Multiple Endocrine Neoplasia 2A with Late-onset Medullary Carcinoma Thyroid and Bilateral Pheochromocytoma: A Complex Presentation

Smita S Rao, Zahir Hussain, Shikhil Puzhakkal

ABSTRACT

Medullary carcinoma thyroid (MTCs) are rare malignancies of the thyroid gland, which arise from the parafollicular C-cells. They account for 5% of thyroid malignancies. The index case presented to us with bilateral pheochromocytomas and MTC. The family treated by us included the index case of MEN2A who underwent bilateral adrenalectomy and total thyroidectomy with central compartment neck dissection, his father with MTC treated with thyroid surgery and brother with a solitary nodule thyroid under evaluation. Father succumbed to the disease 8 months later. Surgery is the primary treatment in MTC with genetic testing, contributing to early diagnosis and treatment. MTC with MEN2A is a rare entity, with our case presenting in the third decade with no metastases. Diagnosis of MEN2A involves the complex biochemical workup followed by adrenal surgery before thyroidectomy. A poor understanding would lead to major catastrophe. Hence, there is a need to report this rare occurrence in a family.

Keywords: Endocrine, Endocrine cancer, Medullary carcinoma, Multiple endocrine neoplasia, Pheochromocytoma, Thyroid cancer.

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BACKGROUND

Medullary carcinoma thyroid (MTCs) are rare malignancies of the thyroid gland arising from the parafollicular C-cells and accounting for 5% of thyroid malignancies.1 Neuroendocrine cells of thyroid were first described in 1976, and Baber named them C-cells due to the secretion of calcitonin.2 Majority of MTCs (75–80%) are sporadic and 20% are hereditary, especially those with MEN2 and familial MTC with specific RET mutations. MTC is an aggressive disease, with 50 to 55% of patients having localized disease at presentation, 35 to 40% with regional lymph node metastasis, and 15% with metastasis to lung, liver, and bone. Metastatic disease has a 10-year survival of only 20%. Therefore, unlike differentiated thyroid carcinoma (DTC), surgery is the mainstay of treatment for MTC due to non-avidity to radioactive iodine. Calcitonin and carcinoembryonic antigen (CEA) levels serve as biomarkers for C cell malignancies, guiding surgery and prognostication.3 We present a case of MEN 2A with bilateral pheochromocytoma and an asymptomatic thyroid nodule with MTC.

CASE DESCRIPTION

Our patient, a 29-year-old well-educated gentleman, presented with 1-year history of sweating, palpitations, headache, and right-sided neck swelling noticed since the past 8 years. The above symptoms were associated with diarrhea, dyspnea on exertion, polyuria, fluctuating sugar levels, and insomnia. He was poorly built with history of chest pain, blurred vision, weakness of proximal muscles, and difficulty in squatting. He underwent right open adrenalectomy and left open cortical sparing adrenalectomy for bilateral pheochromocytoma 1 month ago at our center after adequate volume expansion (2019). He had to be put on oral steroid replacement postoperatively due to unfortunate steroid dependence confirmed by corticotrophin-releasing hormone stimulation test. The neck swelling gradually progressed with no features of hyper- or hypothyroidism and no change of voice.

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Past History
He was a known diabetic and hypertensive for 1 year, noncompliant with medications.

Family History
First Generation
His father succumbed to metastatic MCT at the age of 67, 8 months after surgery. He had initially undergone total thyroidectomy with bilateral central and lateral compartment neck dissections after which there was a drop in postoperative calcitonin levels. He was treated with sorafenib with the detection of metastases. He had subsequent progression of disease with extensive lung and liver metastases and calcitonin-associated diarrhea. Genetic testing was refused by the family at that point. His mother had history of diabetes, hypertension, and hypothyroidism with a known psychiatric disorder. She was diagnosed with Hashimoto’s thyroiditis due to elevated antibody levels. There was no history of consanguineous marriage between the parents. His brother had a
right solitary thyroid nodule under evaluation, with an underlying
diagnosis of Hashimoto’s hypothyroidism.

Second Generation
His paternal and maternal aunts and uncles were hypertensives
who died sudden deaths. Paternal grandfather died at a young
age with no known cause. This history could suggest undiagnosed
hypercatecholaminism.

On Examination
He was conscious, oriented and had no tremors or eye signs with
normal general physical examination. A 5 × 4 cm swelling in the
right side of the thyroid region, moving with deglutition with
well-defined margins, firm consistency, was revealed (Fig. 1A).
Left lobe was just palpable with no palpable lymph nodes on
either side. Bilateral lateral abdominal scars measuring 15 cm,
healed by primary intension with no palpable mass, were noted
on examination of the abdomen (Fig. 1B). Further examination
showed no neurocutaneous markers. Investigations are described
in Table 1. FDG positron emission tomography (PET) scan was
done elsewhere in view of functional imaging of the adrenal
gland, and hence, no other functional imaging (MIBG/DOTA PET)
was repeated at our center. RET genetic testing detected an exon
11 c634s mutation in this patient.

Treatment
He underwent total thyroidectomy with central compartment neck
dissection. Intraoperatively, there was a single large nodule in the
right lobe of the thyroid measuring 5 × 4 × 3 cm with no suspicious
lymph nodes.

Figs 1A and B: Clinical picture showing (A) solitary nodule in the right lobe of thyroid, (B) bilateral adrenalectomy scars

Investigations

Table 1: Investigation profile of our patient

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Investigations</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ultrasound neck</td>
<td>Multinodular goiter (MNG) (R &gt; L), largest nodule in the right lobe measuring 2.6 × 3.3 cm, hypoechoic with solid areas, calcifications within the lesion, no internal vascularity and no lymph nodes TIRADS 3</td>
</tr>
<tr>
<td>2</td>
<td>Contrast-enhanced computed tomography (CECT) abdomen (Fig. 2)</td>
<td>11.3 × 9.5 × 6.3 cm enhancing heterogeneous mass in the right adrenal gland with areas of necrosis (130 HU in the venous phase) and a left adrenal homogeneous tumor with solid areas measuring 2.5 × 2 × 1.2 cm (85 HU)</td>
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<tr>
<td>3</td>
<td>Positron emission tomography (PET) CT (Fig. 3)</td>
<td>Increased uptake seen in bilateral suprarenal regions with a standard uptake value (SUV) of 4.2 s/o pheochromocytoma. Localized disease in the neck with a SUV of 1.4</td>
</tr>
<tr>
<td>4</td>
<td>Fine-needle aspiration cytology (FNAC)</td>
<td>Suspicious of MCT-Bethesda V.</td>
</tr>
<tr>
<td>5</td>
<td>Thyroid function tests (TFT)</td>
<td>TSH: 3.5 (0.5–4.8 mU/mL), fT4-1.2 (0.7–1.8 ng/mL)</td>
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<tr>
<td>6</td>
<td>Parathormone (PTH)</td>
<td>7 pg/mL (Normal 10–65)</td>
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<tr>
<td>7</td>
<td>Calcium</td>
<td>9.2 mg/dL (Normal 8.5–10.8)</td>
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<tr>
<td>8</td>
<td>Phosphorus</td>
<td>2.3 mg/dL (Normal 2.8–4.5)</td>
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<td>9</td>
<td>Calcitonin</td>
<td>150.50 pg/mL (N &lt;11.5)</td>
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<tr>
<td>10</td>
<td>CEA</td>
<td>5.6 ng/mL (Normal &lt;5)</td>
</tr>
<tr>
<td>11</td>
<td>24-hour urinary vanillylmandelic acid (VMA)</td>
<td>75.40 mg/24 hours (Normal up to 15)</td>
</tr>
<tr>
<td>12</td>
<td>Plasma-free metanephrines</td>
<td>1243 pg/mL (N &lt;65)</td>
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<tr>
<td>13</td>
<td>Serum cortisol</td>
<td>12.05 μg/dL (N 6.7–22.6)</td>
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<tr>
<td>14</td>
<td>RET testing</td>
<td>Exon 11:cys634ser mutation</td>
</tr>
<tr>
<td>15</td>
<td>Postoperative 24-hour urine metanephrines</td>
<td>111.15 μg</td>
</tr>
<tr>
<td>16</td>
<td>Histopathology (adrenal gland)</td>
<td>Bilateral pheochromocytoma with architectural atypia (Pheochromocytoma of the Adrenal gland Scoring Scale—PASS score—3)</td>
</tr>
</tbody>
</table>
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Significantly better than other cases with MEN2 owing to limited disease, negative lymph node metastases, and normal calcitonin. Neck ultrasound of the patient showed a nodule with the presence of calcifications, while routine ultrasounds in MTC do not have typical features of malignancy. However, generalized features of malignancy may be noted like suspicious hypoechoic nodules with calcifications and associated lymph nodes. Further, FNAC suggested MTC in two of our cases: index and his father, which included polygonal, spindle cells, hyperchromatic nuclei.

We noticed the elevated calcitonin levels in our index patient and his father, which served as a biomarker of the disease. Hypercalcitoninemia is seen in 40% of patients with MTC with levels more than 50 pg/mL, highly indicative of the presence of disease. Levels more than 200 to 400 pg/mL mandate metastatic workup, while postoperative levels more than 150 pg/mL indicate disease recurrence. Calcitonin could be regarded as a guide to surgery. However, there is a nonspecific rise in several other conditions like chronic renal failure, autoimmune thyroiditis, mastocytosis hyperparathyroidism (HPT), etc. CEA elevation was not seen in our patient. Elevation of CEA (50%) points to dedifferentiation of the disease, indicating poor prognosis in those with negative calcitonin.

A diagnosis of bilateral pheochromocytomas was made with the elevation of plasma fractionated metanephrines and localization with imaging in our case with MEN2A. Bilateral adrenalectomy was performed with the normalization of hypercatecholaminism postoperatively. Total thyroidectomy was planned only after the adrenal surgery in order to avoid an inadvertent hypertensive crisis during surgery. Nguyen et al. had a clinical diagnosis only after CT abdomen and MIBG localization of the disease, which was not required in our case with significantly elevated metanephrines. An FDG-PET was done to rule out metastatic disease.

Finally, RET mutation testing is recommended by the American Thyroid Association in the recent guidelines, though the evidence of which is supported by retrospective studies. Adequate genetic counseling including further available management modalities should be offered to the patient before subjecting them to the relatively expensive tests.

Outcome and Follow-up

Postoperative period was uneventful. Histopathology confirmed MCT with a tumor size of 3.8 × 2.5 × 2.2 cm within the right lobe and negative 4/4 central compartment lymph nodes. On cross section, a gray white tumor with sharp demarcation was seen. Microscopically, tumor consisted of nests of granular eosinophilic cells, polygonal cells, fibrous stroma, round nuclei, no prominent nucleoli, pseudoinclusions, and irregular amyloid deposits (Fig. 4). Postoperative calcitonin was 6.8 pg/mL at 3 months. He is on periodic follow-up.

Discussion

Sporadic MTCs present with female preponderance, usually in the fifth or sixth decade. Hereditary MTCs present much earlier in the first three decades of life. Hereditary MTCs are transmitted as autosomal dominant traits to further generations as MEN2A, MEN2B, and familial MTCs. RET mutations are identified in the chromosome 10q11 and transmitted to 95.6% of hereditary MTCs and 25% of sporadic MTCs, respectively. We had a case of MEN2A diagnosed based on clinical and genetic criteria with another case of MTC from a single family. The index case presented with palpitations, sweating, and headache followed by a painless swelling in the neck, which was ignored by him for a while.

Turner et al. designated specific criteria to diagnose MEN2A: (1) two features of MEN2A, (2) one feature of MEN2A with family history of MEN2A, and (3) genetic testing of RET mutations. MTC is almost always the primary manifestation of the disease followed by pheochromocytoma, unilateral with the contralateral presentation in the next 10 years. In our case, bilateral pheochromocytoma was the primary diagnosis, for which he was operated followed by the diagnosis of MTC and its subsequent management. MTC associated with MEN2 is generally aggressive in nature, presenting with locoregional or metastatic in nature. Our patient had MTC limited to thyroid with no lymph node metastases, very unusual in its behavior. Multifocality and bilaterality with regional metastases are typically seen in hereditary forms (50%) and distant metastases in 10% of cases. Prognosis of MTC in our patient would be

Figs 2A and B: CECT abdomen coronal section showing enhancing bilateral pheochromocytomas with areas of necrosis in the right adrenal gland (arrows pointing to right and left lesions)

Fig. 3: FDG PET image showing an increased FDG avidity in bilateral adrenal glands
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Take-home Messages

MTC is a rare thyroid malignancy requiring multidisciplinary management. Early diagnosis with high index of suspicion in the ultrasound and cytology may help in increasing the survival of the patient. Cases with both pheochromocytomas and MTC have to undergo adrenalectomy first, followed by thyroidectomy in view of averting an inadvertent hypertensive crisis. Disease localized to the thyroid has good prognosis with lower recurrence rates as compared to those that present with palpable lymph nodes, relating to the tumor biology.

Patient’s Perspective

The diagnosis of cancer changed my perspective towards life. When I was told to have an aggressive form of thyroid cancer, also part of a syndrome including tumors of the adrenal gland, I was worried like anybody. I was also told that the disease may manifest in few of my family members. Due to the timely intervention in my case, my disease has been treated and cured. I would advise all patients alike, to consult the doctor at the earliest sign of any disease so that they can be diagnosed and treated like I was, by a specialist team. The follow-up period is as important as the treatment of the disease, which needs to be understood by every patient, including the family members.
REFERENCES