

CASE REPORT

Unusual Presentation of a Thyroid Malignancy: A Case Report

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ABSTRACT

Medullary thyroid carcinoma is a rare malignancy. We report a case of Medullary thyroid carcinoma in a 56-year-old male patient. Patient presented with lower limb paresis and severe hypokalemia. Cushing's syndrome is a rare complication of Medullary thyroid carcinoma [MTC] and is due to ectopic Adrenocorticotrophic [ACTH] secretion by tumor cells. Cushing's syndrome presents a challenging diagnostic and management issue in patients with MTC. Entire clinical history, laboratory investigations, microscopic pictures are discussed in detail.

Key words: Medullary thyroid carcinoma, Adrenocorticotrophic hormone, Ectopic Cushing's syndrome

INTRODUCTION

Medullary thyroid carcinoma (MTC) is a neuroendocrine tumor derived from C cells that is responsible for approximately 5% of the gland malignancies, and most of them occur sporadically.¹ Majority of sporadic MTC patients will present with a palpable thyroid nodule, at which point approximately 75% of these patients would already develop cervical and 10% distant metastases.² The diagnosis is usually confirmed by a fine needle aspiration. After diagnosis of MTC has been established, measurement of serum calcitonin, carcinoembryonic antigen (CEA), genetic testing for germline RET mutations, and biochemical evaluation for coexisting tumors, especially pheochromocytoma should follow.³ Measurement of calcitonin and CEA levels is used to determine a preoperative baseline and therapeutic response.⁴ The first-line treatment for MTC is a surgical resection. Unfortunately, patients with metastatic MTC disease at diagnosis are rarely cured by surgery. A review by Barbosa and co-workers found only 0.7% of patients with MTC develops Ectopic Cushing's syndrome [ECS], while MTC accounts for approximately 2.2–7.5% of patients with ectopic ACTH.⁵ Ectopic Cushing's Syndrome from MTC is associated with significant morbidity and mortality, as secondary complications of hypercortisolism account for 50% of the mortality in MTC.⁶

CASE REPORT

A 56 year old male patient, known case of diabetic since 2 years, who was initially on Oral hypoglycemic drugs [OHA] shifted to insulin 1 month back in view of uncontrolled glycemia with history of using ayurvedic treatment for diabetes, presented to a private institute with severe hypokalemia, progressive bilateral lowerlimb weakness since 3 months without any Central nervous system[CNS] involvement. During physical examination hard palpable thyroid nodule with significant knuckle and palmar crease pigmentation was noted. Thyroid ultrasonography, FNAC, CECT, Low dose and high dose Dexamethasone suppression test were

performed. Thyroid ultrasound reported as TIRADS-5 nodule and FNAC was inconclusive and planned to repeat. CECT showed features of thyroid malignancy with retrosternal extension. Ectopic aetiology of ACTH secretion was suggested in dexamethasone suppression test.

A fine-needle aspiration biopsy (FNAB) of the thyroid swelling performed in our institute showed abundant pleomorphic cells arranged in clusters and discretely with round and hyperchromatic nuclei, coarse chromatin, and occasional nuclear inclusions were identified. These cells ranged in shape from plasmacytoid to fusiform, had abundant cytoplasm with nuclear moulding and overlapping. Binucleated cells are also seen. A pinkish, glassy material was observed occasionally against a haemorrhagic background. [Fig 2]

Gross findings: Received total thyroidectomy specimen measuring 7×3×2 cms. Cut section is solid, firm, and encapsulated with gray white to yellowish cut surface. [Fig 1]

Microscopic findings: Microscopically, tumor cells arranged in sheets, islands, lobules and cribriform pattern. Individual cells show round to oval nuclei with stippled nuclear chromatin and scanty cytoplasm. Extensive areas of amyloid material seen along with lymphoplasmacytic infiltration [Fig 3]. Metastasis to contiguous lymphnodes is also noted. Amyloid stained with congo red stain showed salmon pink colour. Under polarised light amyloid stained with congo red showed apple green birefringence. The patient expired 2 weeks after the surgery.

DISCUSSION

MTC is a rare malignancy that accounts for approximately 5–10% of all thyroid cancers.⁷ The majority of MTCs are sporadic; however, 25% of the patients have familial endocrine syndromes associated with RET proto-oncogene mutation. While RET gene mutation is responsible for majority of familial MTC cases, 50% of sporadic MTC cases have somatic

RET mutation in the tumor tissue.³ Majority of sporadic MTC patients will present with a palpable thyroid nodule, at which point approximately 75% of these patients would already develop cervical and 10% distant metastases.² MTC is usually diagnosed with fine-needle aspiration, and MTC tumour-specific biomarkers such as calcitonin and carcinoembryonic antigen (CEA) increase testing sensitivity.⁸

Neuroendocrine tumors release calcitonin, calcitonin-gene related peptide, biogenic amines, and sometimes other active substances like ACTH, causing systemic symptoms. Ectopic ACTH secretion by a nonpituitary tumor leads to Cushing's syndrome, which is most commonly caused by corticotropin secreting pituitary tumor. Production of ACTH by MTC metastases is a rare occurrence and represents only about 5–10% of ECS.⁹ The time between MTC diagnosis and ECS presentation can vary, with some declaring themselves even before MTC diagnosis, and others over 20 years after.^{10,11} Likewise, cancers such as small cell lung, thymic, pulmonary, pancreatic carcinoid tumours, and pheochromocytomas have the potential to produce ectopic ACTH.¹²

In a retrospective study that included 1,640 adult patients with MTC, Barbosa et al. have described ectopic MTC-related Cushing syndrome in 10 cases, most of them of male gender, as the case presented here and in other reports.^{13,14} Management of Cushing's syndrome in MTC is crucial as secondary complications of hypercortisolism account for 50% of the mortality in MTC with ectopic Cushing's syndrome.⁶

The typical medullary carcinoma may be microscopically circumscribed or more likely will be freely infiltrating into the surrounding thyroid. The pattern of growth is of tumor cells arranged in nests separated by varying amounts of stroma. The tumor nests are composed of round, oval, or spindle-shaped cells; there often is isolated cellular pleomorphism or even multinucleated cells. The nuclei are uniform, the nuclear-to-cytoplasmic ratio is low. Intranuclear cytoplasmic inclusions are commonly noted. Mitotic figures can be seen. The tumor stroma characteristically contains amyloid, although this is not necessary for the diagnosis; approximately 25% of medullary carcinomas do not contain amyloid. The amyloid is most likely derived from precalcitonin and, indeed, immunohistochemical stains for calcitonin often stain the amyloid. Calcifications in areas of amyloid deposition are characteristically present. The tumors commonly invade lymphatics and veins.¹⁵

Several medullary carcinoma variants have been described. In the papillary variant, a papillary or pseudopapillary growth pattern is identified. The pseudopapillary variant is more common and probably results from fixation artifact.¹⁵ The true papillary variant is extremely rare and needs to be differentiated from typical PTC; nuclear morphology is the most important distinguishing feature. The follicular variant is characterized by the presence of follicles, glands, or tubules. Care must be rendered to determine that the follicular structures are not just entrapped normal thyroid within the lesion.¹⁵

The small cell variant of medullary carcinoma has also been described.¹⁵ The giant cell variant is rare and is characterized by large atypical cells admixed with areas of typical medullary carcinoma.¹⁵

The clear cell variant is a rare form of medullary carcinoma and is characterized by cells with abundant clear cytoplasm.¹⁵ Other variants of medullary carcinoma include oncocytic and squamous variants.¹⁵

Immunohistochemically, the tumor cells are reactive for epithelial markers such as keratin; general thyroid markers such as TTF-1; panendocrine markers such as NSE; chromogranin A, B, and C (the latter also known as secretogranin II); synaptophysin; opioid peptides; and – most important – the specific product of C cells, i.e., calcitonin. They are also consistently positive for CEA and generally negative for thyroglobulin. Other products that have been detected in medullary carcinoma include somatostatin, adrenocorticotrophic hormone (ACTH), calcitonin gene-related peptide, serotonin, melanocyte-stimulating hormone (MSH), prostaglandins, bombesin, gastrin-releasing peptide, substance P, L-dopa decarboxylase, histaminase, glucagon, insulin, human chorionic gonadotropin, the polysialic acid of the neural cell adhesion molecule, galectin-3, hepatocyte growth factor and its receptor, matrix metalloproteinases, prohormone convertases, and progesterone receptors (but virtually no estrogen receptors). Medullary carcinoma cells also express BCL2 and MYC, but not BAX or p53.¹⁶ In the present case Immunohistochemistry is not done due to financial constraints of the patient.

Management is often delayed due to difficulties in establishing a diagnosis. Historically, management was limited to debulking metastatic disease and anti-adrenal therapies including medical therapy with ketoconazole, mitotane and metyrapone. Surgical intervention with bilateral adrenalectomy can be offered to some patients, but is a complex procedure in the setting of metastatic MTC. More recently, systemic therapy with Tyrosine kinase inhibitor's [TKIs] offers a further management strategy for disease control of metastatic, unresectable disease or progressive, metastatic disease.³

CONCLUSION

Ectopic ACTH Secreting medullary thyroid carcinoma is very rare and this case is presented in view of its rarity.



Fig 1: Cut section of gross picture is solid, firm, and encapsulated with gray white to yellow colour.

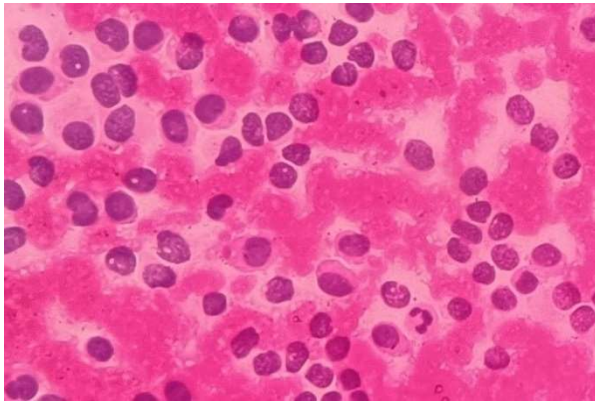


Fig 2: 10×40 ,H&E stained FNAC picture shows plasmacytoid cells arranged discretely, a few with nuclear inclusions.

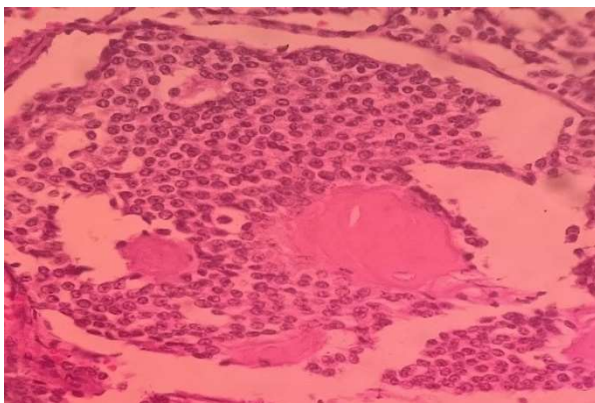


Fig 3: 10×40 H&E stained slide shows small cells arranged in cribriform pattern, along with amyloid.

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