

## Case Report

# MEN 2A Family- Prophylactic Thyroidectomy for Asymptomatic Siblings with Positive 634 Codon Mutation

Sudhi Agarwal\*, Amit Agarwal\*\*, Gyan Chand\*\*\*, Sushil Kumar Gupta\*\*, Manoj Jain†, Pooja Ramakant\*

## Abstract

Multiple endocrine neoplasia 2a (MEN2a) syndrome is one of the rare genetic disorder where prophylactic thyroidectomy is recommended for RET mutation carriers due to increased risk for developing MTC during lifetime. We present a case report of prophylactic total thyroidectomy in a family based on genetic screening that proved to be MTC on histopathology. This is the first reported case in India where siblings underwent codon oriented prophylactic total thyroidectomy based solely on genetic analysis for MEN2a syndrome.

## Introduction

Multiple endocrine neoplasia 2A (MEN2A) syndrome is a rare genetic disorder comprising mainly of medullary thyroid cancer (MTC), primary hyperparathyroidism and pheochromocytoma. RET mutation analysis of codon 634 being highly sensitive and specific for MEN2A, helps in detection of carriers and their timely management. Prophylactic thyroidectomy is recommended for RET mutation carriers in MEN2a syndrome due to increased risk for developing MTC during lifetime. We performed prophylactic total thyroidectomy in two siblings based on genetic screening that proved to be MTC on histopathology. Though one case of prophylactic thyroidectomy is MEN 2B is published in India,<sup>1</sup> to best of our knowledge, these are the first reported cases in India where siblings underwent prophylactic total thyroidectomy based solely on genetic analysis for MEN2A syndrome.

## Case Report

An 11-year-old girl presented with goiter and diarrhea. Serum calcitonin was 4599 pg/ml (normal <11.5 pg/ml) with

<b>Method :</b>	DNA was isolated using standard protocol. Direct sequencing of the PCR products was used to detect mutations in the various exons of the RET gene	
<b>Test Results</b>		
<b>Exon Number</b>	<b>Codon</b>	<b>Presence of Mutation</b>
Exon 10	600/603/606/609/611/618/620	Not Detected
Exon 11	634	Detected
Exon 13	768/777/778/781/790/791	Not Detected
Exon 14	804	Not Detected
Exon 16	918/922	Not Detected

**Fig. 1 : Genetic analysis showing mutation in codon 634 of exon 11 on chromosome 10, which is due to TGC conversion to CGC, substituting cystine to arginine indicative of MEN2a**

\*Senior Resident, \*\*Additional Professor, \*\*\*Assistant Professor, Department of Endocrine Surgery, †Additional Professor, Department of Pathology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh  
Received: 10.02.2010; Revised: 31.08.2010; Accepted: 04.11.2010

other biochemical markers normal for MEN2 syndrome. Total thyroidectomy with central compartment nodal dissection was done. Intra-operatively, both the inferior parathyroid glands were found enlarged that was excised. Histopathology proved to be MTC with parathyroid hyperplasia with no nodal metastasis. Since she also had a strong family history of MTC (grandmother operated for MTC and father died at 34-years of age due to hepatic metastasis from MTC) genetic analysis was done in her siblings for MEN 2 syndrome; 17-year-old brother (A) and 15-year-old sister (B) (Figure 2). Direct sequencing of PCR products was used to detect mutations in various exon of RET gene. In both, mutation was detected in RET proto-oncogene, exon 11 (codon 634) on long arm of chromosome 10 resulting in TGC conversion to CGC, substituting cystine to arginine indicative of MEN2a (Figure 1). Both had normal basal serum calcitonin, normal workup for MEN syndrome and multiple hypochoic areas in thyroid on ultrasonography proven to be nodular C-cell hyperplasia (A) and colloid nodule (B) on cytology. Both underwent prophylactic total thyroidectomy with central compartment nodal dissection (Figure 3). Intra-operatively, bilateral inferior parathyroid glands were found enlarged in (A) that were excised. In both, histopathology was bilateral multiple foci of invasive MTC in the background of C-cell hyperplasia with some thyroid follicles showing partial replacement by C cells with mild nuclear atypia, representing neoplastic cell hyperplasia, which is rarely seen outside the setting of MEN 2 (Figures 4 and 5), there was no nodal metastasis. Parathyroid gland hyperplasia was present in (A). All the three siblings are alive and healthy at 2-years of follow up with normal basal serum calcitonin.

## Discussion

Multiple Endocrine Neoplasia 2a (MEN2a) syndrome is a rare genetic autosomal dominant disorder. It comprises involvement of 2 or more endocrine glands with medullary thyroid Cancer (MTC) being the most common component (100%). Other main components are pheochromocytoma (50%) and primary hyperparathyroidism (30%). It is caused by the mis-sense germline mutation of RET gene which is in the pericentromeric region of chromosome 10, and encodes a trans-membrane protein



Fig. 2 : Index case with Sibling A and Sibling B

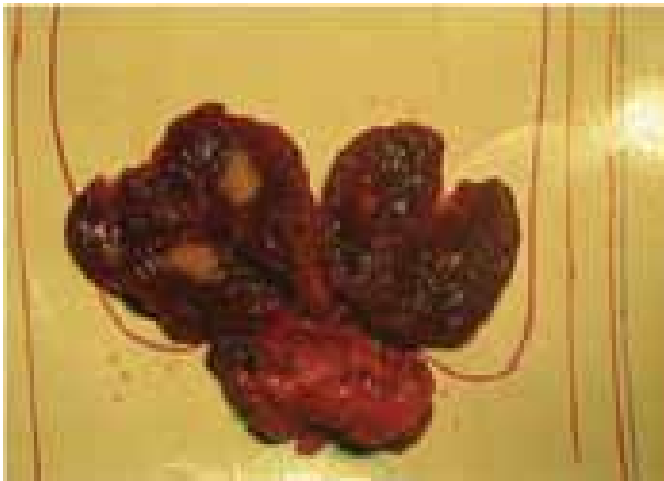


Fig. 3 : Gross thyroidectomy specimen with central compartment lymph nodes of Sibling A showing bilateral tumor foci, characteristic of hereditary MTC

tyrosine-kinase which is detected by direct sequencing, majority of MEN associate mutations involve RET exon 10, 11, 13, 14, 15 and 16, which are tested routinely, however, if negative, then remaining exon are sequenced.<sup>2,3</sup> Since its introduction, in clinical practice the genetic analysis for RET proto-oncogene mutation is considered the gold standard for diagnosing MEN2 carriers.<sup>4</sup> It provides a simple, highly accurate and early diagnosis of mutation carriers and thus the “at risk” individuals who really need to be followed up, equally important is that it assures the unaffected individuals and discharges them from further testing. However, the error the mixing of the samples among the family members, due to the common family name though rare is a serious possibility. The genetic information is stratified in to three levels depending on the aggressiveness of the MTC and RET codon 634 mutations is classified as level 2 where prophylactic thyroidectomy is recommended before the age of 5 years.<sup>2</sup> Prophylactic central compartment nodal dissection is a controversial issue. MEN2a carriers, have a life-long risk of developing medullary thyroid cancer, which is the most important cause of mortality, and thus genetic screening facilitate the codon oriented prophylactic surgery (COPD), which is curative unlike the clinically detected one.<sup>2,3</sup> Studies have shown consistently that despite the normal basal or stimulated calcitonin, prophylactic thyroidectomy revealed microscopic foci of medullary thyroid cancer or C cell hyperplasia, which often makes this surgical removal therapeutic rather than prophylactic.<sup>5,7</sup> Lack of other preventive measures, low morbidity

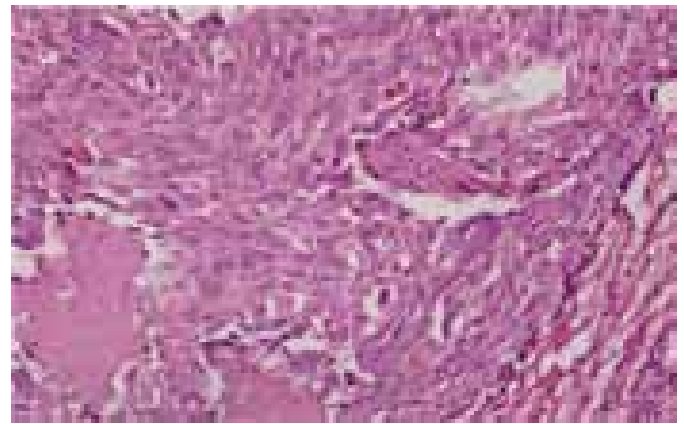


Fig. 4 : HandE staining of photomicrograph (200X) of Index case showing sheets and fascicles of spindle shaped tumor cells with oval nuclei and stippled chromatin with foci of amyloid deposition.

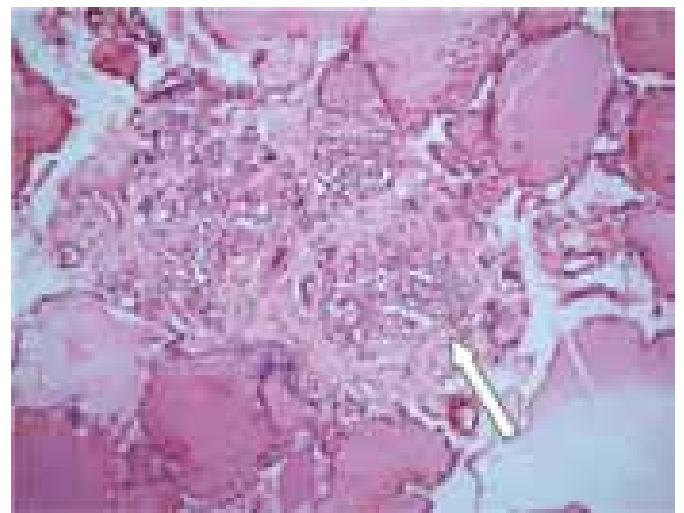


Fig. 5 : HandE of photomicrograph (100X) of prophylactic thyroidectomy of sibling A showing C cell hyperplasia with some thyroid follicles showing partial replacement by C cells with mild nuclear atypia, representing neoplastic C cell hyperplasia characteristic of MEN 2.<sup>6</sup>

associated with total thyroidectomy in experienced hands and the availability of thyroxin replacement has made prophylactic thyroidectomy an acceptable management option. Similarly, follow up studies<sup>6</sup> have also shown better overall and disease free survival in asymptomatic carriers with prophylactic total thyroidectomy than in index cases with known disease.

## References

1. Detroja NM, Bharath R, Ahamad A, Jayakumar RV, Kumar H, Unnikrishnan AG, Nisha B. Multiple Endocrine Neoplasia 2B. *J Thyroid Research and Practice* 2008;5:24-25.
2. Brandi ML, Gagel RF, Angeli A, Bilezikian JP, Beck-Peccoz P, Bordi C, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. *J Clin Endocrinol Metab* 2001;86:5658–5671.
3. Lodish MB, Stratakis CA. RET oncogene in MEN2, MEN2B, MTC, and other forms of thyroid cancer: molecular genetics and therapeutic advances. *Expert Rev Anticancer Ther* 2008;8:625–632.
4. Lips CJ, Landsvater RM, Hoppener JW, Geerdink RA, Blijham G, van Veen JM, et al. Clinical screening as compared with DNA analysis in families with multiple endocrine neoplasia type 2A. *N Engl J Med* 1994;331:828-835.
5. Eit D, Faquin WC, Gaz R, Randolph G, DeLellis RA, Pilch BZ. Histopathologic and clinical features of medullary microcarcinoma

- and C-Cell hyperplasia in prophylactic thyroidectomies for medullary carcinoma: A study of 42 cases. *Arch Pathol Lab Med* 2008;132:1767-1773.
6. Skinner MA, Moley JA, Dilley WG, Owzar K, DeBenedetti MK, Wells SA Jr. Prophylactic thyroidectomy in multiple endocrine neoplasia type 2A. *N Engl J Med* 2005;353:1105-1113.
  7. Perry A, Molberg K, Albores- Saavedra J. Physiological versus neoplastic C-cell hyperplasia of the thyroid: separation of distinct histologic and biologic entities. *Cancer* 1996;77:750-756.