CLINICAL REPORT

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Anatomopathological aspects of a malignant mixed thyroid tumor with multiple metastasis in a dog

Aspectos anatomopatológicos de um tumor misto maligno de tireoide com múltiplas metástases em cão

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ABSTRACT: Thyroid tumors are uncommon. Malignant mixed tumor, or carcinosarcoma, is a rare, malignant, infiltrative, and metastatic neoplasm. This paper aims to report a case of a metastatic malignant mixed thyroid tumor in a 10-year-old mixed-breed female dog. The patient presented respiratory symptoms and had an unfavorable evolution of the clinical scenario. It was euthanized and submitted to necroscopic examination, which led to subsequent histopathological and immunohistochemical (IHC) evaluation. The macroscopic evaluation revealed neoformations in the thyroid, lung, heart, kidneys, and abdominal skeletal muscles. Microscopically, the thyroid presented mixed neoplastic cellularity as well as mesenchymal and epithelial cells. Metastases of the mesenchymal component were observed in the kidneys, heart, and musculature, while there was an invasion of neoplastic epithelial cells in the lung. On the IHC, there was positive staining for thyroglobulin, TTF-1, and vimentin. The histopathological and IHC findings indicated a metastatic malignant mixed thyroid neoplasm.

KEYWORDS: atypical metastasis; histopathology; immunohistochemistry.

RESUMO: Os tumores de tireoide são pouco frequentes nos animais domésticos. O tumor misto maligno, também conhecido como carcinossarcoma, que é uma neoplasia rara, extremamente maligna, exibindo crescimento invasivo e potencial metastático. O objetivo deste trabalho é relatar o caso de um tumor misto maligno e metastático de tireoide em um cão, sem raça definida (SRD), fêmea de 10 anos de idade. A paciente em questão apresentava manifestações respiratórias, e diante da piora do quadro clínico optou-se pela realização da eutanásia e posterior avaliação necroscópica, histopatológica e imuno-histoquímica. A avaliação macroscópica revelou neoformações em tireoide, pulmão, coração, rins e musculatura esquelética abdominal. Microscopicamente constatou-se proliferação neoplásica mista no tecido tireoidiano, caracterizado pela presença de células epiteliais e mesenquimais. Focos metastáticos do componente mesenquimal foram encontrados nos rins, coração e musculatura, enquanto no pulmão evidenciou-se proliferação do componente epitelial. Na avaliação imuno-histoquímica houve marcação positiva para Tireoglobulina, TTF-1 e Vimentina, corroborando com o diagnóstico de um tumor misto maligno de tireoide metastático.

PALAVRAS-CHAVE: metástase atípica; histopatologia; imuno-histoquímica.

INTRODUCTION

The thyroid gland is one of the endocrine organs which are responsible for the production and secretion of hormones, such as triiodothyronine (T3) and thyroxine (T4), both essential for maintaining metabolism. The thyroid's structural organization comprises two types of endocrine cells: follicular cells (responsible for the production of thyroid hormones) and medullary parafollicular or C cells (calcitonin producers). Among the changes commonly found in the thyroid, neoplastic, inflammatory, degenerative, cystic, and hyperplastic processes are the most prominent (Miller, 2018).

Thyroid tumor processes are uncommon in Veterinary Medicine, so reports found in the literature are scarce. No specific epidemiological patterns are recognized, but studies indicate higher incidence in elderly females, with no evidence of

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racial pattern (Tochetto *et al.*, 2017). The prognosis tends to be reserved or unfavorable as a result of the aggressive behavior, high capacity to infiltrate adjacent tissues, and distant metastatic potential of the tumor (Rodrigues *et al.*, 2007; Grubor; Haynes, 2005).

The main thyroid tumors are adenomas and carcinomas, in both follicular cells and parafollicular cells (C cells). Neoplasms such as malignant mixed tumors (carcinosarcomas) and undifferentiated carcinomas, on the other hand, have a low occurrence. The malignant mixed tumor is a neoplasm with two very distinct cellular components, characterized by the presence of epithelial and mesenchymal neoplastic cells; it is highly malignant and has a high metastatic potential (Rosol; Meuten, 2017).

Given the rarity and scarcity of the literature on this tumor, this paper aims to report a case of a malignant mixed thyroid tumor in a dog, with multiple metastases located in the kidney, heart, skeletal muscle, and lung.

CASE REPORT

A large, mixed-breed female dog with a body score of 9/9, approximately 10 years old, was brought for veterinary care after presenting with respiratory distress. In addition, it presented coughing, sneezing, and hoarseness; due to muffled auscultation, bronchitis was initially suspected. Physical examination revealed the presence of a mass in the ventral cervical region at the thyroid level. Due to the respiratory symptoms, a bronchodilator, antibiotic, and anti-inflammatory were prescribed, and the patient should return in seven days for further evaluation and examination of the mass. However, after five days, the patient returned with intense dyspnea and cyanosis, and due to the worsening of the clinical condition, we opted for euthanasia and necroscopic examination.

Chest radiographic evaluation revealed moderate interstitiobronchial opacification (alveolar pattern) with bronchogram formation in caudal lobes. The lateral view of the dorsal portion showed a soft tissue radiopacity structure measuring approximately 3.01 cm x 1.64 cm. Diagnostic impressions of the lung fields revealed possible bronchopneumonia or pulmonary edema with the presence of neoformations or imaging artifacts. Cervical radiography revealed decreased tracheal lumen and ventral displacement of the trachea attributable to the presence of a soft tissue radiopacity structure associated with intermingled mineral radiopacity content (mineralization), suggesting possible neoformation. Blood tests revealed an elevated Alkaline Phosphatase of 746.0 U/L (20.0–156.0 U/L).

The necroscopic evaluation found a volume increase in the ventral cervical region close to the thyroid. It was irregular, whitish, well vascularized, and adhered to the trachea. Its consistency was hard and measured approximately 8.0 cm x 4.5 cm x 3.0 cm (Figure 1). When cut, it was hard and heterogeneous, with a mineralized and cystic center, and presented serosanguinolent fluid flow.

In the parenchyma of the cortical region of the left kidney, light multifocal rounded, regular, and whitish structures measuring up to 0.5 cm were observed. In the heart and myocardium, multifocal, moderate, rounded, whitish, firm structures measuring 0.5 to 1.0 cm in diameter were observed. There were noticeable multifocal rounded, firm structures with colors ranging from yellowish to blackish randomly distributed over the lung parenchyma; they measured 0.5 to 2.0 cm (Figure 2). When cut, all structures were homogeneous and firm. On both sides of the muscles of the abdominal wall (transverse abdominal muscle), rounded, firm, and whitish masses measuring 1.9 cm x 1.4 cm and 1.2 cm x 1.0 cm were observed. When cut, all lesions were firm, homogeneous, and whitish. Finally, tissue fragments were collected and placed in 10% formalin for subsequent histopathological processing.

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Figure 1. Neoplastic proliferation in the patient's thyroid exhibiting a hard and irregular appearance.

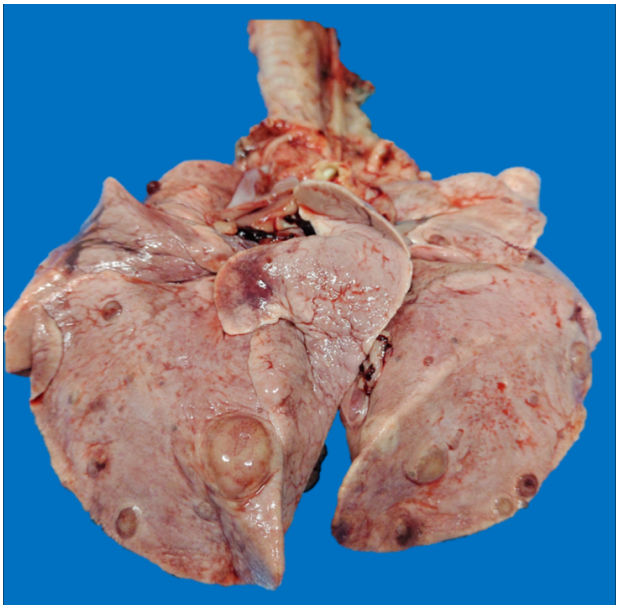

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Figure 2. Multifocal pulmonary nodules, ranging from yellowish to brownish.

In the histological evaluation of the thyroid fragment, neoplastic proliferation of mesenchymal and epithelial cells was observed. The epithelial proliferation had high cell density, was well-defined and expansive, and occasionally invaded the capsule. The cells were cuboidal and occasionally exhibited acinar arrangement, organized into nests, bundles, and trabeculae, defined by thin septa of connective tissue and blood capillaries (Figure 3). The cytoplasm was moderately eosinophilic and poorly defined. The paracentral nuclei had loose chromatin and occasionally displayed a single and small nucleolus. Anisocytosis and anisokaryosis were moderate, and rare mitotic figures were observed. The follicles had different sizes and were covered by one to two layers of epithelial cells, occasionally filled with colloid. There were also multifocal to coalescing areas of hemorrhage, necrosis, and fibroplasia. The mesenchymal neoplastic proliferation was steep, invasive, poorly defined, and not encapsulated. These proliferations were arranged in clusters, under moderate fibrovascular stroma, and exhibited strong features of pleomorphism; they had variable nucleus-to-cytoplasm ratio. The cytoplasm was sparse, poorly defined, and slightly eosinophilic. The nuclei showed noticeable pleomorphism: it was rounded, oval, or elongated, with loose chromatin and evident (sometimes multiple) nucleolus. There was a discrete presence of binucleated and multinucleated cells. Typical and atypical mitosis figures were found, varying between 0 and 1 per high-power field (HPF). Interspersed with the neoplastic proliferation, moderate multifocal areas of cartilaginous metaplasia were observed (Figure 4).

In the evaluation of skeletal muscle, kidneys, and heart, neoplastic infiltrates of mesenchymal cells similar to those described in the thyroid (metastases) were observed. A neoplastic infiltrate of epithelial neoplastic cells was observed in the lungs, arranged in acini with homogeneous intraluminal eosinophilic content, presenting other alterations similar to those described in the thyroid (metastasis).

Based on the histological findings, it was possible to diagnose mixed malignant thyroid tumor, considering the presence of two distinct neoplastic populations and consequent metastatic sites. Immunohistochemical (IHC) evaluation was performed using thyroglobulin and thyroid transcription factor-1 (TTF-1) to confirm the thyroid tissue. Furthermore, vimentin was used as an immunomarker for mesenchymal cells, and synaptophysin and chromogranin were used as immunomarkers for cells of neuroendocrine origin. Thyroglobulin presented strongly positive staining in follicular structures (Figure 5), and TTF-1 showed staining in the thyroid nuclei and lung epithelial cells. Vimentin also showed strong staining for mesenchymal cells present in all evaluated tissues (Figure 6). Synaptophysin and chromogranin were negative.

DISCUSSION

Malignant mixed tumors, also known as carcinosarcoma, are extremely malignant, rare, and under-reported neoplasms. This means the survival rate of patients declines, both in human and veterinary medicine (Yang *et al.*, 2018; Almes; Heaney; Andrews, 2008; Grubor; Haynes, 2005). In addition to the thyroid, primary malignant mixed tumors in dogs are reported in mammary glands, salivary glands, and heart (Ferreira *et al.*, 2017; Almeida *et al.,* 2010; Almes; Heaney; Andrews, 2008). Thyroid carcinosarcoma has also been reported in cats, although less frequently (Rich *et al.,* 2019).

A retrospective study of the main thyroid neoplasms in dogs found a 7.7% prevalence of malignant mixed tumors, which corresponds to 2 cases among the 26 evaluated dogs; both cases occurred in females (Tochetto *et al.*, 2017). Studies show that females have a predisposition for this type of tumor in a

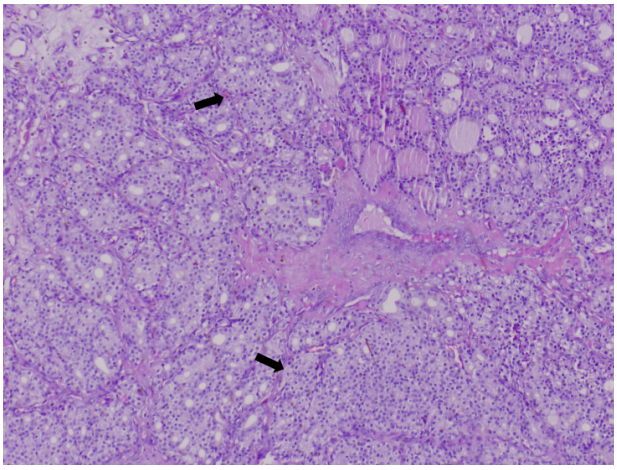

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Figure 3. Histological section of the thyroid showing neoplastic epithelial cells, indicating a bundled pattern of organization surrounded by fibrovascular connective tissue (arrows), Hematoxylin-eosin, 10x.

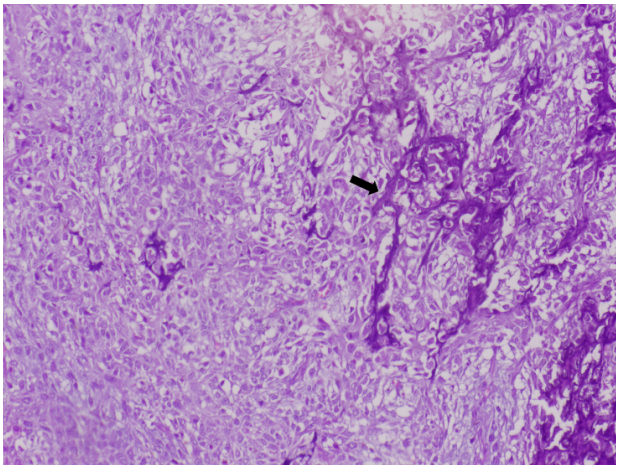

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Figure 4. Histological section of the thyroid displaying mesenchymal cells with interspersed amphophilic matrix (metaplasia) (arrow), Hematoxylin-eosin, 40x.

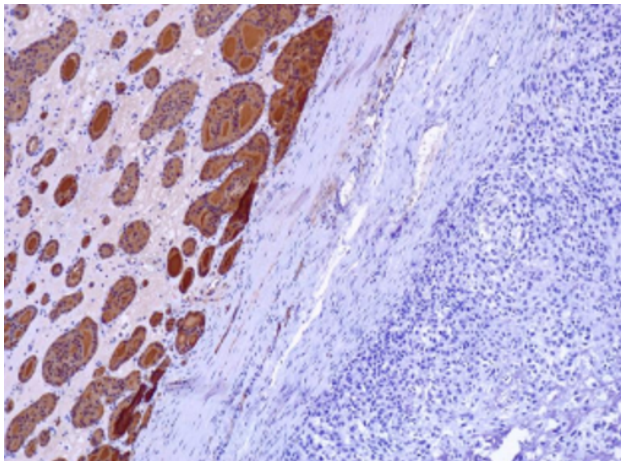

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Figure 5. Immunohistochemical evaluation with positive staining for thyroglobulin in the follicular epithelial cells, 10x.

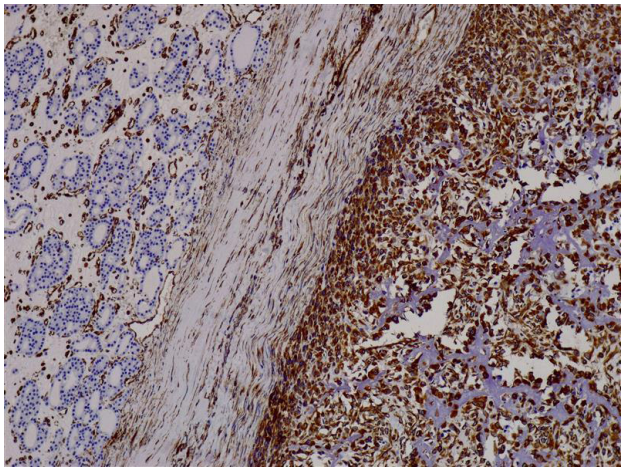

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Figure 6. Immunohistochemical evaluation with positive staining for vimentin, 10x.

ratio close to 2:1, although there are reports in males (Grubor; Haynes, 2005). Even without a consensus or a clear explanation for this predisposition, the main hypotheses are related to nutritional and hormonal causes as a consequence of the expression of estrogen and progesterone receptors in the thyroid epithelium (Johnson; Patterson, 1981). This tumor is usually found in adult and elderly patients: the average age of affected individuals is around nine years old, but younger animals can also be affected by genetic predisposition.

This neoplasm can develop in two possible ways. The first is related to carcinosarcoma of monoclonal origin: the neoplastic populations arise from a single epithelial neoplastic component, which undergoes cell differentiation through a process of mesenchymal metaplasia or epithelial-mesenchymal cell conversion. The second hypothesis, also described as collision tumor, is that of biclonal origin, in which two distinct cell populations proliferate separately, or as a pseudosarcoma (Miyauchi *et al.,* 2018).

Histologically, the main morphological feature of mixed tumors is the presence of two neoplastic cellular components: epithelial and mesenchymal. Epithelial cells tend to form cell bundles/nests, and mesenchymal cells exhibit a more scirrhous aspect with the presence of cartilaginous metaplasia (Rosol; Meuten, 2017), which is compatible with the microscopic findings in the evaluated samples. Positive staining of thyroglobulin (Yang *et al.,* 2018; Rodrigues *et al.*, 2007), TTF-1, and vimentin was found during the IHC evaluation of thyroid tissue; those results support the diagnosis of a malignant mixed tumor.

After conducting the radiographic examinations, the clinical respiratory signs presented by the patient were identified as a consequence of both the pulmonary nodules and the tumor formation located near the trachea: the formation shortened the lumen and displaced the trachea. Serum alkaline phosphatase levels can increase in benign or malignant metastatic tumor formations, especially in bone tumors (Alison, 2015; Mattos; Santana, 1996). In the present study, the neoplasm had cartilaginous differentiation with areas of mineralization, which may explain the increase. Nonetheless, other causes, such as hepatobiliary diseases and drug induction (Miller, 2018), cannot be dismissed.

The metastatic pattern of malignant mixed tumors is perceived as very similar to those of thyroid carcinomas. The lung is the main organ affected due to the invasion of the thyroid vein branches; the invasion of adjacent tissues, such as the trachea, esophagus, and larynx is also frequent (Rodrigues *et al.,* 2007). It is important to note that the two distinct neoplastic components of the mixed tumor can metastasize individually or in a single focus in different tissues (Von Sandersleben; Hänichen, 1974), as observed in the present study: there was metastasization from the epithelial portion to lung, and mesenchymal population to heart, kidney, and muscle.

Pulmonary metastatic foci are most often found when associated with mixed tumors (Ferreira *et al.*, 2017; Grubor; Haynes, 2005), although extrapulmonary metastatic foci can occur, they are extremely rare. Metastases from this tumor have been observed in kidneys, hearts, and intestines (Wells, 1901), but no metastatic focus to muscle tissue has been reported in dogs so far.

The anatomopathological and IHC findings are compatible with a metastatic mixed malignant thyroid tumor, which, although rare in dogs, should be considered as an important differential diagnosis in patients with increased cervical volumes and respiratory manifestations unresponsive to treatment.

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