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

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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 phaeochromocytoma. 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, 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 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 hypoechoic 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 phaeochromocytoma (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
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. Since its introduction, in clinical practice the genetic analysis for RET proto-oncogene mutation is considered the gold standard for diagnosing MEN2 carriers. 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. 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. 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. Lack of other preventive measures, low morbidity 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 have also shown better overall and disease free survival in asymptomatic carriers with prophylactic total thyroidectomy than in index cases with known disease.

References
