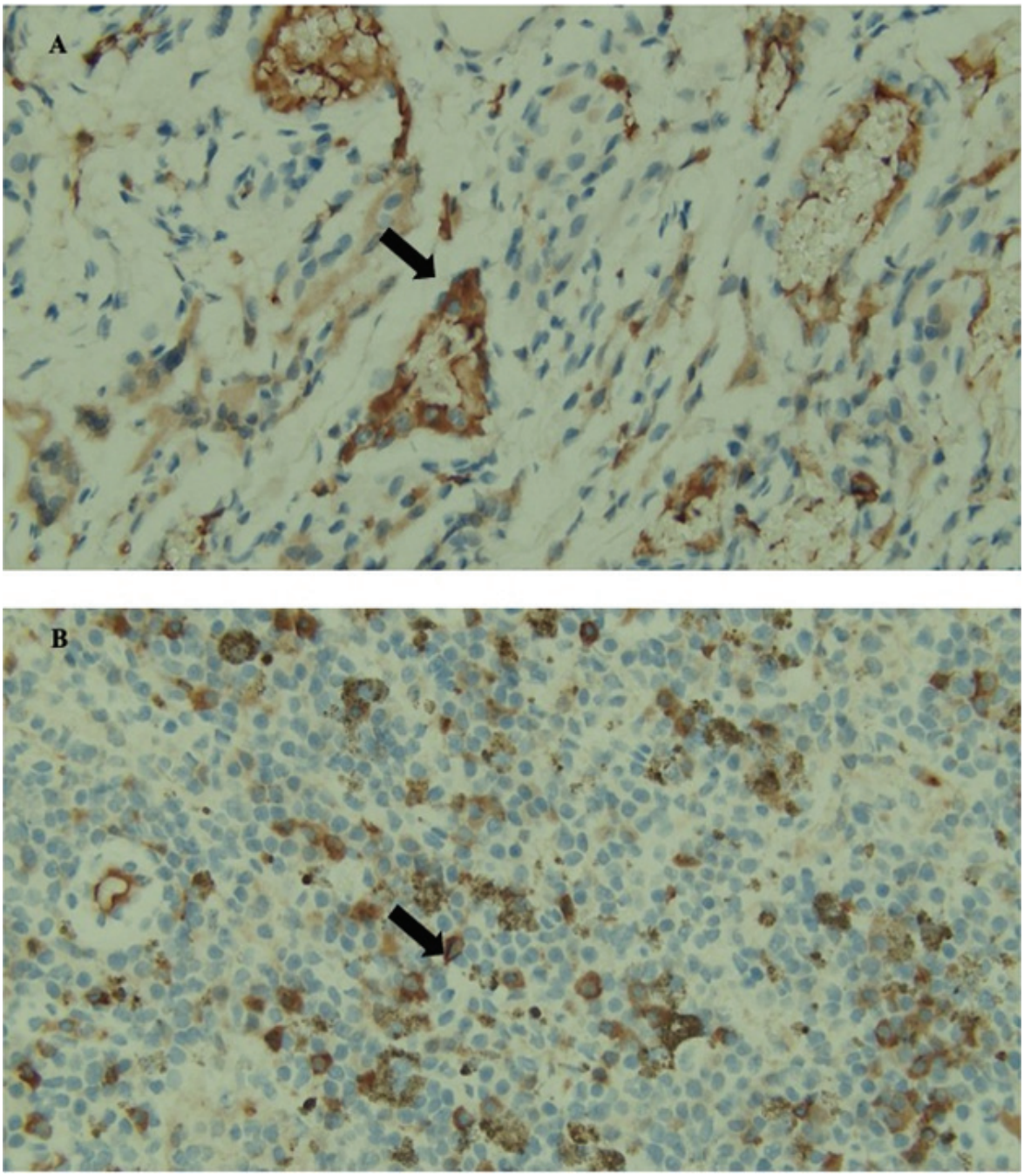

Figure 4. Chromogranin A immunohistochemistry 40x of thyroid and parathyroid gland (A) and submandibular lymh node (B), respectively. The brown-stained positive cells are neoplastic cells (arrows).

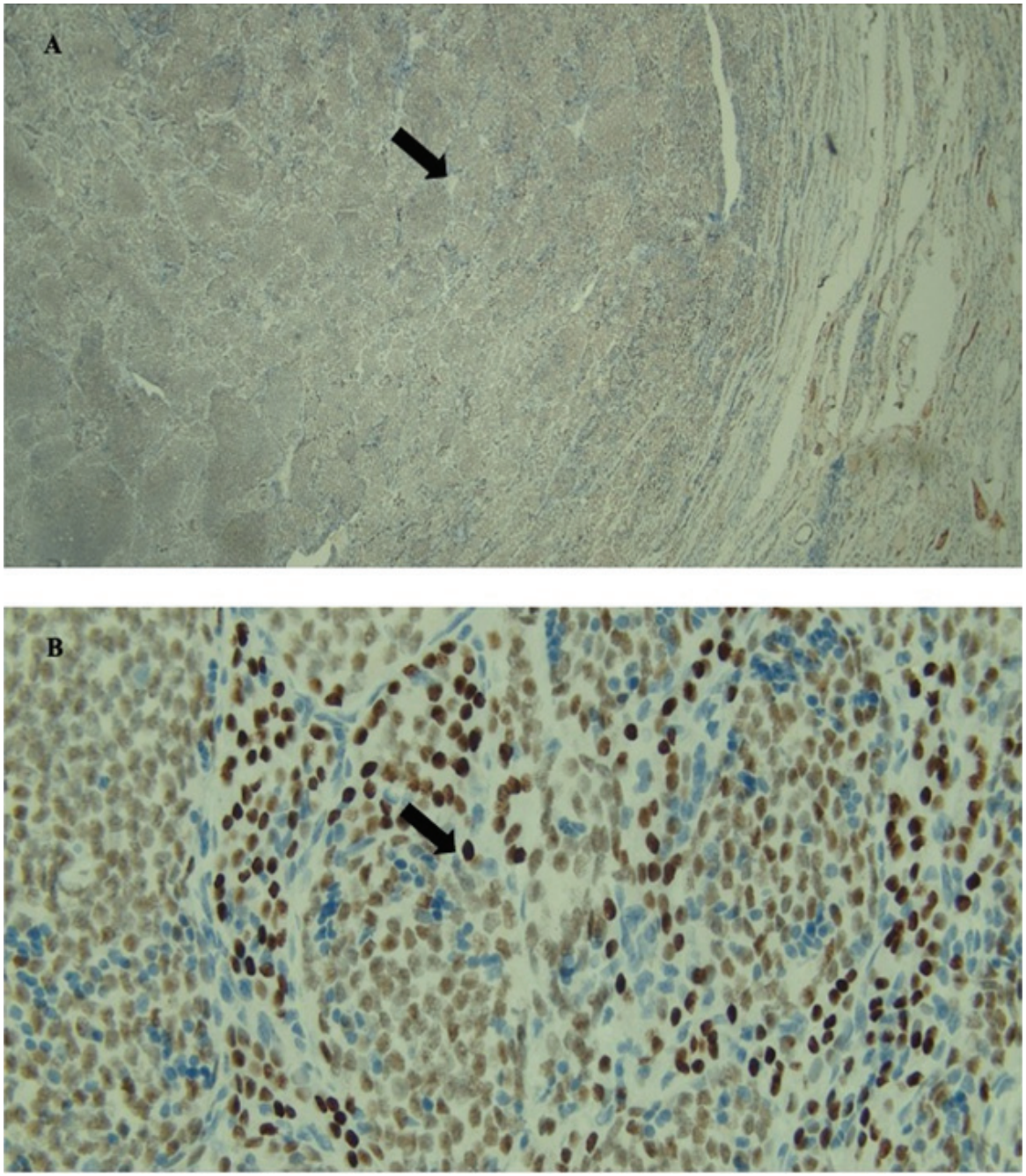

Figure 5. TTF-1 immunohistochemistry 10x of thyroid neoplasm (A) and 40x (B) respectively. The brown-stained positive cells are thyroid-origin neoplastic expressing the TTF-1.

Table 3. Results of blood examination on 10 August 2023, after surgical removal of thyroid and parathyroid gland.

Complete blood count			
Parameters	**10/08/23**	**Reference**	**Unit**
Total white blood cells	13.61	6.0-17.0	$10^3/\mu L$
Monocytes	0.82	0.15-1.35	$10^3/\mu L$
Neutrophils	9.39	3.00-11.50	$10^3/\mu L$
Band neutrophils	0	0-3	%
Lymphocytes	3.40	1.00-4.80	$10^3/\mu L$
Eosinophils	0	0.10-1.25	$10^3/\mu L$
Basophils	0	0.00-0.10	$10^3/\mu L$
Red blood cells (RBC)	5.43	5.0-9.0	$10^6/\mu L$
Hemoglobin (Hb)	12.3	10.0-18.0	g/dL
Hematocrit (Hct)	36.9	35-55	%
MCV	68.0	60-77	fL
MCH	22.7	20-25	pg
MCHC	33.3	32-36	g/dL
Platelet count (PLT)	552	200-500	$10^3/\mu L$
RDW	14.6	12-15	%
Plasma protein	7.2	6.0-7.5	g/dL
Platelet smear	Increase		
Morphology			
Anisocytosis	Few		
Macrocyte	Few		
Blood chemistry			
Parameters	**10/08/23**	**Reference**	**Unit**
BUN	16	7-27	mg/dL
Creatinine	0.98	0.5-1.8	mg/dL
ALT	77	10-100	U/L
ALP	207	23-212	U/L
Total protein	6.9	5.2-8.2	g/dL
Albumin	2.9	2.7-3.8	g/dL
Glucose	105		
Total T4	2.50	1.0-4.0	µg/dL

Table 3. Results of blood examination on 10 August 2023, after surgical removal of thyroid and parathyroid gland. (Cont.)

Blood gas (Venous)	10/08/2023	Reference	Unit
pH	7.464	7.34-7.46	
pCO2	37.1	32-49	
pO2	114.4	24-48	mmHg
Na+	149	144-160	mmHg
K+	6.39	3.5-5.8	mmHg
iCa	1.25	1.25-1.50	mmoL/L
Hematocrit (Hct)	44	35-55	mmoL/L
HCO3	26.0	20.0-29.0	mmoL/L
BE	2.4	-	
TCO2	27.1	21.0-31.0	mmoL/L
O2SAT	98.4	93-100	%
Hemoglobin (Hb)	14.8	12.0-18.0	g/dL

Abbreviation: Mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC), Blood urea nitrogen (BUN), Alanine aminotransferase (ALT), Alkaline phosphatase (ALP), Total T4 (Total thyroxine 4), partial pressure of carbon dioxide (pCO2), partial pressure of oxygen (O2), Sodium (Na+), Potassium (K+), ionized Calcium (iCa), Bicarbonate (HCO3), Base excess (BE), Total carbon dioxide (TCO2), Saturated oxygen (O2SAT).

Discussion

Thyroid neoplasm in dogs is the neoplasm that presents various gross pathological features depending on the type of tumor, its size, and locations and causes various clinical conditions such as upper respiratory tract and digestive tract compression (Morris and Dobson 2008; Dobson and Lascelles 2011; Meuten 2020). The common types of thyroid neoplasms in dogs include adenomas (benign tumors) and thyroid carcinomas (malignant tumors) (Meuten 2020). The appearance of thyroid neoplasm is discrete nodules or masses within the thyroid gland tissue and varies in color ranging from white to tan to brown (Jubb et al., 2012). According to the aggressiveness of tumors, the neoplasm usually invades the surrounding tissues, such as nearby lymph nodes, blood vessels, and adjacent structures in the neck causing hemorrhage, necrosis, or calcification. The compression effects lead to difficulty breathing, and swallowing difficulties. Therefore, total surgical removal is necessary for the survival of the dogs (Erickson et al., 2021). The histopathological examination is compulsory for the definitive diagnosis of the tissue samples obtained during surgery or biopsy (Meuten 2020). In this case report, we used a set of the mouse monoclonal antibodies including, TTF-1, thyroxine, parathyroid hormone receptor, calcitonin, and chromogranin-A to identify the origin of the neoplastic cells (Pessina et al., 2016). Based on the histopathological examination and immunohistochemistry, the neoplasm is strongly positive for TTF-1 and chromogranin A. The TTF-1 is usually expressed in thyroid carcinoma; however, the chromogranin A is expressed in the secretory granules of endocrine cells and plays a role in hormone packaging and secretion. The immunohistochemistry of chromogranin identifies the origin of the C cells of the thyroid gland and parathyroid chief cells (Doss et al., 1998).

Generally, after surgical removal of the thyroid and parathyroid, a retrospective multi-institutional study of 100 cases of dogs (2010-2019 reported that thirty-four percent of dogs developed hypocalcemia within one week after surgery; moreover, the estimated one, two-, and three-year survivals were 84%, 65%, and 51% respectively. The most common clinical signs after surgical removal are polyuria, polydipsia, hindlimb paresis, lethargy, and hypoxia. The median survival time is 2 years (Erickson et al., 2021).

In our case, the clinical signs and the clinical pathological abnormalities data before surgical removal were not obvious such as mild normochromic and normocytic anemia, high level of total T4. However, the additional imaging analysis especially CT-scan suggest the abnormal growth of the neoplasm located at the thyroid and parathyroid gland. Moreover, the multiple masses at the liver are also related to the markedly elevated level of ALT and ALP. Therefore, further investigation of the multiple masses in the liver should be performed. After surgical removal, all clinical pathological data, electrolytes, and hormone level were returned to normal except hypocalcemia, hyperkalemia, and metabolic alkalosis. The possible pathogenesis suggests the hypothyroidism and hypoparathyroidism which cause abnormalities of the metabolism and calcium regulation. Therefore, hormonal supplementation might necessary as adjunctive therapy together with the full course of chemotherapy.

Conclusion

The thyroid neoplasm is a rare neoplasm and the development of abnormal growths or tumors in the parathyroid gland, a vital endocrine organ located in the neck. These neoplasms can encompass both benign (non-cancerous) and malignant (cancerous) tumors. The clinical signs associated with thyroid neoplasms in dogs can vary depending on the size and location of the tumor. The common clinical signs include difficulty breathing and swallowing. The clinical diagnosis typically involves a combination of physical examination, imaging studies (such as radiography ultrasound or computed tomography), clinical pathology levels, and tissue biopsy for histopathological examination. The complete surgical removal is necessary for aggressive tumors with additional radiation therapy and chemotherapy. Overall, the prognosis is guarded, and ongoing monitoring by clinicians to assess for recurrence or metastasis with regular follow-up appointments is compulsory.

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