CASE REPORT

Multiple Endocrine Neoplasia Type IIA with Cutaneous Lichen Amyloidosis

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Abstract

A 35-year-old woman presented with episodic abdominal pain associated with palpitation and frontal headache. Physical examination revealed thyroid nodule along with itchy scapular cutaneous lesions suspicious of cutaneous lichen amyloidosis (CLA). Biochemical and imaging workup showed bilateral adrenal lesions with positive 24-hour urinary metanephrine/normetanephrine levels and fine needle aspiration cytology (FNAC) of the thyroid nodule confirmed medullary thyroid carcinoma (MTC) of the thyroid. Bilateral pheochromocytoma with MTC and CLA prompted us for targeted genetic testing for codon 634 in *rearranged during transfection (RET)* gene which confirmed the diagnosis of multiple endocrine neoplasia type IIA (MEN IIA) CLA variant. The patient underwent bilateral cortical-sparing open adrenalectomy followed by total thyroidectomy with central compartment neck dissection and bilateral modified radical neck dissection. Of her four asymptomatic children, two were found to harbor the mutation and are being managed appropriately. High index of suspicion with detailed history and thorough clinical examination can help us perform targeted genetic testing and appropriate management in resource-constrained settings.

Keywords: Medullary thyroid carcinoma, Multiple endocrine neoplasia, Pheochromocytoma.

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Introduction

Multiple endocrine neoplasia type IIA (MEN IIA), an autosomal dominant tumor syndrome, clinically characterized by the presence of medullary thyroid carcinoma (MTC), bilateral pheochromocytoma, and primary hyperparathyroidism (MEN IIA) caused by germline-activating mutations of the *RET* proto-oncogene and accounts for 80% of hereditary MTC syndromes. Herein, we present a patient with bilateral pheochromocytoma, MTC with cervical lymphadenopathy, and cutaneous lichen amyloidosis (CLA) wherein the identification of CLA helped us perform targeted genetic testing for codon 634 in *RET* gene.

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Case Description

A 35-year-old normotensive female patient presented with complaints of episodic pain in the right upper abdomen for a 2-month duration. Her pain in the abdomen was associated with episodes of palpitation and frontal headache. She also gave a significant family history of sudden death of two of her six siblings at a young age due to unknown cause (Figs 1 to 3). Detailed physical examination showed a firm to a hard nodule in the right lobe of the thyroid, bilateral cervical lymphadenopathy, and a scaly itchy macular lesion on the upper back which was aggravated on exposure to sunlight.

Biochemical workup revealed an elevated urinary metanephrine and normetanephrine level (3504.36 µg/24 hours and 9585.51 µg/24 hours, respectively), suggesting a diagnosis of bilateral pheochromocytoma with elevated serum calcitonin and carcino embryonic antigen (CEA) levels (1074.02 pg/mL and 56.91 ng/mL, respectively). Parathyroid hormone (PTH) level (132.6 pg/mL) was also elevated, in the presence of normal calcium and vitamin D3 levels. Contrast-enhanced computed tomography (CECT) abdomen revealed heterogeneously enhancing bilateral adrenal lesions with a right-sided lesion of size 6.0 × 5.5 × 5.1 cm and a similar lesion of size approximately 21 × 17 × 22 mm in the body of the left adrenal gland. Imaging of the neck and thorax showed a bulky thyroid with a nodule of size approximately 18 × 18 × 33.4 mm in the right lobe with an enlarged left inferior parathyroid gland of size approximately 7.3 × 6.8 mm, with multiple subcentrimetric

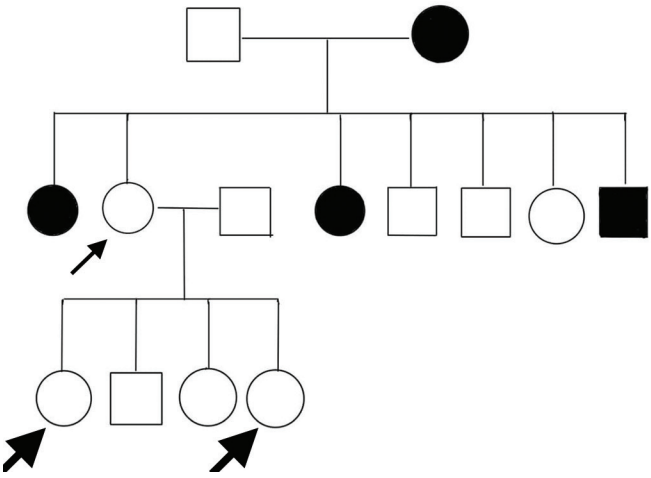

Fig. 1: Single-arrow index patient; double-arrow effected children

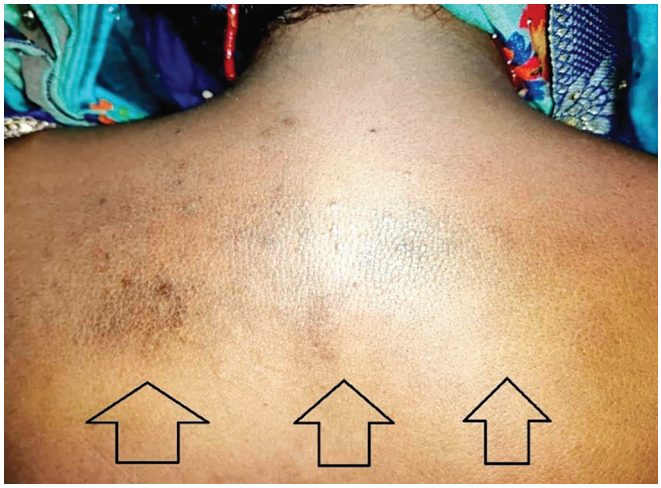

Fig. 2: Cutaneous lichen amyloidosis in multiple endocrine neoplasia type IIA. Hyperpigmented, velvety plaque with fine scales in the right scapular region

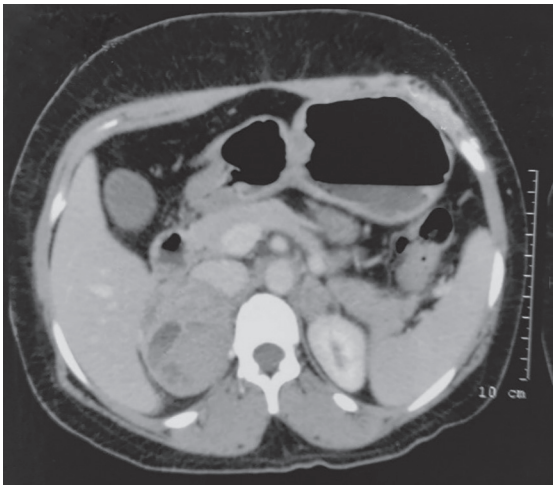

Fig. 3: Axial cross sectional image of CT abdomen with contrast showing bilateral adrenal lesion

bilateral lymph nodes. Fine needle aspiration (FNA) of the thyroid nodule was suggestive of MTC. In view of financial constraints and cutaneous skin lesions with a high index of suspicion for the above-mentioned syndrome, targeted genetic testing of codon 634 in *RET* gene was carried out, which was positive, confirming the diagnosis of CLA variant MEN IIA (Tables 1A to C).

The patient underwent open bilateral cortical sparing adrenalectomy for bilateral pheochromocytoma after adequate blockade and optimization. Postoperative period was uneventful with normalization of urinary metanephrine and normetanephrine levels. Subsequently, she was planned for total thyroidectomy with bilateral central and lateral compartment lymph node dissection for MTC. Intraoperative findings of both surgeries are described in Table 2. Enlarged inferior parathyroid glands observed during thyroidectomy were excised with the specimen. Postoperative period was uneventful. With more than 50% reduction of PTH levels. The patient was discharged on thyroxine and calcium supplements, with physiological dose of steroid supplementation (prednisolone and fluticasone). Out of her four

Table 1A: Biochemical investigations

Sl. No.	*Investigation*	*Patient's values*	*Normal values*
1	Thyroid function test	TSH 3.5 uIU/mL Free T4–10.69	0.4–4 mIU/mL 9–25 pmol/L
2	Parathormone	136.2 pg/mL	14–65 pg/mL
3	Calcium	4.84 mg/dL 9.91 mg/dL	4.6–5.2 mg/dL 8.6–10.3 mg/dL
4	Phosphorus	9.85 mg/dL	2.8–4.45 mg/dL
5	Calcitonin	1074.02 pg/mL	<10 pg/mL
6	CEA	56.91 ng/mL	0–2.5 ng/mL
7	24-hour urinary metanephrine Normetanephrine	3504.36 µg/24 hours 9585.51/24 hours	24–96 µg/24 hours 75–375 µg/24 hours
8	Serum cortisol	14.5 µg/dL	5–25 µg/dL
9	Serum cortisol overnight dexamethasone suppresion test (ONDST)	1.2 µg/dL	<1.8 µg/dL—Suppression

Table 1B: Imaging investigations

Sl. No.	*Investigations*	*Impression*
1	Ultrasound neck	Two well-defined hypoechoic lesion largest: 1.9 × 1.6 cm. S/O colloid nodule; No lymph nodes-thyroid imaging, reporting and data system (TIRADS) 3
2	CECT neck	Right lobe of the thyroid: bulky with multiple soft tissue attenuation lesions in both lobes of the thyroid (18 × 18 × 33.4 mm in the right lobe) Left parathyroid: enlarged with soft tissue attenuation lesion (7.3 × 6.8 mm) Multiple subcentimetric lymph nodes: Ia, Ib, II, III, IV, and V stations
3	CECT thorax and abdomen	A relatively well-defined soft tissue lesion: approx. 6.0 × 5.5 × 5.1 cm in the right adrenal region A soft tissue attenuation lesion: approx. 21 × 17 × 22 mm. Body of the left adrenal gland

Table 1C: Pathological investigations

Sl. No.	*Investigations*	*Report*
1	FNAC of neck swelling	MTC (Bethesda Category VI)
2	Histopathology (adrenal gland)	Right adrenal: pheochromocytoma Pheochromocytoma of the Adrenal gland Scaled Score (PASS-2) Left adrenal: Pheochromocytoma (PASS-2)
3	Histopathology (thyroid)	MTC with 12/39 lymph node positive for metastasis with no extra nodal extension (ENE)

asymptomatic children, two aged 9 and 4 years were positive for codon 634 mutation. The elder of two had subcentimetric thyroid nodule with elevated calcitonin (174 pg/mL). She has been

Table 2: Surgery and operative details

Surgery	*Operative findings*
Transperitoneal open bilateral cortical-sparing adrenalectomy	Right adrenal gland tumor: 6 × 5 × 4 cm Left adrenal gland tumor: 5 × 3 × 2 cm
Total thyroidectomy with central lymph node and bilateral cervical lymph node dissection	Right lobe: 4 × 4 × 4 cm, hard nodule of size 3 × 2 cm Left lobe: 3 × 3 × 2 cm, hard nodule of size 1 × 1 cm at the superior pole Multiple enlarged II, III, and IV lymph nodes bilaterally; largest 1.5 × 1 cm on the left level IV and 2 × 1.5 cm on the right level III Multiple central lymph compartment lymph nodes enlarged, largest 1 × 1 cm in pretracheal region Bilateral inferior parathyroid glands enlarged of size 1 × 1 cm on the right side and 1.5 × 1.5 cm on the left side Bilateral superior parathyroid glands visualized and preserved with vascularity

Fig. 4: The index patient with the four children

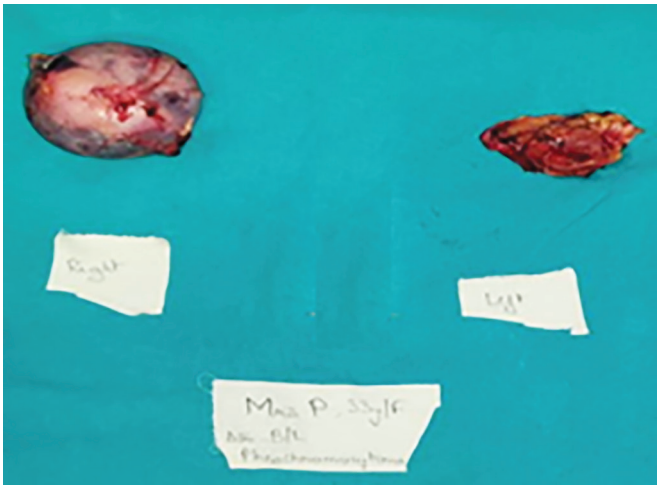

Fig. 5: Specimen of cortical sparing adrenalectomy

planned for therapeutic total thyroidectomy with central lymph node dissection and prophylactic thyroidectomy for the younger sibling (Figs 4 and 5).

Discussion

MEN IIA syndrome is characterized by the development of MTC in virtually all patients, up to 50% pheochromocytomas, and up to 30% hyperparathyroidism depending on the *RET* codon mutation.[1] CLA occurs in approximately 10% of families with MEN IIA with lesions evident in the scapular region of the back corresponding to dermatomes T2–T6 with secondary changes characterized by the deposition of amyloid resulting from pruritus and repetitive scratching. The CLA is seen at a young age and usually precedes MTC, thus serving as a precursor for the syndrome.[2,3] The presence of any germline mutation at codon 634 is highly associated with the development of hyperparathyroidism and pheochromocytoma, the frequency of the latter depending on the *RET* codon mutation: 609 (4%), 611 (0%), 618 (22%), 620 (9%), and 634 (50%),[4] whereas when the patient also has CLA, it is almost always associated with a C634 *RET* codon mutation; however, it has also been reported in a subject with a V804M germline mutation.[5,6]

Workup of a patient with this syndrome involves biochemical investigations and imaging of all the possible involving organs to confirm the diagnosis. The investigations include 24-hour urinary metanephrine, normetanephrine, S. calcitonin, and calcium levels with CECT scan of the neck, thorax, and abdomen to rule out the multiple manifestations of the syndrome. Surgical management should involve tackling the pheochromocytoma first with simultaneous thyroid surgery or planning a thyroidectomy later on to reduce the morbidity of the patient. We need to have awareness about the importance of doing the genetic testing of the patient and their first-degree relatives. Codon 634 mutation falls under the high-risk category and is advised to undergo prophylactic thyroidectomy by the age of 5 years.[7] This case draws attention to the importance of genetic counseling in first-degree relatives of patients with confirmed MEN IIA allowing for timely diagnosis and reduced morbidity and mortality and also the phenomenon of anticipation, in which severity increases and the age of onset decreases in successive generations, the syndrome being discovered earlier and with a worse prognosis.

Our patient as described in literature had a benign pheochromocytoma with an aggressive MTC component with a parathyroid adenoma. CLA and the targeted testing for codon 634 mutation helped us confirm our diagnosis with minimal financial burden on the patient. The genetic testing of the children was a boon as the effected children have been planned for surgery. A high index of suspicion, detailed history with thorough general physical examination can help us narrow down the diagnosis and an organ-specific investigation protocol with targeted genetic testing can reduce the financial burden on the patient. Hence, the presence of CLA with pheochromocytoma and/or MTC can help us perform targeted genetic mutation in resource-constrained settings to clinch the diagnosis and also perform targeted genetic testing in kindred.

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