Case Report

Multiple endocrine neoplasia-2A-revisited

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ABSTRACT

Multiple endocrine neoplasia-2A (MEN-2A) is a rare syndrome. MEN-2 is characterized by medullary thyroid carcinoma (MTC), pheochromocytoma, and hyperparathyroidism. MTC is the most consistent feature in all subtypes of MEN-2. In MEN-2A, approximately 70–95% of individuals develop MTC, 50% develop pheochromocytoma, and 15–30% develop hyperparathyroidism. Identification of a germline REarranged in transfection mutation or the identification of the clinical features of MEN-2A in other first-degree relatives is required to make the diagnosis, in those patients with only one or two clinical features. We present the case of a family with MEN-2A syndrome. Here, the patient was first operated for MTC and following further investigation was detected to have pheochromocytoma. In her family history, she had a daughter who was earlier operated for MTC. After 5 years of follow-up, she is doing well. This is an additional case of MEN-2A.

Key words: Adrenal tumor, catecholamine-secreting tumor, medullary carcinoma thyroid, multiple endocrine neoplasia, pheochromocytoma, thyroid cancer

INTRODUCTION

Multiple endocrine neoplasia type 2 (MEN) is historically composed of three clinical subtypes, MEN-type 2A (MEN-2A), familial medullary thyroid carcinoma (MTC), and MEN-2B. All the three are associated with germline mutations in the REarranged in Transfection (RET) proto-oncogene.[1] MEN-2A is a rare autosomal dominant inherited cancer syndrome.[2] MEN-2A makes up approximately 70–80% of cases of MEN-2.[1] It is characterized by occurrence of distinct proliferative disorders of endocrine tissue. The incidence of MEN-2A is 1 in 200,000 live births.[3] MEN-2 is clinically characterized by MTC, pheochromocytoma, and hyperparathyroidism.[2,3] It is subclassified into three distinct syndromes: MEN-2A, MEN-2B, and familial MTC.[3] In patients with only one or two clinical features, identification of a germline RET mutation or the identification of the clinical features of MEN-2A in other first- degree relatives is required to make the diagnosis.[3] We present the case of a family with MEN-2A syndrome. Here, the patient was operated for MTC and following further investigation was detected to have pheochromocytoma. In her family history, she had a daughter who was earlier operated for MTC.

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CASE REPORT

A 45-year-old postmenopausal female presented with the chief complaint of swelling in front of neck for last 3 years. She also complained of a headache and weight loss. There was no history of tuberculosis, hypertension, diabetes mellitus, or epilepsy. In her family history, she had a daughter who was operated for thyroid swelling, later on diagnosed as medullary carcinoma of thyroid [Figure 1]. On examination, she did not have pallor, and her systemic examination findings were within normal limit. Routine hematological examinations did not reveal any abnormality, and her thyroid function tests were also within normal limit. There was no hypercalcemia. She

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underwent fine needle aspiration cytology, which revealed spindle-shaped cells and few thyroid follicles. The cytology was reported as medullary carcinoma of thyroid [Figure 2]. Following this, she underwent total thyroidectomy and central neck dissection. Peroperatively, there was 3 cm × 2 cm swelling in the left lobe of thyroid. The right lobe of thyroid also had multiple nodules of variable consistency. There were multiple lymph nodes of size 0.5 cm × 0.5 cm present in level-VI. All four parathyroids and both recurrent laryngeal nerves were identified. She made an uneventful postoperative recovery. The postoperative histopathology was reported as medullary carcinoma of thyroid [Figure 3a]. There was the presence of intercellular amyloid which showed positivity in Congo red stain and apple-green birefringence under polarizing microscopy [Figure 3b and c]. Immunohistochemically, the medullary carcinoma of the thyroid was positive for calcitonin [Figure 3d].

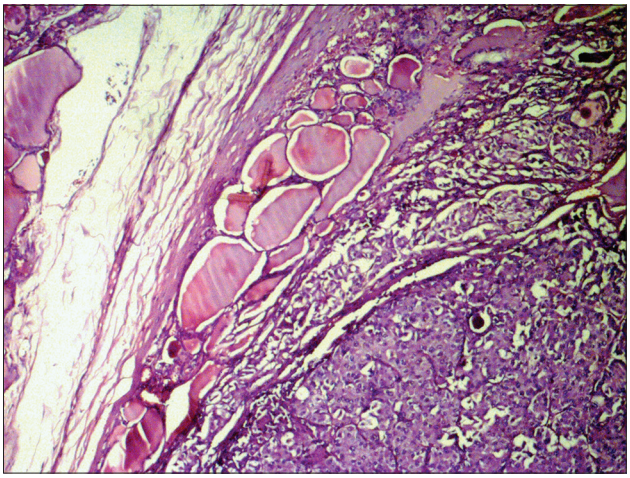

Figure 1: Medullary carcinoma of thyroid with adjacent normal thyroid follicles (patient's daughter) (H and E, ×40)

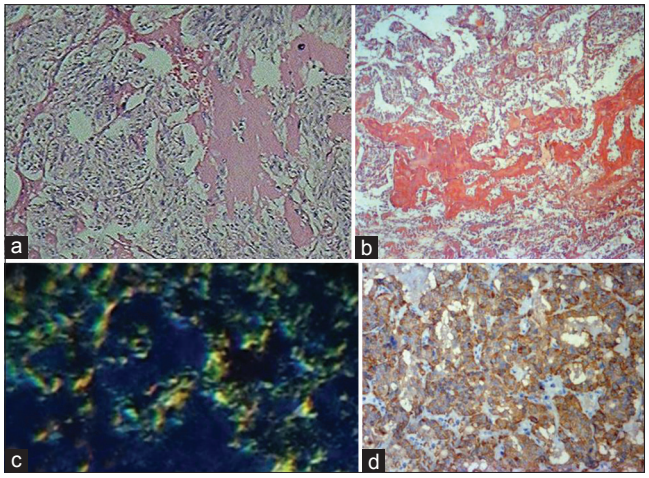

Figure 3: (a) Histopathology of medullary carcinoma of the thyroid with intercellular amyloid (patient) (H and E, ×100). (b) Amyloid showing positivity in Congo red stain (Congo red, ×40). (c) Apple green birefringence of amyloid under polarizer (polarizer, ×40). (d) Intense positivity for calcitonin in medullary carcinoma of thyroid (immunohistochemistry, ×400)

She was further investigated and her 24 h urinary metanephrine (736 μg/24 h, normal - <350 μg/24 h) and normetanephrine (933 μg/24 h, normal - <600 μg/24 h) were found to be elevated. Her computed tomography scan revealed heterogeneously enhancing mass lesion with central hypodensity in the left suprarenal area. She underwent left adrenalectomy. Preoperatively, she received alpha-blockade with prazosin. After 3 days of alpha-blockade, she was given atenolol for 1 week. Prior to surgery, her serum calcium and phosphorus levels were normal. The histopathology showed the presence of typical Zellballen pattern and was reported as pheochromocytoma [Figure 4].

Hence, the final diagnosis was MEN-2A. She is currently under regular follow-up for the past 5 years and is doing well.

DISCUSSION

MEN-2A is a rare syndrome.[2] It is a complex autosomal dominant inherited syndrome characterized by MTC,

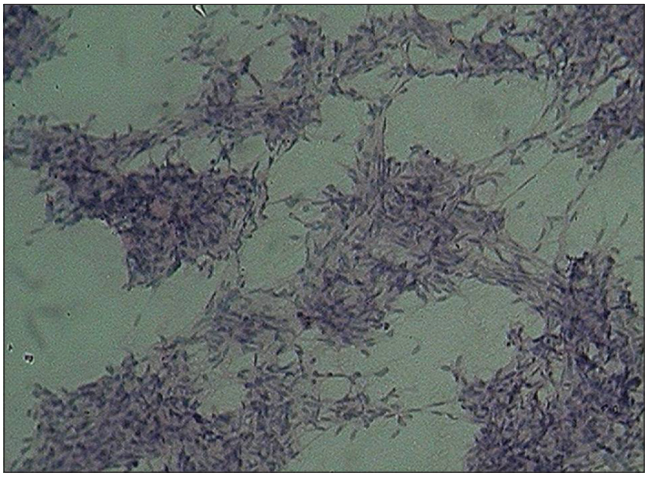

Figure 2: Fine needle aspiration cytology smear showing spindle-shaped cells (H and E, ×100)

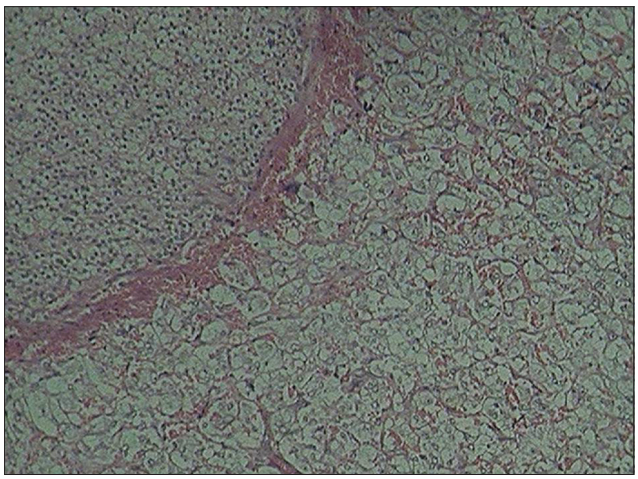

Figure 4: Pheochromocytoma with Zellballen pattern (H and E, ×200)

pheochromocytoma, and primary parathyroid hyperplasia. In patients with only one or two clinical features, identification of a germline RET mutation or the identification of the clinical features of MEN-2A in other first-degree relatives is required to make the diagnosis.[3]

In our case, the patient was first diagnosed and operated for MTC. On further investigations, she was detected to have left adrenal mass, which was operated and was reported as pheochromocytoma.

In MEN-2A, approximately 70–95% of individuals develop MTC, 50% develop pheochromocytoma, and 15–30% develop hyperparathyroidism.[1,3-5] MTC is the most consistent feature in all subtypes of MEN-2. It is usually the first clinical manifestation of MEN-2 syndrome. It typically presents with a neck mass or neck pain. The age at presentation is usually before age 35.[2,6]

A case of MEN-2 reported recently from India showed the simultaneous presence of giant pheochromocytoma, primary hyperparathyroidism, and mixed medullary-papillary thyroid carcinoma. This patient was managed for all the three lesions at the same hospital admission.[2]

MEN-2 is caused by germline activation of an oncogene, RET.[3,7] The MEN-2 gene is localized to centromeric chromosome 10 (10q11.2).[2] RET encodes a receptor tyrosine kinase which is required for the normal growth and maturation of cells derived from the neural crest.[3,8] Mutational analysis of the RET gene is used in the diagnosis and management of patients with MEN-2 variants. Early diagnosis by screening of family members in MEN-2 is essential because medullary thyroid cancer associated with morbidity and mortality. MTC can be cured or prevented by early thyroidectomy.[3,9] Surgical removal of thyroid and lymph node dissection is the standard mode of treatment for medullary carcinoma of the thyroid. The surgery includes complete resection of the thyroid tumor with any local or regional metastases.[10] Total thyroidectomy is recommended as the frequency of multicentric lesions is very high.[3] A comprehensive prophylactic central node dissection is recommended for all patients with palpable primary tumors or recurrent disease.[3] Our patient underwent total thyroidectomy and central node dissection.

Pheochromocytoma occurs in approximately 50% of patients with MEN-2A.[2,3] They usually present after MTC or concomitantly. They produce the first symptom in 13–27% of individuals with pheochromocytomas and MEN-2A.[2] For most of the cases, age at diagnosis is between 30 and 40 years of age. About one-third are bilateral and <5% reported to be malignant. In MEN-2 patients, pheochromocytomas often secrete both adrenaline and noradrenaline episodically. Pheochromocytomas metabolize them continuously into metanephrines. The measurement of plasma free metanephrines or urinary fractionated metanephrines is the investigation of choice, sensitivity being 100%.[2]

If pheochromocytoma is diagnosed, it should be operated first.[2] In our patient, MTC was diagnosed prior to that of pheochromocytoma.

Bilateral adrenalectomy should usually be limited to patients with bilateral pheochromocytomas and in patient with unilateral disease in whom other family members have had unusually aggressive bilateral adrenal medulla disease. Unilateral adrenalectomy in those patients who have a normally appearing contralateral gland is more appropriate.[3]

Our patient underwent left adrenalectomy. She is doing well after 5 years of follow-up. This is an additional case of MEN-2A.

In the present case, the patient's daughter who was previously operated for MTC was the first member of the family to come to medical attention with a known manifestation of MEN-2. The mother was only diagnosed with MTC later. This phenomenon, known in genetics as "anticipation" (i.e., the occurrence of manifestations of a genetic disorder earlier in succeeding generations) has only been described once in literature, as occurring in MEN-2. In this previous case report of MEN-2 in a family, the phenomenon of anticipation was well-demonstrated, wherein the daughter presented as the index case, and father was later detected to have MTC following mutational analysis.[3]

Though MEN-2A is rare, the presence of MTC should alert a clinician to resort to proper work-up for MEN-2. Mutational analysis and screening of other family members should be done for detection of MEN-2.

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Conflicts of interest
There are no conflicts of interest.

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