MEDULLARY CARCINOMA OF THE THYROID GLAND

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Introduction: Medullary carcinoma of the thyroid (MTC) is a distinct thyroid carcinoma that originates in the parafollicular C cells. Recognition of patognomonic features observed by light microscopy using different methods of specimen preparation, leads to the right pathohistologic diagnosis.

Patient and methods: Partial thryeoidectomy was performed in 49 year old male patient with solitary node in the left thyroid lobe and intraoperative consultation was requested. There were no data regarding familial history, preoperative laboratory tests or cytologic examination. Intraoperative analysis included imprint cytology stained with Hemacolor quick method, and frozen tissue sections stained with fast hematoxillin and eosin (H&E) stain. Rest of material was formaline fixed, parafine embeded, sliced and stained with standard H&E. Representative sections were additionally stained by Congo red special stain and immunoanalyzed with anti-calcitonin (Dako monoclonal antibody) using autostainer, LSAB method and DAB chromogen.

Results: Gross examination in the mid portion of slightly enlarged thyroid lobe revealed solid, nonencapsulated, firm white-gray tumor measuring 2,2 cm in the largest diameter. Tumor was mostly well circumscribed with small foci of macroscopic infiltrative growth to adjacent thyroid tissue. Cytologic smears were highly cellular, with isolated to loosely cohesive malignant cells. The cells were polygonal and bipolar, with round to oval nuclei and coarsely granular (“salt and pepper”) chromatin. In some cells nuclei were eccentrically placed which gives them a plasmacytoid appearance. In addition, multinucleated and binucleated tumor cells were seen. A few globules of amorphous material were scattered in the background, but there were no colloid and no evidence of a papillary or follicular architecture. On frozen section tumor was composed of moderately polymorphic tumor cells forming sheets, nests and trabecules intersected by small amount of fibrous stroma. Large multinucleated tumor cells were also seen. Based on these finding and additional histological evidence of infiltrative growth, diagnosis of malignant tumor, most probably medullary carcinoma has been made. On permanent sections part of the tumor showed more prominent fibrous stroma with deposits of pink amorphous material, which analyzed by Congo red stain showed apple-green birefringence on polarized microscopy. In rest of the tumor, mixture of polygonal, plasmacytoid and bipolar cells formed sheets, irregular nests and short trabecules. Mitotic activity was low, but a few foci of lymphovascular invasion had been observed. Immunohistochemical analysis showed strong diffuse calcitonin positivity in most of the tumor cells and stromal amyloid. With combination of histological features, Congo red positivity and calcitonin immunoreactivity, diagnosis of thyroid medullary carcinoma was confirmed. Rest of the left lobe and additionally dissected right thyroid lobe were unremarkable. However, amyloid rich tumor deposits were found in two pretracheal lymph nodes and in soft tissue adjacent to left lobe.

Discussion: Medullary thyroid cancer (MTC) comprises 5 to 10% of all thyroid cancers. Sporadic, or isolated, MTC occurs in 75% of patients, rest 25% in familial settings. Familial MTC
syndromes include MEN 2A, which is the most common; MEN 2B; and familial non-MEN syndromes. These tumors usually present as a mass in the neck or thyroid, often associated with lymphadenopathy, or they may be diagnosed through screening family members. MTC can also be preoperatively recognized by fine-needle aspiration, or intraoperatively by imprint cytology. Most of MRC originates from mid or upper portion of the gland, in familial cases can be multicentric and bilateral. (2) The tumors are macroscopically solid, firm and grey to tan in color, relatively well circumscribed but not encapsulated. Cytologic smears typically show hypercellular material with isolated to loosely cohesive polygonal, plasmacytoid or spindle-shaped cells with oval nuclei and finely to coarsely granular chromatin. (1) Classic histologic appearance of MTC is represented by sheets and irregular nests of polygonal to oval cells with amphophilic, sometimes granular cytoplasm and medium size, round to oval nuclei. Nuclear chromatin is neuroendocrine type or “salt and pepper” appearance, with inconspicuous nucleoli. Sheets and nests of tumor cells are intersected by different amount of fibrous stroma containing amyloid deposits in up to 80% cases. It is strongly highlighted by Congo red special stain, which in addition shows a characteristic apple-green birefringence on polarized microscopy. A number of histologic variations has been recognized including plasmacytoid, oncocytic, spindle cell, giant cell/anaplastic, papillary, glandular/follicular, paraganglioma-like, carcinoid-like and microcellular MTC. (1,2) According to some investigators, microcellular variant is linked to poor prognosis, while others had no prognostic meanings. (3) MTC can secrete calcitonin and other peptide substances. Determining the level of calcitonin is useful for diagnostic purposes and for following the results of treatment. It is also widely used as immunohistochemical marker of C-cell origin of thyroid tumors, which is particularly valuable in diagnosis of some rare histologic variants and metastatic MTC. MTC invades locally and metastases to cervical and mediastinal lymph nodes. Distant metastases occur in lungs, liver and bone. Metastases may be initial presentation of disease and usually contain amyloid. The overall survival of patients with MTC is 83.2% at 5 years and 73.7% at 10 years. (4) Good prognostic factors include young age, female sex, familial forms (MEN 2A) and tumor smaller than 1 cm, while poor prognostic factors include advanced age, advanced stage, male sex, sporadic forms, high mitotic activity and microcellular variant. (1-3)

**Conclusion:** During diagnostic process pathologist is challenged by many histological variants and occurrence of sporadic as well as familial forms of MTC. Continuous education and use of complementary methods will ensure correct diagnosis, proper treatment, and adequate patient follow-up.
Methods used in MTC diagnostics: imprint cytology (A); frozen section (B); standard H&E (C); calcitonin immunoanalysis (F); Congo red stain (E); polarisation microscopy (F)

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