Missed Diagnosis of Multiple Endocrine Neoplasia Type 2 B

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Introduction

Multiple endocrine neoplasias (MEN) are autosomal dominant hereditary cancers which have their origin in hormone secreting glands [1]. These produce specific syndromes due to the hormones secreted. Also these hormones act as tumour markers which can be used in screening and follow up. MEN have been classically classified as MEN 1 (primary hyperparathyroidism (PHPT), pituitary adenomas, pancreatic islet cell tumours), MEN-2A (medullary thyroid carcinoma (MTC), pheochromocytoma, PHPT) and MEN-2B (MTC, pheochromocytoma, Marfanoid habitus, mucocutaneous neuromas). At times these syndromes have overlapping or additional features. We report a case of MEN-2B which has many unusual features.

Case Report

A 31 year old lady, born out of a second degree consanguineous marriage reported to a gynaecologist for evaluation of primary infertility. During evaluation, an ultrasound of pelvis was ordered. When this was being performed she told the radiologist that she was operated for a 'Pheo' in past. When the probe was placed on the abdomen a mass in the left suprarenal region was seen. She was referred to the endocrine department for further evaluation. She gave history of unprovoked episodic giddiness, sweating and palpitations of five years duration. On examination she had multiple neuromas on the conjunctiva, lips, tongue, trunk and extremities (Fig. 1). Her height was 151 cm, upper segment to lower segment ratio was 0.9, arm span was 150 cm and she weighed 37 kg. She didn't have Marfanoid habitus. She had tachycardia, collapsing pulse and her blood pressure (BP) was 150/110 mm of Hg with significant postural fall (30 mmHg). Slit lamp examination demonstrated thickened corneal nerves (Fig. 2). Her systemic examination was normal. Twelve years back when she was being evaluated for pain in the right upper quadrant of abdomen, she was found to have a hydatid

cyst in the liver. She was taken up for surgical removal of the same. When the abdomen was opened a huge right suprarenal mass was seen and the operation deferred. Further evaluation confirmed a diagnosis of pheochromocytoma (24 hour urinary vanillyl mandelic acid (VMA) level was 4.2 mg/day). A well encapsulated pheochromocytoma measuring 18 cm x 11 cm x 5 cm weighing 675 g was removed at a later date. At the age of four years she was evaluated by an ophthalmologist for bilateral swellings in eyelid margins. Biopsy report from the tissue was inconclusive. With this history a diagnosis of pheochromocytoma was made and possibility of MEN-2B kept in mind.

Her haemoglobin was 10.3g/dl, blood urea nitrogen (BUN) 8.0 mg/dl, serum creatinine 0.7 mg/dl, total bilirubin 0.6 mg/dl, total protein 6.6 g/dl, albumin 4.2 g/dl, aspartate/alanine aminotransferases (AST/ALT) 30/35 U/l, serum calcium 10.3 mg/dl, (9.0-11.0), inorganic phosphorous 2.9 mg/dl, (2.5-4.5), alkaline phosphatase 70 U/l. Pheochromocytoma was confirmed biochemically. The 24 hour urinary metanephrines was 6931.12 µg (52.00-341.00), and normetanephrine was 13550.5 µg (88.00-444.00). Serum calcitonin was 847.0 pg/ml (<11.50), serum carcinoembryonic antigen (CEA) level 68.26 ng/ml (<3.0), parathormone (iPTH) 199.40 pg/ml (15.00-68.30), T3 1.2 ng/ml (0.9 – 2.6), T4 101.3 nmol/l (60 – 160) and thyroid stimulating hormone (TSH) 1.7 µIU/ml (0.3- 6.5). Computed tomography (CT) scan of abdomen showed a left suprarenal mass consistent with pheochromocytoma (Fig. 3). Ultrasonography of neck showed a well defined heteroechoic lesion seen in right lobe of thyroid measuring 1.6 cm x 1.0 cm x 0.93 cm with calcification within the lesion. The left lobe and isthmus were normal. Fine needle aspiration cytology (FNAC) was consistent with medullary thyroid carcinoma. Bone scan showed no skeletal metastases. Colonoscopy showed no ganglioneuromas. Radiograph of hip and pelvis was normal.

Patient was started on α blockade (prazosin 1mg thrice daily to start with and gradually increased to 2 mg 6 hourly). Once adequately blocked, volume expansion was done and β blocker added (propranolol 40 mg thrice daily). After adequate preparation patient underwent left adrenalectomy for

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Fig. 1: Shows subconjunctival neuromas.

Fig. 2: Slit lamp examination shows thickened corneal nerves (white lines).

Fig. 4: Histopathological examination of specimen from left adrenal showing cells in nest and trabeculae separated by thin vascular stroma consistent with pheochromocytoma.

Fig. 5: Histopathological examination of specimen from medullary thyroid carcinoma in right lobe of thyroid showing amyloid interspersed between tumour cells.

Fig. 6: Histopathological examination of specimen from parathyroid showing hyperplasia.

Fig. 3: CT scan abdomen showing characteristic pheochromocytoma lesion – heterogeneous adrenal masses. Panel A shows right sided lesion which was removed twelve years back and panel B shows left sided lesion which was successfully removed.

pheochromocytoma. Postoperative period was uneventful and she received hydrocortisone and fluocortisone replacement as she now had bilateral adrenalectomy status. Perioperative findings didn't show evidence of megacolon or neuromas on the intestinal wall. At a later date she underwent total thyroidectomy and central lymph node clearance. Parathyroid exploration was carried out and the glands were removed. Biopsy reports confirmed pheochromocytoma (Fig. 4), MTC (Fig. 5) and parathyroid hyperplasia (Fig. 6). She was started on thyroxine replacement. On second postoperative day she developed spontaneous carpopedal spasm secondary to hypoparathyroidism and was managed with α -calcidiol and calcium supplements.

Discussion

MEN-2B (MIM 162300) is a very rare syndrome with incidence of about one in a million [2]. MEN-2B is also called Wagenmann-Froboese or mucosal neuroma syndrome. It accounts for 5% of cases of MEN-2. It is transmitted as autosomal dominant trait but a significant number of cases represent new mutations. About 95% of MEN-2B are caused due to a specific germline mutation in RET proto oncogene on chromosome 10q. MEN-2B syndrome is usually diagnosed at a mean age of 11.5 years [3]. Our patient was diagnosed at an age of 31 years. The hallmark of this disease is the

occurrence of mucocutaneous neuromas especially on the tongue and subconjunctival areas. In fact, the subconjunctival neuromas are amongst the earliest manifestations of this disease [4]. In this patient her mother had noticed swellings in the eyelid margins at birth and she was evaluated by an ophthalmologist at the age of four years, however diagnosis was missed. These neuromas are an important clue to underlying MEN-2B. Thickened corneal nerves can be appreciated on slit lamp examination. Intestinal gangliomatosis is found in nearly all patients [5]. The earliest presentation in a child could be constipation or intestinal obstruction secondary to the neuromas and manifest before extraintestinal endocrine manifestations. Our patient didn't have this finding on colonoscopy and direct visualisation of the intestine during operation.

The next common component is MTC which can have an onset as early as first year of life [6]. In contrast to MEN-2A in which MTC has an indolent course in 80% of cases, in MEN-2B MTC has a very aggressive course and is rarely curable. These hereditary MTC are typically bilateral. MTC initially presents with diarrhoea, having about 10 – 20 stools per day which are voluminous in contrast to islet cell tumors. These tumours are located at the junction of upper and middle third of thyroid lobes coherent with the maximum density of c – cells in this area. It was unusual that our patient of MTC was asymptomatic and diagnosed at the age of 30 years, was in stage II and the tumour was localised to right lobe of thyroid.

Pheochromocytoma occurs in 50% of patients with MEN-2B [7]. They present at around 30 years. It was unusual that our patient presented with pheochromocytoma at the age of 19 years. About half of the tumours are bilateral and >50% of patients who have had unilateral adrenalectomy develop a pheochromocytoma in the contralateral gland within a decade [7]. Our patient also developed pheochromocytoma in contralateral gland after the first surgery. The pheochromocytoma in this syndrome differs from the sporadic and other familial pheochromocytoma in that it secretes predominantly epinephrine. This could be explained by the enzyme phenylethanolamine *N*-methyltransferase (PNMT) being positively regulated by RET proto oncogene leading to increased methylation of norepinephrine to epinephrine. Clinically this biochemical finding can be observed in the form of relative lack of hypertension and predominance of α adrenergic symptoms [3]. It is interesting to note that pheochromocytoma in our patient probably secreted predominantly norepinephrine as evidenced by markedly elevated urinary normetanephrine compared to metanephrine levels and

also had hypertension.

PHPT is very rare in MEN-2B [8]. These patients have normal calcium levels. Histologically the parathyroid glands are normal in most of the patients but hyperplasia can be seen occasionally [9]. The glands don't exhibit the normal involution with increasing age. Our patient had asymptomatic normocalcemic PHPT which is yet to be reported. This could be due to either initial stage of HPHT or vitamin D deficiency. Vitamin D levels were not measured in our patient; however her serum alkaline phosphatase was normal.

The complete syndrome with mucosal neuromas, pheochromocytoma and MTC occurs in only 50% of the cases [3]. Generally, pheochromocytoma is the first clinical manifestation of the disease in 25% of cases, MTC in 40% and in 35% of cases MTC and pheochromocytoma are diagnosed at the same time. Treatment consists of removal of pheochromocytoma first, if present, followed by that of MTC and removal of parathyroid gland and implantation in the forearm. As 50% of patients are found to have pheochromocytoma bilaterally the trend now is to perform cortex sparing adrenalectomy. In our patient genetic studies for RET proto oncogene could not be performed due to local constraints. Family screening has been advised.

Conflicts of Interest

None identified

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