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# HISTOPATHOLOGICAL AND IMMUNOHISTOCHEMICAL FEATURES OF SPORADIC MEDULLARY THYROID CARCINOMA

**Abstract**: We show 60 cases of sporadic medullary thyroid carcinoma (MTC) with many histological variants. Patients' age ranged from 37 to 75, with the average being 47. Sporadic medullary carcinoma appeared as unilateral, circumscribed tumor, with diameter from 22 to 55 mm. Classical variant of MTC was present in 30 cases (50%). Microscopically, sheets and irregular islands of polygonal and round cells, traversed by fibro-vascular septa with amyloid (pink-staining amorphous material in the form of globules or massive deposits), were seen. Occasionally dystrophic calcifications were present. Immunohistochemistry revealed diffuse calcitonin positivity of variable intensity. Spindle cell variant of MTC was present in 8 cases (13.3%). Tumors were composed of intersecting spindle cell fascicles with scanty amyloid deposits. These neoplasms mimicked mesenchymal tumors, yet tumor cells showed strong calcitonin immunopositivity. Papillary variant of sporadic MTC was present in 7 cases (11.6%). Pseudopapilliform structures composed of fragmented tissue, with scanty amyloid deposits in fibro-vascular septa, were seen. This variant of MTC can be distinguished from papillary thyroid carcinoma by its nuclear features and poor positive calcitonin immunoreactivity. Glandular form of MTC was found in 6 cases (10%). Microscopically, glands and follicles containing eosinophilic secretion were present. Fibrohyaline stroma in these cases lacked amyloid. Glandular variant of sporadic MTC can be distinguished from follicular thyroid neoplasms by its positive calcitonin immunoreactivity. Carcinoid-like MTC was present in 5 cases (8.34%). Tumors were composed of islands separated by delicate fibrohyaline stroma without amyloid deposition. Giant cell – anaplastic variant of sporadic MTC was recognized in 4 cases (6.7%). Microscopically, large cells with bizarre nuclei and nuclear pseudoinclusions also lacking amyloid deposits in fibrohyaline stroma were seen. MTC was confirmed using immunohistochemistry. The most helpful immunostain is calcitonin, which ought to be positive in all cases of MTC. S-100 protein is negative in sporadic MTC. Pan-neuroendocrine marker such as chromogranin A is always positive in MTC cells. CEA, a sensitive but non-specific marker for MTC, is positive in 88-100% of cases. C-cell hyperplasia is not present in sporadic form of MTC.

**Keywords**: Sporadic medullary thyroid carcinoma, histopathology, immunohistochemistry.

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## *BACKGROUND*

Medullary thyroid carcinoma (MTC) is a malignant tumor showing parafollicular (C-cell) differentiation. C-cells derive from ultimobranchial body, from where they migrate to middle to upper thirds of thyroid gland's lateral lobes. They are polygonal or round with clear to pale cytoplasm and dark nuclei. C-cells occur singly or in small groups within the follicular basal layer and in the interfollicular interstitium. MTC typically secrets calcitonin and somethimes produces a variety of other peptide products.

Approximately 70-80% of MTC are sporadic. It presents as a unilateral thyroid mass, causing pain and dysphagia with the tendency to metastasize to lymph nodes of the neck and upper mediastinum. C-cell adenoma as an entity doesn't exist. Sporadic MTC is often circumscribed but rarely encapsulated. On cut-section sporadic MTC appears as grayish-white or reddish-brown nodule. Larger tumors often have areas of central necrosis. Microscopically, sheets and irregular islands of polygonal and round cells, traversed by fibro-vascular septa, are seen. Beside classical histological presentation of sporadic MTC, many other histological variants may be seen: trabecular, pseudopapillary, tubular, microglandular, cribriform and anaplastic.[1] Tumor cells exhibit finely granular cytoplasm and round or oval nuclei without pleomorphism. Mitotic figures are infrequent. Lymphatic infiltration and permeation is common. Amyloid is present in variable amounts, as pink-staining amorphous material in the form of globules or massive depostits with calcification. It is absent in 15-20% of cases.[2,3]

Conventional (classical) MTC has deposits of amyloid and packets of tumor cells.

Glandular histological variant of MTC has tubules or follicles containing eosinophilic secretion, surrounded by fibro-vascular septa without amyloid. Finely granular cytoplasm of tumor cells and calcitonin immunoreactivity support the diagnosis of MTC.[4] Giant-cell (anaplastic) MTC exhibit large cells with bizarre nuclei and nuclear pseudoinclusions. Mitoses are numerous and aberrant. These tumors have a more aggressive biologic behavior.[1] Spindle cell histological variant of MTC has plump spindle cells mimicking mesenchymal neoplasms. Papillary form of MTC is composed of psudopapillae covered by cells which express calcitonin. Carcinoid-like MTC shows Tumor Island separated by fibrohyaline stroma.[5, 6] Histological variants of MTC have no impact on patients' prognosis.

In sporadic MTC C-cell hyperplasia is not present.[7]

Diagnosis of MTC must be confirmed by immunohistochemistry. Calciton is positive in all cases showing intense staining in nearly all tumor cells. MTC with poor calcitonin immunopositivity is more aggressive then calcitonin-rich MTC.[8] Pan-neuroendocrine marker such as chromogranin A is always positive in MTC cells.[6, 9] CEA, a sensitive but non-specific marker for MTC, is positive in 88-100% of cases.[8] S-100 protein immunopositivity is uncommon in sporadic MTC.[5]

## *AIMS*

This study aims to analyze the histopathological and immunohistochemical features of sporadic MTC.

## *MATERIALS AND METHODS*

In this study we analyzed 60 cases of sporadic MTC, which were diagnosed and surgically treated over a period of 2 decades, in the Center for Endocrine Surgery, Diabetes and Metabolism Disorders, Clinical Center of Serbia, Belgrade. Surgical specimens were diagnosed intraoperatively, by frozen-section methodology, and afterwards paraffin-embedded and treated by standard histological staining methods (Haematoxyllin and eosin). All cases were subjected to immunohistochemistry, using antibodies to calcitonin and chromogranin A. In some cases, antibodies to NSE (neuron-specific enolase), CEA (carcinoembryonic antigen) and S-100 protein were also applied. Sporadic MTC were grouped in histological categories.

## *RESULTS*

Age of patients with sporadic MTC ranged from 37 to 75, with the average being 47. Female to male ratio was 1.4:1. Grossly, sporadic MTC were solitary lesions, with diameter ranging from 20 to 55 mm.

Conventional (classical) variant of MTC was diagnosed in 30 cases (50%). Microscopically, sheets and irregular islands of polygonal and round cells, with finely granular eosinophilic cytoplasm, were seen. Tumor cells' nuclei were slightly irregular, dark stained, with moderate number of mitoses. Stromal amyloid deposits were present in all cases of sporadic MTC. Some cases showed disperse dystrophic calcifications. In the surrounding thyroid tissue, there was no C-cell hyperplasia. Immunohistochemistry reveled calcitonin positivity in most tumor cells. Pan-neuroendocrine markers (chromogranin A and NSE) were also immunopositive. Cases with lymphoglandular dissemination were intensively CEA immunopositive. Differentiation between classical MTC and parathyroid carcinoma may be difficult. Parathyroid carcinoma may contain stromal amyloid, uniform cells, and numerous mitoses, but it lacks distrophic calcifications. Immunohistochemically, parathyroid carcinoma is chromogranin A positive and calcitonin negative, in all cases.

Spindle cell variant of MTC was present in 8 cases (13.3%). Tumors were composed of intersecting spindle cell fascicles with scanty amyloid deposits. These neoplasms mimicked mesenchymal tumors, yet tumor cells showed strong calcitonin immunopositivity.

Papillary variant of sporadic MTC was present in 7 cases (11.6%). Pseudopapilliform structures resulting from tissue fragmentation, with scanty amyloid deposits in fibro-vascular septa, were seen. This variant of MTC can be distinguished from papillary thyroid carcinoma by its nuclear features and poor positive calcitonin immunoreactivity.

Glandular form of MTC was found in 6 cases (10%). Microscopically, glands and follicles containing eosinophilic secretion were present. Fibrohyaline stroma in these cases lacked amyloid. Glandular variant of MTC can be distinguished from follicular variant of papillary thyroid carcinoma by its lack of hypochromic nuclei. Positive calcitonin immunoreactivity distinguishes MTC from both follicular thyroid carcinoma and follicular variant of papillary thyroid carcinoma.

Carcinoid-like MTC was diagnosed in 5 cases (8.34%). Tumors were composed of islands separated by delicate fibrohyaline stroma without amyloid. These cases can be mistaken for follicular neoplasm or metastatic carcinoid.

Giant cell (anaplastic) variant of sporadic MTC was recognized in 4 cases (6.7%). They were composed of large cells with bizarre nuclei and nuclear pseudoinclusions, lacking amyloid deposits in fibrohyaline stroma. Despite their similarity to anaplastic thyroid carcinoma originating from follicular epithelium, the cells of anaplastic variant of MTC show calcitonin immunopositivity.

## *DISCUSSION*

Sporadic medullary thyroid carcinoma (MTC) is a neoplasm originating from C-cells. It occurs in middle aged patients, as a solitary, well circumscribed lesion.[10]

Because numerous histological variants are present, their differential diagnoses include diverse thyroid gland lesions, but also mesenchymal and other neuroendocrine tumors. All histological variations have their distinctive characteristics, which distinguish them from other neoplasms.[1] Immunohistochemistry is necessary for making the diagnosis of MTC, using antibodies against tumor-specific marker - calcitonin and pan-neuroendocrine markers such as: chromogranin A, neuron-specific enolase (NSE) and synaptophysin.[5, 6] All mentioned markers are also positive in hereditary MTC. Non-specific tumor marker carcinoembryonic Antigen (CEA) is positive in 88-100% of sporadic MTC cases.[8] Absence of C-cell hyperplasia, combined with negative S-100 protein immunostain is an important feature which differentiates sporadic MTC

from its hereditary form. Hereditary MTC shows S-100 protein immunopositivity in 100% of cases.[9, 10]

Classical variant is the most often diagnosed histological form of sporadic MTC. Histological presentation corresponds to cell nests, surrounded by fibrohyaline stroma in which moderate to large amounts of amyloid are deposited.[4] Tumor cells are round to oval in shape, with eosinophilic cytoplasm and infrequent mitoses. Confirmation of histopathological diagnosis by positive calcitonin, chromogranin A, CEA[10], as well as negative S-100 protein immunostain is obligatory.[1] After differential diagnosis analysis, other, relatively rare histological variants of sporadic MTC are identified by their tumor marker expression.[9, 11] C-cell hyperplasia is not present in sporadic MTC.[7]

## *CONCLUSIONS*

Sporadic medullary thyroid carcinoma is the most frequently seen clinical form of MTC. It is diagnosed in middle aged patients with the peak incidence in the fifth decade of life, as a solitary lesion in all cases. Significant variations in its histopathological presentation are seen. Amyloid is not found in all MTC variants. Because of these variations, diagnosis of sporadic MTC should always be confirmed by immunohistochemistry.

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