IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 14, Issue 9 Ver. I (Sep. 2015), PP 70-73
www.iosrjournals.org

Suggestive Ocular Findings in a patient with Sporadic Multiple Endocrine Neoplasia type 2B syndrome: A case report

[1]Dr. Jayanta Thakuria, [2]Prof (Dr.) Dipali C Deka,
[1]Registrar, Department of Ophthalmology, Gauhati Medical College& Hospital, Guwahati, Assam, India
[2]Director and Head, Department of Ophthalmology, Gauhati Medical College& Hospital, Guwahati, Assam, India

Abstract: *Multiple endocrine neoplasia (MEN) syndrome is a group of disorder with neoplasms in two or more different hormonal tissues often presenting in several members of a family. The association of Medullary Thyroid Carcinoma, pheochromocytoma, mucosal neuromas, and a marfanoid habitus is designated MEN2B. Pheochromocytoma occurs in more than half of MEN2B patients. The mucosal neuromas and marfanoid body habitus are the most distinctive features and are recognizable in childhood.*

We present a case of a 24 year old male patient attending Ophthalmology-OPD presenting with mild diminution of vision and swelling of the eyelids (both eyes) since childhood with typical features of apparent marfanoid body habitus, sub mucosal neuromas of lips, tongue and eyelids and thickening of corneal nerves.

Keywords: *Multiple Endocrine Neoplasia 2B, Medullary thyroid carcinoma, Pheochromocytoma, Mucosal neuroma*

I. Introduction

Multiple endocrine neoplasia (MEN) encompasses several distinct syndromes featuring tumours of endocrine glands, each with its own characteristic pattern along with benign or malignant tumours of non-endocrine tissues occurring as components of these tumour syndromes often presenting in several members of a family. Several distinct genetic disorders predispose to endocrine gland neoplasia and cause hormone excess syndromes.

Table 1 :Disease Associations in the Multiple Endocrine Neoplasia (MEN) Syndromes

MEN1	**MEN2**	**Mixed Syndromes**
Parathyroid hyperplasia or adenoma Islet cell hyperplasia, adenoma, or carcinoma Pituitary hyperplasia or adenoma Other less common manifestations: foregut carcinoid, pheochromocytoma, subcutaneous or visceral lipomas	**MEN2A** -MTC -Pheochromocytoma -Parathyroid hyperplasia or adenoma -MEN2A with cutaneous lichen amyloidosis -MEN2A with Hirschsprung disease -Familial MTC **MEN2B** -Medullary Thyroid Carcinoma -Pheochromocytoma -Mucosal and gastrointestinal neuromas -Marfanoid features	Von Hippel–Lindau syndrome Pheochromocytoma Islet cell tumor Renal cell carcinoma Hemangioblastoma of central nervous system Retinal angiomas Neurofibromatosis with features of MEN1 or 2 Carney complex Myxomas of heart, skin, and breast Spotty cutaneous pigmentation Testicular, adrenal, and Growth Hormone-producing pituitary tumors Peripheral nerve schwannomas

The association of Medullary Thyroid Carcinoma, pheochromocytoma, mucosal neuromas, and a marfanoid habitus is designated as MEN2B. Pheochromocytoma occurs in more than half of MEN2B patients. Unlike MEN2A, hypercalcemia is rare in MEN2B, and there are no well-documented examples of hyperparathyroidism.

The mucosal neuromas and marfanoid body habitus are the most distinctive features and are recognizable in childhood. Neuromas are present on the tip of the tongue, lips, under the eyelids, and throughout the gastrointestinal tract and are true neuromas, distinct from neurofibromas. The most common presentation in children relates to gastrointestinal symptomatology including intermittent colic, pseudoobstruction, and diarrhea.

Genetic Considerations:

Mutations of the *RET* proto-oncogene have been identified in most patients with MEN2 .*RET* encodes a tyrosine kinase receptor, that in combination with a co-receptor, GFR, is normally activated by glial cell–derived neurotrophic factor (GDNF) or other members of this transforming growth factor–like family of peptides including artemin, persephin, and neurturin. In the C cell there is evidence that persephin normally activates the *RET*/GFR-4 receptor complex and is partially responsible for migration of the C cells into the thyroid gland, whereas in the gastrointestinal tract, GDNF activates the *RET*/GFR-1 complex. *RET* mutations induce constitutive activity of the receptor, explaining the autosomal dominant transmission of the disorder.(1)
Thus, MEN type 2 b is a rare congenital syndrome associated with hyperplastic and neoplastic changes affecting the thyroid gland, medulla as well as nervous and connective tissues. MEN 2B is characterised by the presence of medullary thyroid carcinoma (90%), uni- or bilateral pheochromocytoma (45-50%), marfanoid body habitus (65- 75%) and other hyperplastic lesions such as neuromas of the tongue and mucous membrane typically of lips, cheeks, tonsils and eye lids as well as thickening of the corneal nerves observed during slit lamp examination. These neuromas are true neuromas, distinct from neurofibromas. The most common presentation in children relates to gastrointestinal symptomatology including intermittent colic, pseudoobstruction, and diarrhea.

Skeletal anomalies including kyphoscoliosis, lordosis, feet and femoral bone deformation and dislocation of joints have been reported.(2,3)

Medullary thyroid carcinoma originating from Para follicular cells(C-cells) producing calcitonin, associated with MEN 2B is very aggressive and has a poor prognosis(4). MEN 2B represents less than 10% of MEN 2 syndromes and is associated with a higher mortality rate than MEN 2A (5).
Medullary thyroid carcinoma is the first sign of MEN 2B in 40% of cases. Catecholamine- producing pheochromocytoma occurs in around 50% of MEN 2 B cases, and is the first sign of the disease in around 25% of cases. Pheochromocytoma is usually benign, and its bilateral occurrence is reported in 50-80% cases. (6,7)

II. Case Study

A 24 year old male attended the out patient department of our institute i.e., Regional Institute of Ophthalmology,Gauhati Medical College & Hospital,Guwahati, Assam in January 2015 with complains of mild diminution of vision and swelling of the eyelids (both eyes) since childhood and occassional itching and dryness of both eyes since 6 months.

He gives history of mild swelling in the neck since childhood without any suggestive symptoms of hyperthyroidism or hypothyroidism. He had occasional pain in lower chest (both sides) and there were four episodes of spells of sweating, headache and palpitation during last one year, which he ignored initially. Later he consulted some local physician for his paroxysmal spells and chest discomfort and got some relief. No family history of similar conditions.

On ocular examination, his unaided visual acuity was RE : 6/12 and LE: 6/18 corrected with minus glasses to 6/6 (BE). Slit lamp examination showed mucosal neuromas of his upper and lower lids in both eyes leading to tylosis. (Figure 1) There was mild perilimbal conjunctival congestion and the cornea showed markedly thickened corneal nerves(Figure 2) but was otherwise clear. Anterior chamber was deep and quite with clear lens in position in both eyes. The intra ocular pressure (IOP) was 12 and 14 mm Hg in Right and Left eye respectively. The dilated funduscopic examination was normal.

General examination revealed the apparent marfanoid body habitus,(Fig. 3) height 172 cm, weight 55 kg, BMI of 18.59 kg/m2, with long arms and legs (arm span of 174cm), multiple neuromas of mucous membrane of lips and tongue (Fig 4), blood pressure 154/90 mm Hg and slight enlargement of right thyroid lobe.

Table 2: Routine blood and Biochemical investigations:

Total Leucocyte count	15,600/ mm3
Differential Leucocyte count	N=75%, L= 19%, M=1%, E=5%
Hemoglobin%	12.6 g/dl
ESR	40 mm AEFH
Random Blood Sugar	126 mg/dl
Blood urea	24 mg/dl
Serum creatinine	0.7 mg/dl
Serum Bilirubin	0.6 mg/dl
Total Protein	8.2 mg/dl
Serum Albumin	5.0 mg/dl
SGOT	24 U/L
SGPT	26 U/L

Table 3 : Hormonal investigations:

Tri iodo thyronine (T3)	1.55 ng/ml
Tetra iodo thyronine (T4)	9. 65 µg/dl
Thyroid Stimulating Hormone (TSH)	1.25 µ IU/dl
Serum Calcitonin	1732 pg/ ml
Metanephrine	689 pg/ml
Nor-metanephrine	453.5 pg/ml

With high degree of suspicion, we referred the patient to the Departments of Endocrinology, General Surgery and Urology of our institute i.e., Gauhati Medical College & Hospital. After a series of investigative procedures v.i.z., Fine Needle Aspiration Cytology(FNAC),Ultrasonography of the thyroid gland, CECT Thyroid, Abdominal Ultrasound, Computerised Tomography(CT) scan abdomen and a battery of tests for hormone levels and tumour markers concluded the diagnosis of solitary nodule of Medullary Carcinoma in Right lobe of Thyroid with Left sided supra renal mass suggestive of Pheochromocytoma. He underwent laparotomy and left adrenalectomy in March 2015. Immunohistochemistry and histopathology of the specimen confirmed pheochromocytoma.(Fig. 5). Four months after the adrenal surgery, in July 2015, the patient underwent Total thyroidectomy with resection of right cervical and superior mediastinal lymph nodes.(Fig. 6). At present, the patient is on replacement therapy with L-thyroxin, Calcium and Vit D3 treatment and is stable.

III. Discussion:

Along with MTC and Pheochromocytoma, patients with MEN 2B manifest a spectrum of additional characteristics like typical facial appearance with swollen lips, neuromas of the mucous membranes of eye, mouth, tongue and nasal cavity , gangliomatosis of the gastro intestinal tract, enlarged colon and skeletal abnormalities.(8,9,10)

Because of the aggressive and life threatening nature of MTC and Pheochromocytoma in MEN 2B along with the high risk of early metastasis of MTC (to liver and lungs); it is essential to recognize the condition as early as possible(11,12,13).

The mucosal neuroma of the inner eyelids, tongue,lips are hallmark findings in MEN 2B.(14,15) But many primary health care professionals, often fail to detect these neuromas of MEN 2B because of the rarity and unfamiliarity with its symptoms.(14)

As found in our case, prominent corneal nerves are observed in almost all cases as reported in the literature; eyelid neuroma, lid margin thickening and eversion, subconjunctival neuromas and ptosis have also been reported.(8,10) Fundus findings are rare except for choroidal metastases in patients with advanced MTC.(16)

The early detection of conditions like pheochromocytoma and medullary thyroid carcinoma can be life saving, hence

Ophthalmologist have a crucial role in recognizing the ocular signs of these rare yet fatal syndromes.(8,9,17)

In this case report, we thus highlight the ocular findings of this patient with MEN 2B and describe how the timely referral to Endocrinologist and Surgical specialities for further investigation, detection and management of the potentially life- threatening conditions associated with the syndrome immensely benefitted the patient.

Acknowledgement:

The authors would like to thank the residents and faculties of the departments of Endocrinology, General Surgery and Urology of Gauhati Medical College &Hospital, Guwahati for their helpful collaboration.

Competing interests: The authors declare that they have no competing interests.

Source of support: Nil

References:

[1]. Jameson JL et al. Endocrinology and Metabolism: Harrison's Principles of Internal Medicine 15th edn. :2187-2189
[2]. Brandii ML, Gagel RF, Angeli A et al. Guidelines for diagnosis and therapy of MEN type 1 and type2. J Clin Endocrinol Metab 2001; 86: 5658-5671
[3]. Schuman H, Laufer L, Barki Y et al. Ganglioneuroma an 'incidentaloma' of childhood. Eur Radiol 1998; 8: 582-584
[4]. Utiger RD. Medullary thyroid carcinoma,genes, and the prevention of cancer. N Engl J Med 1994; 331: 870-871
[5]. Skinner MA, De Benedetti MK, Moley JF et al. Medullary thyroid carcinoma in children with multiple endocrine neoplasia types 2A and 2B. J Pediatric Surg 1996; 31: 177-181
[6]. Sippl J.H. The association of pheochromocytoma with carcinoma of thyroid gland. Am J Med 1961; 31: 163-166
[7]. Marini F, Falchetti A, Del Monte F et al. Multiple endocrine neoplasia type 2. Orphanet Journal of Rare Diseases 2006; 1: 1172-1186
[8]. Jacob S, Hawes M: From eyelid bumps to thyroid lumps: report of a MEN type II b family and review of literature. Ophthal Plast Reconstr Surg 2001, 17: 195-201

[9]. Fink A, Lapidot M, Spierer A: Ocular manifestations in multiple endocrine neoplasia type 2b. Am J Ophthalmol 1998,126: 305-307
[10]. Eter N, Klingmuller D, Hoppner W, Spitznas M: Typical ocular findings in a patient with multiple endocrine neoplasia type 2b syndrome. Graefe's Arch Clin Exp Ophthalmol 2001, 239: 391-394
[11]. Sallai A, Hosszu E, Gergics P, Racz K, Fekete G: Orolabial signs are important clues for diagnosis of the rare endocrine syndrome MEN 2B: presentation of two unrelated cases. Eur J Pediatr 2008,167 : 441-446
[12]. Barrows F , Shockley W et al: Metastatic medullary thyroid cancer in a pediatric patient with MEN 2B: emphasion the need for early recognition of extra thyroidal clinical findings associated with MEN 2B. Clin Pediatr 2006, 45: 463-467
[13]. Lee NC, Norton JA: Multiple endocrine neoplasia type 2B genetic basis and clinical expression. Surg Oncol 2008, 15: 293-301
[14]. Wray C, Rich T et al: Failure to recognize multiple endocrine neoplasia type 2B: more common than we think? Ann Surg Oncol 2008,15: 293-301
[15]. Morrison PJ, Nevin NC: Multiple endocrine neoplasia type 2B (mucosal neuroma syndrome, Wagenmann-Froboese syndrome) . J Med Genet 1996,33: 779-782
[16]. Shields JA, Shields CL, Perez N 2002. Choroidal metastasis from medullary thyroid carcinoma in multiple endocrine neoplasia. Am J Ophthalmol 134: 607-609
[17]. Nakata S, Okugi H, Saitoh Y, Takahashi H, Shimizul K: Multiple endocrine neoplasia type 2B. Int J Urol 2001, 8: 398-400.