

## Case Report

# Simultaneous presentation of giant pheochromocytoma, primary hyperparathyroidism, and mixed-medullary–papillary thyroid cancer in MEN 2A

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### ABSTRACT

The aim of this study was to describe a young man with probably the largest pheochromocytoma associated with MEN 2A, described till date. The patient, a non-vegetarian, fifth of eight siblings, married, having five children, presented with episodes of difficult-to-control hypertension requiring over five antihypertensives. He was referred to us with an abdominal CT scan that revealed a 16 cm left-sided adrenal mass. Biochemical testing confirmed a catecholamine secreting pathology. Histopathology confirmed the mass as a pheochromocytoma weighing 1.8 kg. Further evaluation suggested a parathormone-dependent hypercalcemia and a left-sided thyroid mass. Histopathology confirmed parathyroid hyperplasia and medullary carcinoma of the thyroid mixed with papillary carcinoma of thyroid. Putting all the findings together showed that the patient was suffering from multiple endocrine neoplasia 2. Multiple endocrine neoplasia 2A is a rare syndrome. The case is unique in the way it presented, with all the three tumors at the same time. The management was bold and addressed all the three lesions in the same hospital admission. We are also reporting the largest described case of pheochromocytoma from India.

**Key words:** Adrenal tumor, catecholamine-secreting tumor, hypercalcemia, hyperparathyroidism, medullary carcinoma thyroid, multiple endocrine neoplasia, parathyroid adenoma, pheochromocytoma, thyroid cancer

## INTRODUCTION

Multiple endocrine neoplasia 2A (MEN 2A) is a rare autosomal dominant inherited cancer syndrome occurring in 1:200,000 live births. It is caused by germ-line mutations of the RET proto-oncogene. The MEN 2 gene is localized to centromeric chromosome 10 (10q11.2). It is characterized clinically by medullary thyroid carcinoma (MTC), pheochromocytoma, and hyperparathyroidism. Approximately 70-95% of individuals with MEN 2A develop

MTC, 50% develop pheochromocytoma, and 15-30% develop hyperparathyroidism.<sup>[1-3]</sup> MTC is the most consistent feature in all subtypes of MEN 2 and is usually the first clinical manifestation of MEN 2 syndrome. It is also the principal cause of morbidity and mortality. It typically presents with a neck mass or neck pain, usually before age 35 years.<sup>[4]</sup>

## CASE REPORT

A 40-year-old, married man, having five children, fifth of eight siblings, was referred to our tertiary care referral centre, with the complains of persistent headache and palpitations (at rest), that had increased since the last 2 months, on the background of hypertension (14 years) and a single episode of renal calculi 7 years ago. His treating physician admitted him at a local hospital for difficult-to-control severe hypertension and undertook a computed tomography (CT) scan of the abdomen,

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which revealed a mass in the abdomen. He was then subsequently referred to the surgical department with the aim of removing the mass. The surgeons on suspecting an underlying catecholamine secreting adrenal mass, referred the patient to our endocrine team for further evaluation. Family history suggested hypertension in three of his siblings. His parents expired at a young age. He was a nonsmoker, nonethanolic, on the following antihypertensive medication (calcium-channel blocker, angiotensin converting enzyme inhibitor, and beta-blocker).

Examination revealed a young man with weight of 70 kg, body mass index 23.5 kg/m<sup>2</sup>, pulse 100 beats/minute and a blood pressure 160/100 mm of mercury pressure supine, without any postural fall. Systemic examination revealed a mass in the region of the left thyroid gland that was firm without obvious lymphadenopathy. There was no other significant finding of note.

We considered workup for a possible catecholamine secreting pathology associated with a thyroid mass in a young patient.

### Biochemistry

Biochemistry revealed normal blood counts, blood film, liver function tests (albumin 4.5 g%); impaired renal function (creatinine 1.71 mg%, urine routine + protein); hyperuricemia (uric acid 10.2 mg%), hypomagnesemia (1.4 mg%); impaired fasting glucose (oral glucose tolerance test 75 g: 0 hours 108 mg% 1 hour 201 mg% 2 hours 138 mg%) and parathormone-dependent hypercalcemia [calcium 13.8 mg/dl, corrected calcium 13.4 mg/dl, inorganic phosphorous 1.7 mg/dl, alkaline phosphatase 140 IU/l (50-136), parathormone 326 pg/ml (10-69), vitamin D3 11.2 nmol/l (11-42)].

The patient was euthyroid [Ft4 1.1 ng/dl (0.9-1.7) Ft3 2.8 ng/dl TSH 0.76 mIU/ml (0.4-5)] with 9 am adrenocorticotrophic hormone (ACTH) 31 pg/ml (0-46 pg/ml), 9 am cortisol 23 mcg/dl; midnight cortisol 1.6 mcg/dl (collected within 10 minutes of awakening)

and normal overnight dexamethasone suppression test (9 am cortisol 0.9 mcg/dl).

Tumor markers, thyroglobulin 1980 ng/ml (<33), calcitonin 590 pg/ml (<18.2) and carcinoembryonic antigen 15.31 ng/ml (<5) were elevated suggesting possible medullary carcinoma of thyroid. Twenty-four-hour urinary metanephrines 4810 mcg/day (0-350 mcg/day) and normetanephrines 3660 mcg/day (0-650 μg/day) were significantly elevated suggesting catecholamine secreting tumor.

An echocardiogram showed a reduced left ventricular ejection fraction of 40%.

### Imaging

*CT scan whole body:* [Figure 1a] revealed a 16.4 cm × 14 cm mass with multiple hypodense areas of necrosis in the left para and suprarenal area, compressing and displacing the left kidney [Figure 1b]; multiple bilateral renal calculi (largest 2.4 cm × 1.3 cm in the left kidney); mild left-sided hydronephrosis and a 3.4 cms mass in the left lobe of the thyroid.

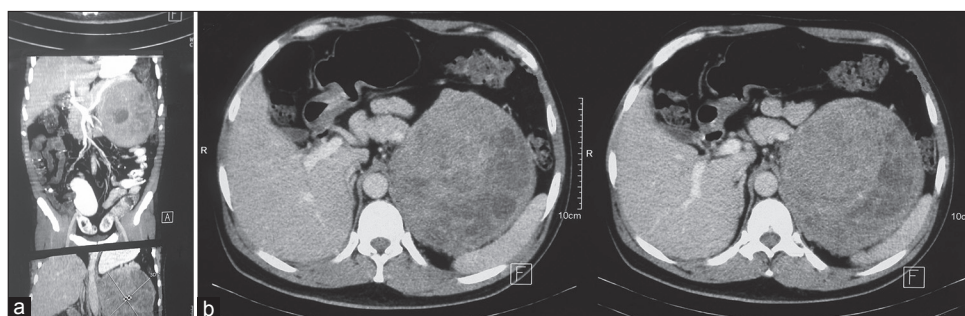
*Doppler ultrasound of neck:* [Figure 2] showed a 4 × 3.7 × 3 cm mass in the left lobe of thyroid.

*Tc thyroid uptake scan:* Enlarged left lobe of thyroid with cold nodule in the left lobe and isthmus.

*SESTAMIBI:* Localized to the thyroid mass with a brisk wash out, ruling out a parathyroid lesion. This however was on the background of a parathormone-dependent hypercalcemia.

The imaging confirmed a thyroid mass, but localizing studies for a parathyroid adenoma or hyperplasia was unrewarding.

The patient's calcium was corrected using fluid resuscitation with diuretic cover and pamidronate. Calcitonin was used



**Figure 1:** (a) Whole body CT scan showing a 16.4 cms × 14 cms mass in left para and supra-renal area, compressing and displacing left kidney. (b) CT scan of adrenals

in a single dose before we realized that the patient had a possible medullary thyroid carcinoma. Fortunately the blood for serum calcitonin was analyzed in a sample that was collected prior to administering calcitonin. He was rendered normocalcemia prior to pheochromocytoma surgery.

He was alpha blocked using intravenous phenoxybenzamine for 3 days and volume resuscitated before surgery. An adrenal mass weighing 1.8 kg was removed. The postoperative course was complicated by acute tubular necrosis. During this time he was conservatively managed while keeping a close eye on his serum calcium. His blood pressure had normalized and was off all antihypertensives. Histopathology confirmed pheochromocytoma [Figure 3].

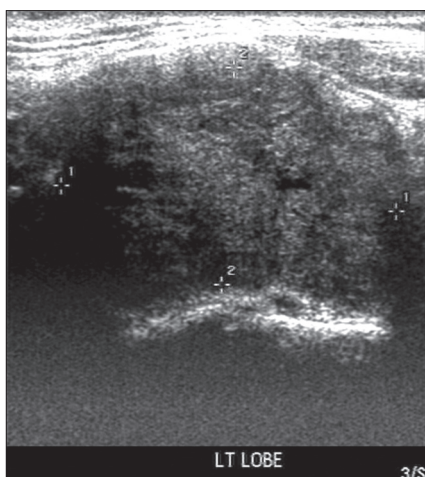
*Histopathology of adrenal mass* showed a large circumscribed tan tumor weighing 1.836 kg [Figure 4]. Cut surface was fleshy, friable, tan-coloured with cystic spaces containing

foci of hemorrhage consistent with pheochromocytoma. The immunohistochemistry profile was strongly positive for synaptophysin, chromogranin A, and S-100.

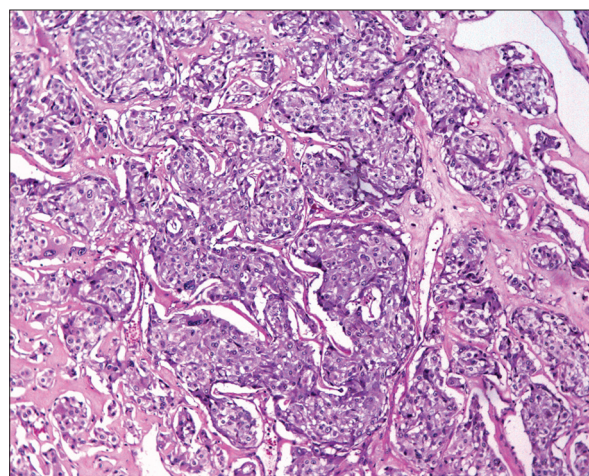
On the eighth postoperative day, surgery addressing of the parathyroids and thyroid was planned. The surgeon undertook a total thyroidectomy and removed all the parathyroid glands. Frozen section confirmed by histopathology revealed parathyroid hyperplasia [Figure 5] and medullary carcinoma of the thyroid [Figure 6].

*Histopathology of the thyroid* showed a  $4 \times 3.7 \times 3$  cm gray white firm tumor [Figure 7] replacing most of the thyroid parenchyma. Microscopy was consistent with medullary thyroid carcinoma mixed with papillary thyroid carcinoma [Figure 8 a, b].

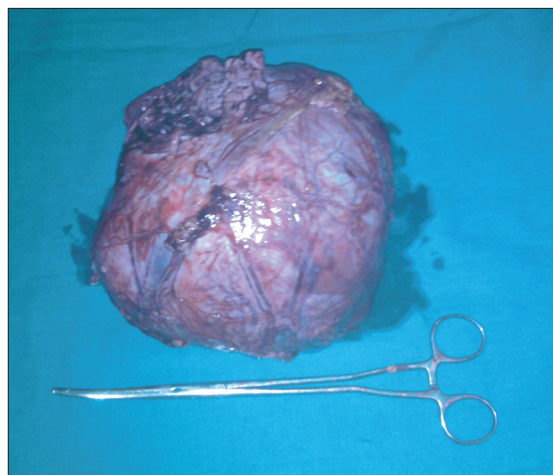
Postoperatively the patient became hypocalcemic requiring 2 days of intravenous calcium therapy. A repeat calcitonin done on the seventh postoperative day was 17.8 pg/ml,



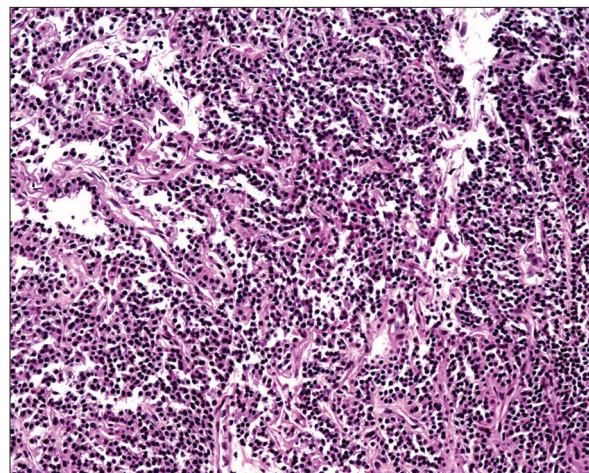
**Figure 2:** Sonography of thyroid showing  $4 \times 3.7 \times 3$  cms mass in the left lobe of thyroid



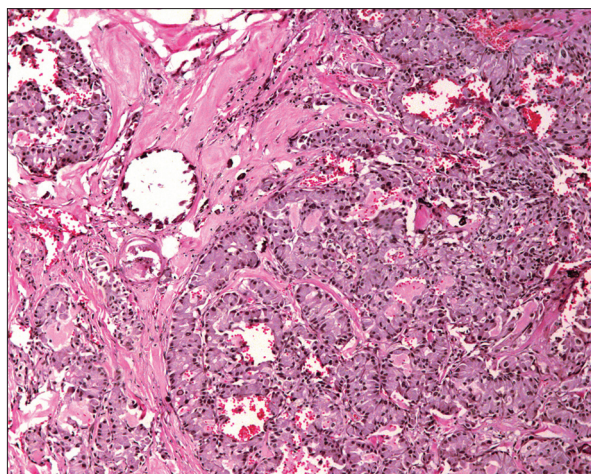
**Figure 3:** Microphotograph showing adrenal pheochromocytoma with characteristic Zellballen growth pattern (H and E,  $\times 100$ )



**Figure 4:** Macroscopic appearance of large circumscribed tan pheochromocytoma weighing 1.836 kg



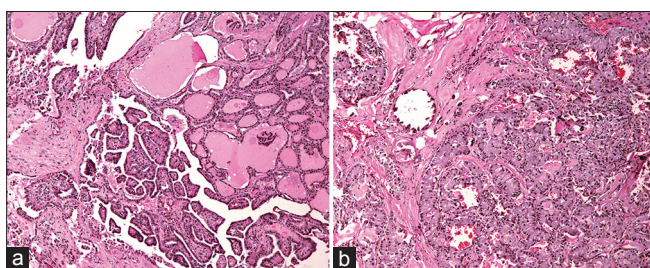
**Figure 5:** Microphotograph showing parathyroid hyperplasia (H and E,  $\times 100$ )



**Figure 6:** Microphotograph showing MTC (H and E, ×100)



**Figure 7:** Macroscopic appearance of MTC, 4 × 3.7 × 3 cms grey white firm tumour



**Figure 8:** (a) Microphotograph showing papillary thyroid carcinoma (H and E, ×100) (b) microphotograph showing Medullary thyroid carcinoma (H and E, ×100)

ensuring adequacy of surgery. The patient was finally discharged with a follow-up to discuss genetic counseling; however he denied any further assistance and was lost to follow-up.

## DISCUSSION

Mixed medullary-papillary thyroid cancer is a rare phenomenon with an incidence of approximately 19%. Coexistence of papillary cell carcinoma is coincidental and

does not change the overall prognosis of patients with MTC. Mixed medullary-papillary thyroid cancer is defined as “a tumor showing morphological features of MTC (calcitonin immunoreactivity) and follicular carcinoma (thyroglobulin immunoreactivity).” The only way to cure patients with MTC is surgery. If pheochromocytoma is diagnosed it should be operated first. The association of a mixed tumor (medullary along with papillary thyroid cancer) is very rare and has not been described before in association with MEN 2A.<sup>[5-9]</sup>

Pheochromocytomas usually present after MTC or concomitantly; however, they are the first symptom in 13-27% of individuals with pheochromocytomas and MEN 2A.<sup>[2]</sup> They are most often diagnosed between 30 and 40 years of age. About one-third are bilateral with less than 5% reported to be malignant. Up to 30% have an underlying causative genetic defect (VHL {von-hippel-lindau}, NF1 {neurofibromatosis-1}, germline mutations in SDH {succinate dehydrogenase} B,C,D,SDHAF2 {succinate dehydrogenase complex assembly factor 2}, SDH-A, KIF1B[beta] {Kinesin-like protein}, PHD2 {prolyl hydroxylase domain 2}, and TMEM127 {-spanner transmembrane protein, transmembrane protein 127}).<sup>[10,11]</sup> Cardiovascular diseases such as stroke and myocardial infarction are known to occur, but are rare. Pheochromocytomas in MEN 2 patients often secrete both adrenaline and noradrenaline episodically but metabolize them continuously to metanephrines. Measurement of plasma free metanephrines or urinary fractionated metanephrines is the best investigation of choice (100% sensitivity).<sup>[12]</sup> Medical literature reports multiple cases of isolated sporadic giant pheochromocytoma (although rare), but the association of giant pheochromocytoma with MEN2A has been rarely reported.

The case is unique in the way it presented, with all the three tumors at the same time. The management was bold and addressed all the three lesions in the same hospital admission. We also are reporting the largest described case of pheochromocytoma associated with MEN2A from India.

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