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Case Report

Histopathological and immunohistochemical characterization of a mixed tubule papillary thyroid carcinoma in a Nellore cow

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Abstract

Reports on thyroid carcinomas in bovines are scarce. An 18-year-old Nellore cow was referred to a veterinary hospital due to lateral recumbency lasting one day after falling on irregular terrain. The patient was clinically diagnosed with spinal cord injury. Necropsy and histopathology revealed a thyroid tubule papillary carcinoma. Immunohistochemical analysis revealed discrete positive cells for calcitonin, moderately positive cells for thyroid transcription factor 1 (TTF-1), and strongly positive cells for thyroglobulin in the thyroid gland. Thus, this report describes a case of a mixed tubule papillary carcinoma derived from both medullary and follicular cells in a Nellore cow.

Keywords: bovine, thyroid carcinoma, histopathology, immunohistochemistry

Introduction

Thyroid neoplasms are rarely diagnosed in cattle because these tumor types generally develop in older animals (4, 15, 17) and are rarer in cows (2, 4). However, these tumors are usually reported in aged dogs (1, 3).

Epidemiological factors associated with thyroid neoplasms may be directly related to environmental and genetic factors. These include thyroid weight, sable iodine level, thyroid-stimulating hormone (TSH) plasma level, thyroxine (T4), and cortisol level alterations in cattle exposed to radiation in Fukushima after iodine radioisotope exposure to a nuclear power plant accident (7). No breed predisposition was mentioned in the studies (2, 3, 4, 15, 17).

Reports on thyroid carcinomas in bovines are scarce, including follicular, papillary, and solid-pattern carcinomas with and without metastatic ability; bilateral thyroid carcinoma; (10, 17) and ultimobranchial tumors (18). Tubular, microfollicular, or papillary, and solid carcinomas have also been reported in dogs (17).

This is the first case report to our knowledge detailing the histopathological and immunohistochemical characteristics of papillary thyroid carcinoma of mixed medullary and follicular cell origin in a Nellore cow. This report aims to emphasize the importance of further studies on the breed predisposition, diagnosis, treatment, and prognosis of this disease in cows, which affects their quality of life and may result in unidentified economic losses during production.

Case description

An 18-year-old cow of the Nellore breed was referred to a veterinary hospital presenting with lateral recumbency for one day after falling on irregular terrain. The patient had a history of discrete, intermittent claudication of the pelvic limbs, which started 20 days prior to the accident. Furthermore, the patient had a four-month-old calf. Neurological examination revealed decreased bilateral patellar and flexor reflexes, absent proprioception, and flaccid paresis, all observed in

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the pelvic limbs. The patient's head and neck coordination and temperament were normal. The patient was treated with omeprazole 4 mg/kg PO SID, flunixin meglumin 1.1 mg/kg IV SID, dipyrone 25 mg/kg IV SID, hydroeletrolytic solution SEO fluid therapy, and suspension on a stretcher twice a day for 30 min. The patient was euthanized after five days of follow-up due to a lack of clinical improvement secondary to probably spinal cord injury.

A macroscopic evaluation revealed a blackish cyst in the left thyroid with a firm white area measuring 2.0 cm x 0.7 cm × 0.7 cm after cross-section evaluation (Fig. 1). Necropsy also revealed the following: diffuse pallor, deep kidney infarctions with multifocal to coalescent yellowish areas; multifocal cysts measuring 0.5–1.0 cm in the right ovary; and hemorrhage in cervical spinal cord meninge, due to trauma.

Histopathological examination of the left thyroid tubular cyst revealed papillary proliferation of epithelial cells interspersed with scarce fibrovascular stroma, which sometimes formed bulky cysts filled with amorphous eosinophilic content and red blood cells. The cell cytoplasm was cubic to columnar, eosinophilic, well-delimited, moderate, and had occasional golden granules. The nuclei were round to oval, dotted with dense chromatin, and contained multiple conspicuous nucleoli. Slight anisocytosis, anisokariosis, pleomorphism, and a single mitotic figure were observed in ten fields of greatest increase (2.5 mm²). Extensive areas of desmoplasia and discrete-to-moderate macrophage multifocal inflammatory infiltrates were observed. These features led to the diagnosis of thyroid tubule papillary carcinoma. Microscopical evaluation of the kidneys showed a discrete multifocal mononuclear interstitial inflammatory infiltrate, moderate glomeruli sclerosis and discrete cystic areas. These findings were compatible with chronic glomerulonephritis. Serum biochemical analysis revealed uremia during *in vivo* examination of the patient. This finding, in conjunction with the *post-mortem* kidney microscopic analysis, leads us to the conclusion that the cow presented mild chronic kidney injury.

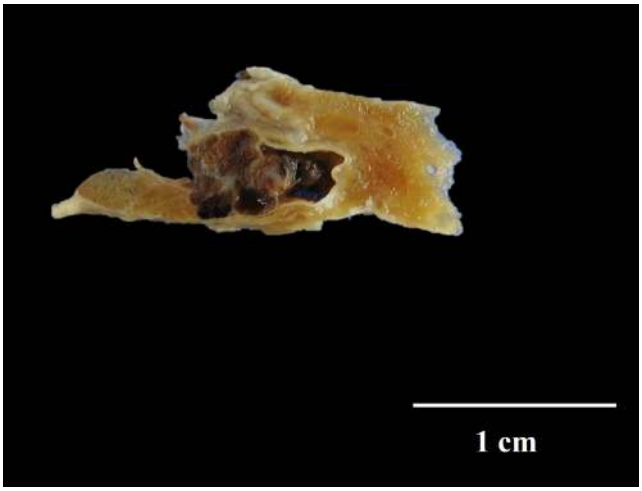

Figure 1. Bovine, Nellore, thyroid carcinoma. A blackish cyst in the thyroid gland presents a firm white area visualized in a cross-section cut.

The tissue sections obtained from the FFPE blocks were placed on charged slides (Starfrost, Knitell, Bielefeld, Germany) to immunohistochemistry. For the antigen retrieval, the slides were incubated in a citrate solution (pH 6,0) in a pressure cooker (Pascal, Dako, Carpinteria, CA, EUA) for 45 minutes. Endogenous peroxidase was blocked by hydrogen peroxide 8% diluted in methyl alcohol for 15 minutes and treated with skim milk 8%, at room temperature. The sections were incubated overnight at 4°C with primary antibodies anti-calcitonin (polyclonal), anti-thyroid-transcription factor (TTF-1) (clone 8G7G3/1) and thyroglobulin (polyclonal). Immunohistochemical analysis revealed discrete positive cells for calcitonin, moderately positive cells for TTF-1, and strongly positive cells for thyroglobulin in the thyroid gland (Fig 2). The immunohistochemical importance of these markers lies in characterizing the tumor's origin, showing if the neoplasm derives from medullary or follicular cells of the thyroid (Fig 2).

Discussion

This study reports, for the first time, the histopathological and immunohistochemical characteristics of papillary thyroid carcinoma of mixed medullary and follicular cell origin in a Nellore cow. In human medicine, papillary thyroid carcinoma comprises 80% of thyroid cancers (14). Some studies show that pregnant women have favorable conditions for the development of thyroid tumors, being the second most frequent tumor diagnosed during pregnancy, due to the influence of hormones such as HCG and estrogen, which in high concentrations during pregnancy, stimulate thyroid growth and can generate the development of neoplastic lesions (1). Therefore, it is possible that hormonal stimulation resulting from pregnancy, as seen in humans, generated neoplastic lesions in the thyroid of the cow in this report, which was pregnant 4 months prior to her euthanasia. However, there are no studies yet on this mechanism in cows, and it is only a hypothesis of the possible etiology of this tumor.

A study in ruminants showed a lower concentration of free thyroxine (T4) in cows with ovarian cysts, when compared to normal cyclic cows, This reduction in T4 levels is probably due to a reduction in the thyrotrophic activity of thyroid-stimulating hormone (TSH) or to an increased activity of peripheral deiodinases, an enzyme responsible for the homeostasis of thyroid hormones (12). Thyroid conditions are also known to cause changes in the glomerular filtration rate, tubular secretion, absorptive capacities, and renal structure in humans and dogs (11). Therefore, we believe that the thyroid neoplasm could have played a role in the renal and ovarian lesions in the cow.

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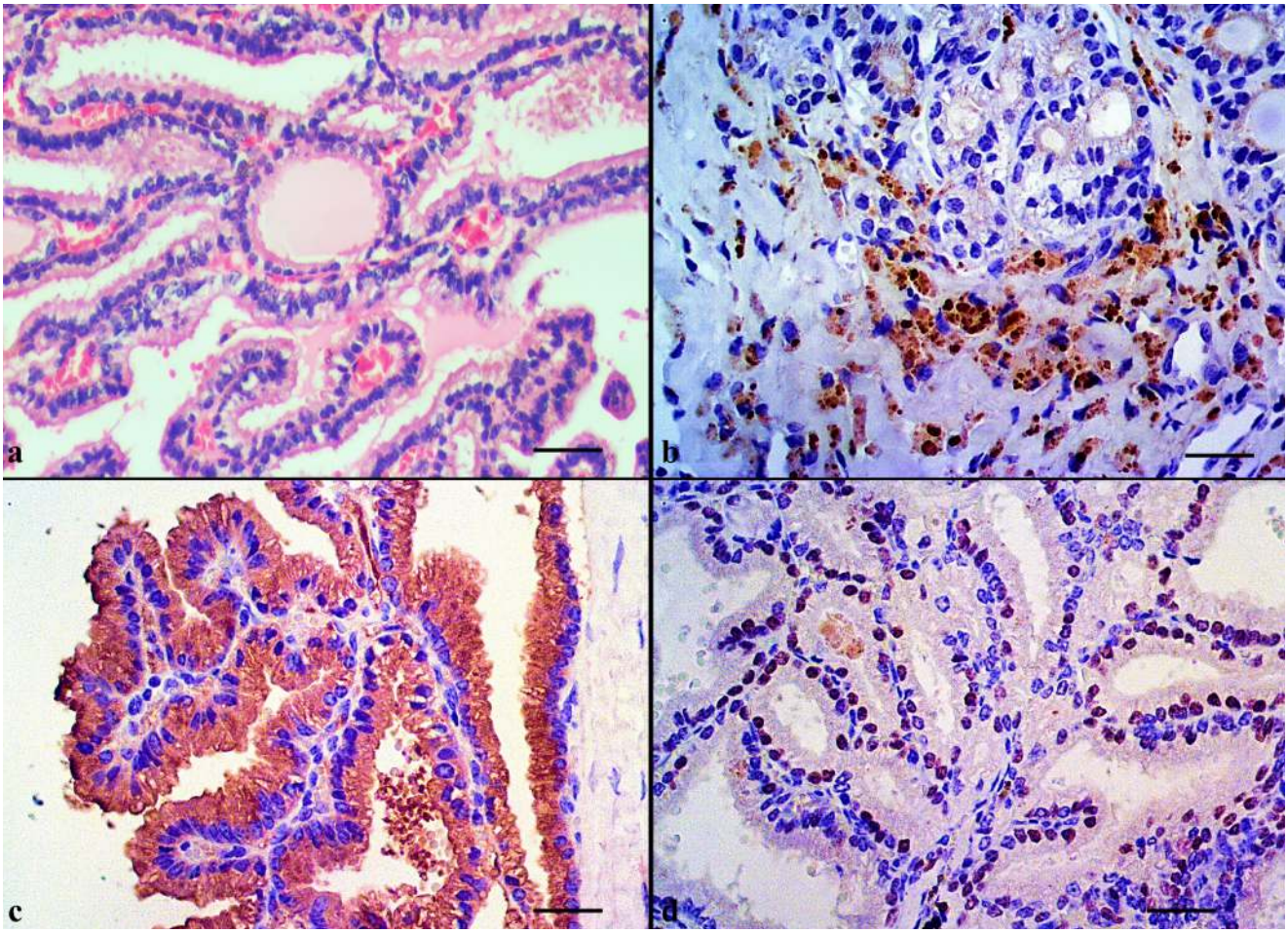

Figure 2. Bovine, Nellore, thyroid carcinoma. Photomicrographs of the histological and immunohistochemical sections of the thyroid mass (A–D). A- Tubule-papillary proliferation of epithelial cells separated by scarce fibrovascular stroma, which sometimes form bulky cysts filled with amorphous eosinophilic content and red blood cells. The cells were well delimited with cubic to columnar eosinophilic cytoplasm, moderate, with occasional golden granules. The nucleus was round to oval, with dense chromatin and multiple conspicuous nucleoli. (H&E stain; bar = 20 µm). B-D- Neoplastic cells with discrete immunoreactivity for calcitonin (B), moderate immunoreactivity for TTF-1 (C), and strong immunoreactivity for thyroglobulin (D). (IHC, bar = 20 µm).

Thyroid carcinomas in humans are more common in adult men than in younger individuals, and the risk of mortality from these neoplasms increases with age. In humans, the activation of the MAPK pathway contributes to thyroid tumorigenesis based on genetic predisposition. Therefore, we believe that the etiology of this case may be associated with animal age, as mentioned before (1, 19). Thyroid gland medullary carcinomas have been described in dogs and rats, showing histological, structural, and biological features similar to those observed in humans. However, human medullary carcinomas bear structural resemblance to ultimobranchial tumors in bulls (13, 17, 19).

Studies have suggested a relationship between ultimobranchial tumors and bulls fed a diet with supplementary calcium. Parafollicular cell hyperplasia has also been described in bulls fed this diet. This may be due to the abnormal levels of calcitonin and osteopetrosis in humans with medullary thyroid carcinoma and thyroid neoplasms in bulls (8, 18). Ultimobranchial tumors have rarely been reported in cows. The absence of this disease in females supplemented with dietary calcium is attributed to the utilization of calcitonin for fetal growth and lactation (16, 17, 18). In this case, the weak immunoexpression of calcitonin may be associated with hypocalcemia, common in cases of pregnancy, caused by the use of calcium during lactation and pregnancy (7), causing less stimulation of C cells, which leads to lower production of calcitonin, physiologically responsible for causing hypocalcemia. Therefore, the low immunoexpression of calcitonin may be related to the cow's previous pregnancy.

In this case, the positive immunoexpression of calcitonin, TTF-1, and thyroglobulin characterized the origin as a mixed neoplasm derived from both medullary and follicular

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cells. This classification refers to a tumor that exhibits features of a medullary-derived carcinoma and positive calcitonin on IHC. In contrast, follicular thyroid carcinomas exhibit positive staining for thyroglobulin. Notably, only a few cases of multiple immunoexpression of these markers have been reported in thyroid carcinomas (5, 14).

Gross histological and immunohistochemical findings revealed papillary thyroid carcinoma of mixed medullary and follicular cell origin in a Nellore cow. To the best of our knowledge, this is the first report of a papillary thyroid carcinoma in Nellore cows. Autopsy and histopathology revealed findings consistent with previous studies involving this type of neoplasm in cattle. However, as this malignant tumor interferes with bovine quality of life and may result in unidentified economic losses in cattle production, we emphasize the importance of further studies on the breed predisposition, diagnosis, treatment, and prognosis of thyroid carcinoma in cows.

Conflict of Interest

The authors declare no competing interests.

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