

Incidental Detection of Synchronous Medullary Thyroid Carcinoma, Pheochromocytoma and Parathyroid Adenoma Leading to Diagnosis of Multiple Endocrine Neoplasia Type 2A

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Abstract

Introduction:

Multiple endocrine neoplasia type 2 (MEN2) is an autosomal dominant neoplastic syndrome with an estimated prevalence of 1 per 30,000 in the general population. MEN2 is subclassified into two subtypes: 2A (MEN2A) and 2B (MEN2B). MEN2A is a rare disease and the affected patients are generally asymptomatic. Cutaneous lichen amyloidosis is an early clinical marker. The morbidity and mortality in these patients are mainly due to medullary thyroid carcinoma, therefore proper clinical workup is warranted for proper surgical intervention.

Case Description:

We report a case of sporadic MEN2A with no family history of any thyroid or adrenal tumors. She presented with neck mass and complaints of sweating, breathlessness, tremors and impending doom. Contrast enhanced computed tomography revealed a well-defined smoothly margined, heterogenous enhancing mass in left lobe of thyroid gland. The patient also had a maculopapular rash on upper back suggestive of cutaneous lichen amyloidosis. A finding of a solid necrotic mass in left suprarenal location of size 6x5x4.5 cm likely of left adrenal origin was also noted. The laboratory parameters including serum calcitonin, plasma metanephrines and parathyroid hormone levels were elevated. Tc^{99m} Sestamibi scan revealed a left inferior parathyroid adenoma near lower pole of left thyroid lobe. She underwent left adrenalectomy and total thyroidectomy with central neck dissection one month apart. Histopathological examination confirmed the presence of synchronous medullary thyroid carcinoma (MTC), pheochromocytoma and parathyroid adenoma.

Conclusion:

This case report highlights the importance of recognizing the clinical manifestations of MEN2A. Early diagnosis with proper and complete workup allows for timely and proper intervention and decrease the morbidity and mortality associated with MEN2A due to MTC.

Keywords: Cutaneous lichen amyloidosis, medullary thyroid carcinoma, multiple endocrine neoplasia type 2A, parathyroid adenoma, pheochromocytoma.

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Introduction

Multiple endocrine neoplasia type 2 (MEN2) is a rare neoplastic autosomal dominant inherited syndrome comprising of MEN2A, MEN2B, and familial medullary thyroid carcinoma (MTC) [1]. Reported cases of MEN2 have been identified in 500–1000 families and the prevalence is estimated to be 1 in 30,000 [2]. MEN2 is characterized by the presence of MTC in almost all cases with an increased risk of developing other tumors affecting endocrine glands like parathyroid and adrenal due to the mutations in the RET gene, located on chromosome 10q11.2. This mutation leads to the alterations in the C cells

which derived from the neural crest [1]. Major characteristics of MEN2A include MTC, pheochromocytoma and parathyroid adenoma. MEN2B is characterized by MTC, pheochromocytoma with multiple mucosal neuromas and often a marfanoid habitus [3].

MEN2A constitutes 95% of all MEN2 while MEN2B constitutes 5% of the remaining cases. MTC in a case of MEN2A leads to fatal outcomes if it is not properly diagnosed or treated inappropriately, therefore proper diagnosis is required clinically and to be confirmed on histopathology. In familial cases where RET gene mutation is identified, a prophylactic

thyroidectomy significantly reduces morbidity and mortality [4]. Pheochromocytoma occurs only in 40% of MEN2A patients and is usually become evident about 10 years later after MTC or C cell hyperplasia [5].

Cutaneous lichen amyloidosis (CLA) is a pruritic, maculopapular skin lesion which is noticed about 15 years before the patient noticed the classical triad of episodic headache, palpitation and increased sweating along with associated episodic hypertension. It has been estimated that more than 30% of patients with MEN2A with a c634 RET mutation develop cutaneous lichen amyloidosis (CLA) during their lifetime, it may actually help in the early diagnosis and intervention of MEN2A syndrome [6]. We report a case of rare case of sporadic MEN2A with no family history of any thyroid or adrenal tumors.

Case Presentation

A 38-year-old female of South East Asian origin presented to surgery outpatient department with history of painless, slowly progressive neck swelling for last two years along with itchy lesions in the upper back for more than five years. On further evaluation, patient also complained of increased sweating, palpitations, breathlessness, tremors and feeling of impending doom. On examination, patient was normotensive and had a maculopapular rash on upper back suggestive of cutaneous lichen amyloidosis. (Figure 1a) In view of patient symptoms, thyroid profile was done which was normal.

Ultrasound neck showed a TIRAD 4 lesion in left lobe of thyroid, 3 cm in largest dimension with irregular borders and intranodular vascularity. Fine-needle aspiration cytology (FNAC) was done and showed cellular smears with ovoid cells arranged in sheets, clusters as well as scattered singly exhibiting moderate pleomorphism, nuclear crowding and overlapping, salt-and-pepper chromatin and scant cytoplasm. However, no nuclear features of papillary carcinoma were identified. A final diagnosis of Bethesda category V, Suspicious for Malignancy was given.

Computed tomography scan (CT) showed well defined smoothly margined, heterogenous enhancing mass (4x3x3 cm) in left lobe of thyroid gland. [Figure 1b] A finding of a solid cystic mass in left suprarenal location of size 6x5x4.5 cm likely of left adrenal origin was also noted suggestive of an adrenal neoplasm. (Figure 2a)

In view of CT findings, patient was referred to endocrinology department for further work up. Further clinical evaluation revealed no evidence of cushingoid habitus or mucosal neuromas. No significant family history was noted. Also, for the evaluation of adrenal lesion, patient underwent workup for Cushing syndrome which revealed high cortisol levels with loss of diurnal variation. Morning cortisol was 7.15 mcg/dl with ACTH of 18.90 pg/ml. Overnight dexamethasone suppression test (ONDST) and Low dose dexamethasone suppression test (LDDST) were non

suppressible [13.40 mcg/dL and 15.87 mcg/dL respectively]. Subsequent 24 hour urinary free cortisol estimation revealed normal results, while high dose DST resulted in >50% reduction of cortisol from the baseline. Contrast enhanced magnetic resonance imaging of pituitary was negative. False positive ONDST and LDDST could be resulted from non compliance to Dexamethasone ingestion, interference from medications and substances affecting cortisol and Dexamethasone metabolism. In this case the patient was on oral contraceptives which could explain these findings.

Other laboratory tests including serum adjusted calcium (12.4 mg/dl), calcitonin (1989 pg/ml), 24-hour urinary metanephrines (4004.22 mcg/24 hour), nor-metanephrines (1288.68 mcg/24 hour), plasma CEA (30 ng/ml), and intact parathyroid hormone levels (130.7 pg/dl) were done, all of which were elevated. The patient was not symptomatic for the hypercalcemia. Table 1 summarizes the biochemical laboratory parameters of the patient.

TC99m Sestamibi scan was also done which revealed focal area near lower pole of left lobe of thyroid gland possibly a left inferior parathyroid adenoma. Based on above findings, a possibility of medullary thyroid carcinoma with parathyroid adenoma and pheochromocytoma was suggested.

Thereafter, left adrenalectomy was performed followed by total thyroidectomy and left inferior parathyroidectomy with central neck dissection one month later. The other parathyroid glands were visible during surgery and were preserved. The adrenal on gross examination showed a well circumscribed unencapsulated tan-yellow mass of 6x5 cm with focal areas of hemorrhage. (Figure 2b) Microscopic examination revealed tumor cells exhibiting Zellballen and trabecular arrangement with peripherally compressed normal adrenal gland. The tumor cells were large, polygonal with abundant granular cytoplasm and uniform nuclei with prominent nucleoli and were surrounded by sustentacular cells. (Figure 2c-d) There was no lymphovascular, capsular or periadrenal adipose tissue invasion. No necrosis, increased cellularity or mitotic activity, cellular spindling, marked pleomorphism or hyperchromasia was noted. On immunohistochemistry, the tumor cells were positive for synaptophysin, chromogranin while the sustentacular cells were highlighted by S-100 (Figure 2e-f).

The thyroid specimen on gross examination showed a tan brown unencapsulated tumor measuring 4.5x4.5 cm and replacing almost the entire left lobe (Figure 1c). Microscopic examination revealed a tumor to spindle cells arranged in nests and cords with eosinophilic to amphophilic cytoplasm, round nuclei, finely stippled chromatin and indistinct nucleoli. Stroma also showed presence of pale pink, extracellular amyloid deposits (Figure 1d-e). No lymphovascular invasion, extrathyroidal extension, necrosis or increased mitotic activity was observed. On immunohistochemistry, the cells were positive for calcitonin, chromogranin and synaptophysin. (Figure 1f-g)

Table 1: The biochemical laboratory parameters of the patient

Biochemical parameters	Patient Value	Normal value
Serum adjusted calcium	12.4 mg/dl	8.5 to 10.5 mg/dl
Serum phosphate	3.7 mg/dl	3.4 to 4.5 mg/dl
Serum calcitonin	1989 pg/ml	≤14 pg/mL
25(OH) Vitamin D	30 ng/ml	20 to 40 ng/ml
Serum alkaline phosphatase	50 IU/l	44 TO 147 IU/l
Urine calcium creatinine clearance ratio	0.12	<0.14
24-hour urinary metanephrines	4004.22 mcg/24 hour	24 to 96 mcg/24 hours
24-hour urinary nor-metanephrines	1288.68 mcg/24 hour	75 to 375 mcg/24 hours
Intact parathyroid hormone	130.7 pg/dl	15 to 65 pg/mL
Plasma CEA	30 ng/ml	0 to 2.5 ng/mL

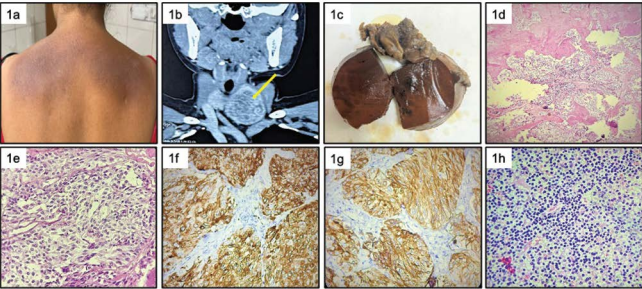


Figure 1: Lichen amyloidosis with medullary thyroid carcinoma and parathyroid adenoma a) The maculopapular rash seen on back of the patient suggestive of cutaneous lichen amyloidosis, b) Contrast enhanced computed tomography images showing a heterogeneous enhancing mass (4x3x3 cm) in left lobe of thyroid gland, c) Gross examination showed a tan brown tumor completely replacing the left lobe of thyroid gland, d-e) Hematoxylin and eosin stained sections from medullary carcinoma thyroid show a tumor arranged as nests and composed of polygonal to spindle cells with abundant extracellular amyloid deposits. [x10, x40], f-g) The tumor cells are positive for synaptophysin (f) and calcitonin (g). [x40], h) Hematoxylin and eosin stained sections from the parathyroid adenoma with clear cells arranged as nests with minimal pleomorphism. [x40]

The specimen of left inferior parathyroid was sent separately. It was a 2x2 cm nodular gray white mass which was processed entirely. Microscopic examination showed a well-circumscribed tumor comprised of predominantly chief cells with clear cytoplasm and central round nuclei. (Figure 1h)

Thus, a final diagnosis of synchronous pheochromocytoma (pT2), medullary thyroid carcinoma (pT3a) and parathyroid adenoma was confirmed based on macroscopic and microscopic features. A positron emission tomography scan was done to look for the presence of metastatic disease which was negative. The patient was advised genetic testing for RET mutation on peripheral blood sample due the presence of synchronous tumors whose presence was confirmed after histopathology. She was positive for V804M RET germline mutation which confirmed the diagnosis of MEN2A. Genetic testing of family resulted in similar mutation in her 6 year old daughter.

Six months following surgery, the patient is under close follow-up. She is currently asymptomatic and her laboratory parameters have come to normal.

Discussion

MEN2A is a rare inherited disorder characterized by the presence of MTC, unilateral or bilateral pheochromocytoma and parathyroid adenoma [3]. The lifetime penetrance of MTC in these patients is nearly 100%, with variability in the other manifestations [7]. Patients should be properly worked up for MEN2A when one of the

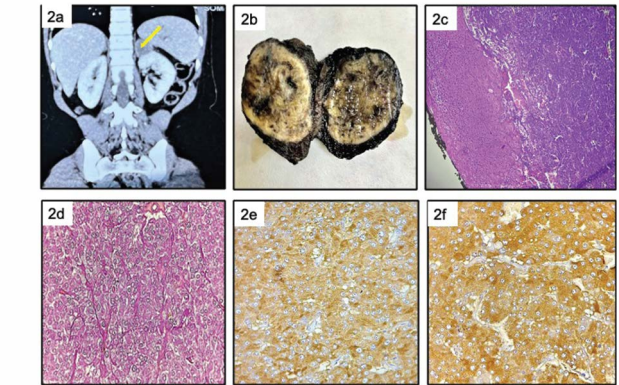


Figure 2: Pheochromocytoma a) Contrast enhanced computed tomography images show a solid cystic mass in left adrenal gland, b) Gross examination revealed a well circumscribed unencapsulated tan-yellow mass of 6x5 cm with focal areas of hemorrhage, c-d) Hematoxylin and eosin stained sections showed tumor cells arranged in Zellballen and trabecular arrangement with peripherally compressed normal adrenal gland. [x10, x40], e-f) The tumor cells are positive for synaptophysin (e) and chromogranin (f). [x40]

manifestations is identified and proper family history should also be elicited.

Follow-up routine surveillance for MTC is a must every year with serum metanephrines or 24-hour urinary metanephrine levels [8]. Hyperparathyroidism is often asymptomatic in these patients and yearly screening should be performed with serum calcium levels. If calcium levels are elevated, an intact parathyroid hormone (iPTH) is indicated [9].

If a pheochromocytoma is detected along with MTC then adrenalectomy should be performed before thyroidectomy or other surgery to avoid intraoperative catecholamine release. The American Thyroid Association guidelines recommend that prophylactic lateral neck dissections should be done on the basis of serum calcitonin levels. Prophylactic ipsilateral central and lateral neck dissection should be performed in patients with serum calcitonin level >20 pg/mL, and contralateral lateral neck dissection should be performed in patients with serum calcitonin level >200 pg/mL [10,11].

It has been reported that mortality in MEN2A is mainly due to MTC. Mathiesen et al observed that the 10-year survival rate in these patients was 98%, 93%, 87%, and 53% for MTC stages I, II, III, and IV, respectively with an overall 10-year survival of 64%.12 Death due to pheochromocytoma is rarely seen in MEN2A patients [5]. The most important prognostic factor is the stage of the disease and the presence of extrathyroidal metastases at the time of presentation [12,13]. Patients with normal postoperative calcitonin levels have a 10-year survival rate of 98% while calcitonin doubling times were associated with

aggressive disease progression and decreased overall survival^[12, 14].

Firstly, the mode of presentation in this case is noteworthy. The patient exhibited a protracted history of CLA preceding the classical triad of episodic headache, palpitation, and increased sweating associated with pheochromocytoma. While CLA is a recognized manifestation of MEN2A, its prolonged presence in this patient for over 5 years before the onset of typical symptoms raises intriguing questions about the utility of dermatologic findings as early indicators of underlying endocrine neoplasia. The extended duration of CLA without further investigation underscores the importance of heightened clinical suspicion and proactive screening for underlying systemic pathology.

Furthermore, the diagnostic journey and management of this case occurred within a resource-constrained setting, presenting unique challenges and considerations. The availability of diagnostic modalities, such as genetic testing for RET mutations or advanced imaging techniques, may have been limited, necessitating a more pragmatic approach to diagnosis and management. The successful navigation of diagnostic uncertainties and therapeutic decisions in such contexts offers valuable insights into the adaptability and efficacy of healthcare delivery in resource-limited settings.

Moreover, the identification of a specific RET mutation, namely the V804M mutation, in this patient merits attention. While MEN2A is commonly associated with various RET mutations, the specific mutation profile can influence disease penetrance, clinical phenotype, and management strategies. The presence of the V804M mutation, characterized by a moderate risk of medullary thyroid carcinoma (MTC) development, highlights the importance of genotype-phenotype correlations and tailored management approaches based on molecular profiles.

In conclusion, this case provides a unique perspective on the clinical spectrum, diagnostic challenges, and management nuances of MEN2A, particularly in resource-limited settings. By elucidating the intricacies of the patient's presentation, diagnostic journey, and therapeutic interventions, this report contributes valuable insights into the nuanced management of MEN2A and underscores the importance of individualized care guided by clinical phenotype, genetic profile, and contextual factors. Ultimately, this case serves as a catalyst for reevaluating existing paradigms, exploring novel diagnostic strategies, and optimizing therapeutic approaches in the management of MEN2A and related syndromes. Cutaneous lichen amyloidosis is such an early manifestation that warrant to keep the patient in follow-up. Family members of the affected should undergo genetic testing for RET mutation and follow-up regarding the diagnosis. MTC is the most common cause of mortality in these patients, therefore prophylactic total thyroidectomy is warranted. Patients will also require long-term follow-up and surveillance.

Declarations

Declaration of patient consent : The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal.

Conflict of Interests Statement : The authors have no conflicts of interest to declare.

Funding Sources : None

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