H77 Medullary Thyroid Carcinoma (MTC) With Diabetic Ketoacidosis: An Autopsy Case Report and Literature Review

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Learning Overview: After attending this presentation, attendees will better understand an uncommon case of MTC with ectopic Cushing's Syndrome (CS).

Impact on the Forensic Science Community: This presentation will impact the forensic science community by helping medical examiners in diagnosing MTC-related hypercortisolism by chemical analysis and tumor histology and by sharing an experience of an unusual immunostaining pattern.

MTC is a rare neuroendocrine tumor of parafollicular C cells. The majority of MTCs occur sporadically, but about 30% of patients are associated with Multiple Endocrine Neoplasia type 2 (MEN2) syndrome or familial MTC.[1] Generally, MTCs have no sign of clinical manifestation, but infrequently they develop symptoms of hypercortisolism by secretion of Adrenocorticotropic Hormone (ACTH) or Corticotropin-Releasing Hormone (CRH). Although ectopic CS is found only in 0.7% of MTC, it can lead to fatal consequence if left untreated.[2] There have been over 50 cases reported of MTC-related CS, and very few autopsy cases exist in the literature.

A 22-year-old woman was found dead in her residence. Her father stated that she lost weight in recent months in spite of no chronic illness and could not eat well after wearing a brace on her teeth in July. At autopsy, the body was significantly thin in appearance with a body mass index of 7.8kg/m^2. The surface of the thyroid gland was unremarkable; however, the cut section revealed an ill-defined whitish lesion involving almost the entire right lobe. Other major internal organs showed no abnormalities. Microscopic examination revealed infiltrative MTC with insular growth pattern separated by thin fibrovascular cores. Immunostaining for calcitonin and chromogranin showed positive reaction in a few cells.

Clinicochemical analysis of vitreous humor showed a highly elevated glucose level at 674mg/dL. The tests for blood ketone bodies revealed a high β-hydroxybutyrate level of 1,304mg/L and a high acetone level of 574mg/L, confirming the diagnosis of diabetic ketoacidosis. The result of additional immunohistochemical study for ACTH was negative. The patient had no family history of MTC and germline genetic testing for RET mutation was not performed. There was no evidence of other medical disorders that could have caused hypercortisolism. Considering all the information, it was concluded that death was due to diabetic ketoacidosis, which was a complication of MTC-related CS.

There are several studies dealing with alteration in immunostainability of MTC in the course of disease progression. In one study, initially MTC showed high-intensity calcitonin staining with a homogenous pattern; however, the metastatic tumor tissue obtained at autopsy displayed diffusely negative staining for calcitonin.[3] This study presumed these different patterns of immunostaining was reflecting the presence of a poorly differentiated, biologically aggressive population of cells. This theory can also explain the poor immunoreactivity on calcitonin in this case. With regard to ACTH immunostaining, only a few cases are reported positive for ACTH, CRH, or Proopiomelanocortin (POMC) despite the evidence of ectopic hormonal secretion. Negative ACTH immunoreactivity has been suggested to reflect reduced cellular storage due to a high secretion rate, or inefficient translation and processing of POMC messenger RNA (mRNA).[4]

It is of importance for both forensic pathologists and clinicians to recognize that hypercortisolism can be the presenting symptom of MTC. Immunohistochemical detection of calcitonin and hormonal markers are helpful in determining the diagnosis of MTC and the reason for associated complications, but there are still things to consider in terms of immunoreactivity on postmortem tumor tissue.

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