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Case Report

Unlocking the Potential of Multigene Parallel Sequencing: A Concomitant Germline RET and BRCA1 Mutation in a Hereditary Medullary Thyroid Carcinoma

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Abstract

We report a rare case of a 33-year-old South Asian woman who visited the Molecular Pathology and Genomics Department referred for hereditary germline cancer genetic testing after being diagnosed with high-grade, multifocal medullary carcinoma of the thyroid. Genetic counselling showed an elaborate family history of cancer. Germline cancer testing on 113 genes for pancancer panel by next-generation sequencing showed a pathogenic heterozygous single nucleotide variant in RET gene c.1901G>C p.Cys634Ser (codon10) and an incidental finding of the presence of a pathogenic splice variant in BRCA1 gene c.213-1G>C at the intron 4 of the gene. The patient was further managed with a paradigm of Precision Medicine (PM) based on the 5Ps like participation, psychological support, and prediction of risk assessment, prevention, and personalisation.

Introduction

In the early 1980s, the identification of Rearranged during transfection (RET) as a novel transforming gene in NIH3T3 cells marked a pivotal moment in cancer research [1]. RET gene is located on chromosome 10, and plays a vital role in embryonic development, particularly in kidney development and the enteric nervous system [2]. The gene has been linked to Hirschsprung's disease and has defined its oncogenic role in multiple cancer subtypes like non-small cell lung cancer, thyroid cancer, and breast cancer, prompting its recognition as an optimal therapeutic target [3]. Its constitutive activation is mediated by RET homo-dimerization, leading to the activation of proliferation pathways such as MAPK, PIK3, JAK-STAT, PKA, etc. [4,5].

Medullary Thyroid Carcinomas (MTCs) emerge as a rare subtype of thyroid tumor originating in parafollicular C cells, constituting 5% - 10% percentage of malignant thyroid neoplasms, and exhibit both sporadic and hereditary origins [6]. Germline constitutes 30% of total cancers, and are frequently bilateral and multifocal, presenting as an autosomal dominant disease with a high penetrance and variable phenotype [7]. The clinical spectrum of familial MTCs encompasses distinct subtypes such as classical Multiple Endocrine Neoplasia (MEN) as MEN2A, 2B and familial medullary thyroid cancer (FMTC) [8].

MEN2A, first characterized in 1961, is associated with the coexistence of MTC, pheochromocytoma, and/or primary hyperparathyroidism, potentially including Hirschsprung's disease or CLA, representing the majority of hereditary MTCs [9,10] (Figure 1). Conversely, the MEN2B subtype is distinguished by the coexistence of aggressive MTC and pheochromocytoma, accompanied by intestinal tumors, neuromas, and a Marfanoid body habitus [11]. FMTC subtype

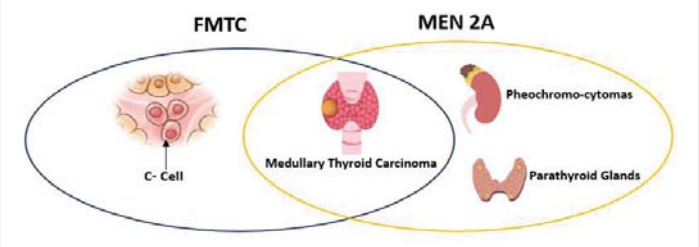

Figure 1: Venn Diagram highlighting the overlap in clinical presentation in FMTC and MEN2A.

stands out for its exclusive manifestation of hereditary MTC, characterized by the development of only MTC without the additional features of MEN syndromes [10].

On a parallel genetic front, the tumor suppressors BRCA1 and BRCA2 have been implicated in elevating the risk of epithelial malignancies, specifically breast and ovarian cancers. Accounting for a significant percentage of breast cancer cases, Hereditary Breast and Ovarian Cancer syndrome (HBOC) underscores the need for advancements in recognizing genetic predispositions, understanding risk patterns, and improving access to testing. In this dynamic landscape, early identification of at-risk individuals and tailored management strategies for those with BRCA1 mutations, including increased surveillance and preventive measures, have gained prominence [12].

As we navigate the intricate pathways of these genetic connections, our article aims to shed light on the concomitant presence of BRCA1 and RET on multigene sequencing which aided in patient management by early screening and prevention directing towards a better prognosis.

Case report

A 33-year-old female came with a complaint of swelling in her right side neck since March 2023. Histopathology detected multifocal high-grade medullary carcinoma of the thyroid; Perithyroidal, right lateral cervical, and multiple central compartment lymph nodes show metastasis with pathological stage pT3aN1bMx. USG showed an ill-defined hypoechoic right lobe of the thyroid with macro and micro calcification. PET-CT revealed heterogeneous appearing nodules in both lobes of the thyroid gland with discrete macro-calcifications larger measuring 2.9 x 2.8 cm (right) showing relatively focal tracer uptake with SUV max 13.8, showing relatively increased SSTR expression is consistent with known malignant pathology. The patient didn't show any symptoms of hypertension or hypoglycaemia. The hormone levels of plasma epinephrine, noradrenaline, metanephrines, parathyroid hormone level, or calcium levels were within limits. There was an increase in Calcitonin level to 1852 pg/ml and an increased CEA level of 134 ng/mL was noted.

The procedures that were performed included Central Neck Dissection (CND), bilateral Modified radical Neck Dissection (MND), and total thyroidectomy in August 2023. Post which she was advised to no adjuvant therapies. Family history revealed malignant hypertension, acute renal failure, and sudden death of the mother at the age of 57 years. Two of her maternal aunts are diagnosed with thyroid and uterine cancer.

Germline Cancer testing on 113 genes (Illumina Kit) for pancancer panel by next-generation sequencing [13] reported two heterozygous pathogenic variants, detected in exon 11 of the *RET* gene and intron 4 of the BRCA1 gene, highlighting the significance of screening the patients on bigger panels. The identified heterozygous missense substitution in RET gene c.1901G>C p.Cys634Ser (codon10) alters a highly conserved residue in the protein and it has been shown to impair the protein function, the possible cause of multifocal medullary thyroid Cancer in the patient. The incidental finding of the identified heterozygous variant in the BRCA1 gene (c.213-1G>C) lies in the essential splice acceptor site on intron 4. In silico splice prediction tools predict that this variant is likely to impede splicing at the junction of intron 4 and exon 5 of the BRCA1 gene. Hence, the patient was categorized among 2 clinical syndromes of MEN2A and HBOC. FMTC was ruled out keeping in mind the early age of onset, and the family history of the mother with symptoms possibility of undiagnosed MEN2A syndrome. Genetic counselling on such genetic alterations is crucial for informed patient management, including genetic counselling, surveillance, and consideration of targeted therapies. Recommendations based on the possibility of MEN2A syndrome were placed as the family history showed the mother with clinical phenotype of malignant hypertension, acute renal failure, and sudden death at age 57, potentially linked to the RET gene mutation. The patient was recommended monitoring based on NCCN guidelines like annual serum calcitonin and Carcinoembryonic Antigen (CEA), along with neck ultrasounds, to detect recurrence or progression. Additionally, screening for pheochromocytomas through annual testing of plasma-free metanephrines or 24-hour urinary fractionated metanephrines should begin as early as age 8, with imaging studies like CT or MRI if results are abnormal. Monitoring for parathyroid adenoma/hyperplasia with annual serum calcium and parathyroid hormone (PTH) testing was also advised. During the genetic counseling session, the implications of the identified BRCA1 pathogenic variant enhanced breast and ovarian cancer surveillance was emphasized. Recommendations included annual mammograms and breast MRI with contrast. Risk-reducing surgeries, such as mastectomy and salpingo-oophorectomy (RRSO), were discussed, considering the patient's childbearing options. This combination of genetic mutations heightens the patient's risk prediction for varied cancers (Figure 1).

Discussion

Multiple Endocrine Neoplasia (MEN2) syndromes constitute 25% of all medullary thyroid cancers and have been

classified into three distinct clinical forms: multiple endocrine neoplasia type 2A (MEN 2A), type 2B (MEN 2B) and Familial Medullary Thyroid Carcinoma (FMTC). [14] Of which MEN 2A is found in 70% - 80% of cases and MEN 2B in 5%, and FMTC are 10% - 20% of cases. The MEN 2A subtype is characterized by the presence of MTC (95%), pheochromocytoma (30% - 50%), and hyperparathyroidism (HPT) (10% - 20%). [4] Familial medullary thyroid carcinoma (FMTC) is primarily characterized by the development of MTC without the additional features commonly associated with MEN syndrome [15]. The present case had a clinical presentation of only Medullary thyroid cancer and the family history suggests a strong hereditary component comprising of two maternal aunts diagnosed with thyroid and uterine cancer, and the mother experienced malignant hypertension, acute renal failure, and sudden death at age 57, potentially linked to the RET gene mutation (Figure 2). Hence, a diagnosis of MEN2A was made and counselled for all the features consistent with the syndrome.

Additionally, a 2nd maternal aunt associated with uterine cancer indicated with familial predisposition to cancers, most likely associated with the BRCA1 mutation. The presence of both RET and BRCA mutations in the patient, along with a family history of Medullary Thyroid Carcinoma (MTC) and uterine cancer, suggests that the family may have two distinct hereditary cancer syndromes. The RET mutation indicates a predisposition to MTC, fitting within MEN2A or FMTC, while the BRCA mutation is associated with increased risks for breast, ovarian, and uterine cancers. This dual genetic profile raises the possibility that multiple hereditary syndromes coexist in the family. It's not uncommon for patients to carry multiple hereditary cancer syndromes, though they typically manifest independently. Hence, multigene testing was useful in the management of the patient.

In majority (>90%) of MEN 2A syndrome cases present with missense SNVs mutations in the *RET* protooncogene, with notable impact on specific codons within exons 10 (609, 611, 618, 620) and 11 (630, 634), encoding the extracellular cysteine-rich domain, as well as codons 13 (768, 790), codon 14 (804) and 15 (891) in the intracellular tyrosine kinase domain. In 60% of MEN2A-positive cases, the most common

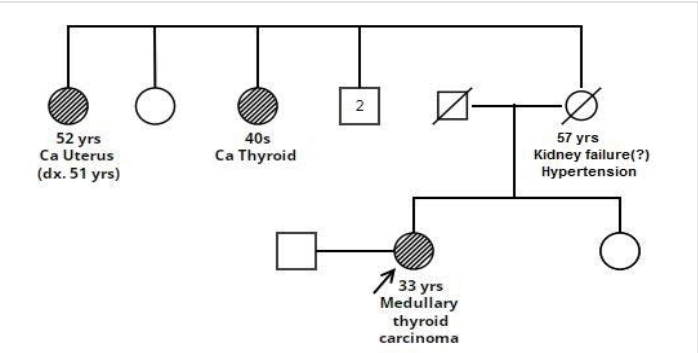

Figure 2: Pedigree chart of the family identified with Carcinoma thyroid and Endometrium.

mutations are located on codon 634 [16,17]. Phenotypic expression usually changes in each family with the same gene mutation. Puñales *et al*. described that the change in genotype C634R (T>C) presented with distant metastases at diagnosis while Milos et al found that RET C634W (C>G; C>A) showed a penetrance is high for the MTC and [18,19] The present case had 634S which presented with lymph node metastasis but no distant metastasis. Such statistics are useful in risk prediction of the disease and planning future preventive screening strategies. To date, 39 distinct RET germline mutations have been identified in MEN syndromic families (Figure 1) [20]. An overview of current knowledge concerning germline RET mutations, their location, and the phenotypic spectrum described in MEN2A can be seen in Table 1.

The American Thyroid Association (ATA) has established guidelines regarding prophylactic thyroidectomy in asymptomatic carriers of RET mutations, with recommendations stratified according to the mutation's aggressiveness. Risk levels, ranging from ATA categories A to D, guide the timing of surgery. Mutations classified as ATA level A or B are associated with moderate risk, allowing for potential postponement of thyroidectomy beyond age 5, contingent on family history and serum calcitonin levels. Mutations under ATA level C carry a higher risk, with thyroidectomy recommended before the age of 5, while ATA level D mutations, which present the highest risk, warrant thyroidectomy within the first year of life. For example, M918T mutations fall under ATA level D, necessitating early intervention; C634 mutations are categorized as ATA level C, whereas codons 609, 611, 618, 620, and 630 are ATA level B, and codons 768, 790, 791, 804, and 891 are classified as ATA level A risk mutations [21,22].

Germline mutations in RET and BRCA1 genes may predispose carriers to thyroid carcinoma and could increase susceptibility to additional malignancies. This risk often adds to the psychological burden of affected individuals, who may face concerns regarding quality of life and future reproductive decisions. Genetic counselling, along with ongoing 5Ps like participation, psychological support, and prediction of risk assessment, prevention, and personalisation was provided to address these challenges, alongside discussions on clinical screening, monitoring, early intervention, and the role of prenatal testing in family planning [23]. Preimplantation genetic testing for monogenic disorders (PGT-M) was recommended to prevent transmission of the mutation to offspring. Family members were encouraged to participate in counselling sessions to enhance their understanding of the disease's genetic and psychological dimensions. Cancer risk prediction was also discussed according to the National Comprehensive Cancer Network (NCCN) guidelines.

As part of a personalised treatment strategy, tyrosine kinase inhibitors such as Vandetanib and Cabozantinib were suggested for the potential future management of metastatic medullary thyroid cancer. Additionally, on September 27,

Table 1: RET gene with common hot spot mutation associated with MEN2A with level of ATA risk classification

Variation	Protein Change	Exon	Phenotype	Location of the mutation	Level of classification
NM_020975.6:c.1825T>C	p.Cys609Arg	10	MEN 2A, FMTC, MEN 2B	CSD	Level A and B Risk
NM_020975.6:c.1826G>A	p.Cys609Tyr	10	MEN 2A	CSD	Level A and B Risk
NM_020975.6:c.1831T>G	p.Cys611Gly	10	FMTC	CSD	Level A and B Risk
NM_020975.6:c.1833C>G	p.Cys611Trp	10	MEN 2A, FMTC, MEN 2B	CSD	Level A and B Risk
NM_020975.6:c.1832G>A	p.Cys611Tyr	10	MEN 2A, FMTC, MEN 2B	CSD	Level A and B Risk
NM_020975.6:c.1852T>A	p.Cys618Ser	10	MEN 2A, FMTC	CSD	Level A and B Risk
NM_020975.6:c.1852T>C	p.Cys618Arg	10	MEN 2A, FMTC, MEN 2B	CSD	Level A and B Risk
NM_020975.6:c.1853G>A	p.Cys618Tyr	10	MEN 2A, FMTC	CSD	Level A and B Risk
NM_020975.6:c.1853G>C	p.Cys618Ser	10	MEN 2A, FMTC, HCPS	CSD	Level A and B Risk
NM_020975.6:c.1853G>T	p.Cys618Phe	10	MEN 2A	CSD	Level A and B Risk
NM_020975.6:c.1852T>G	p.Cys618Gly	10	MEN 2A	CSD	Level A and B Risk
NM_020975.6:c.1858T>C	p.Cys620Arg	10	MEN 2A, FMTC	CSD	Level A and B Risk
NM_020975.6:c.1858T>A	p.Cys620Ser	10	MEN 2A, HCPS	CSD	Level A and B Risk
NM_020975.6:c.1858T>G	p.Cys620Gly	10	MEN 2A, MEN 2B	CSD	Level A and B Risk
NM_020975.6:c.1859G>C	p.Cys620Ser	10	MEN 2A, MEN 2B	CSD	Level A and B Risk
NM_020975.6:c.1859G>T	p.Cys620Phe	10	MEN 2A, HCPS	CSD	Level A and B Risk
NM_020975.6:c.1859G>A	p.Cys620Tyr	10	MEN 2A	CSD	Level A and B Risk
NM_020975.6:c.1889G>T	p.Cys630Phe	11	FMTC	CSD	Level A and B Risk
NM_020975.6:c.1900T>A	p.Cys634Ser	11	MEN 2A, FMTC, HCPS	CSD	Level C Risk
NM_020975.6:c.1901G>T	p.Cys634Phe	11	MEN 2A, FMTC, MEN 2B	CSD	Level C Risk
NM_020975.6:c.1901G>A	p.Cys634Tyr	11	MEN 2A, FMTC, MEN 2B	CSD	Level C Risk
NM_020975.6:c.1901G>C	p.Cys634Ser	11	MEN 2A, FMTC	CSD	Level C Risk
NM_020975.6:c.1900T>C	p.Cys634Arg	11	MEN 2A,HCPS	CSD	Level D Risk
NM_020975.6:c.1900T>G	p.Cys634Gly	11	MEN 2A, MEN 2B	CSD	Level C Risk
NM_020975.6:c.1902C>G	p.Cys634Trp	11	MEN 2A, MEN 2B	CSD	Level C Risk
NM_020975.6:c.2304G>C	p.Glu768Asp	13	FMTC, MEN 2A, MEN 2B	TKD	Level A and B Risk
NM_020975.6:c.2370G>T	p.Leu790Phe	13	MEN 2A, FMTC	TKD	Level A and B Risk
NM_020975.6:c.2370G>C	p.Leu790Phe	13	MEN 2A, FMTC, MEN 2B	TKD	Level A and B Risk
NM_020975.6:c.2372A>T	p.Tyr791Phe	13	FMTC, MEN 2A, MEN 2B	TKD	Level A and B Risk
NM_020975.6:c.2410G>T	p.Val804Leu	14	FMTC, MEN 2A, MEN 2B	TKD	Level A and B Risk
NM_020975.6:c.2410G>A	p.Val804Met	14	FMTC, MEN 2A, MEN 2B	TKD	Level A and B Risk
NM_020975.6:c.2417A>G	p.Tyr806Cys	14	MEN 2A, MEN 2B	TKD	Level A and B Risk
NM_020975.6:c.2647_2648delinsTT	p.Ala883Phe	15	MEN 2A, MEN 2B	TKD	Level A and B Risk
NM_020975.6:c.2671T>G	p.Ser891Ala	15	FMTC	TKD	Level A and B Risk
NM_020975.6:c.2753T>C	p.Met918Thr	16	MEN 2A, MEN 2B	TKD	Level A and B Risk
c.1741_1742insGAGGAGTGT	p.531_532GluGluCys	8	FMTC, MEN 2A, MEN 2B		
c.2056_2057insTCGCGCACG	p.636–637CysArgThr	11	MEN 2A		
c.2049_2050insACGAGCTGTGCC	p.634_635CysArgThr	11	MEN 2A		

Abbreviations: MEN2: Multiple Endocrine Neoplasia, type 2; HCPS: Hereditary Cancer-Predisposing Syndrome; CRD: Cysteine-Rich Domain; TKD: Tyrosine Kinase Domain

2024, the U.S. Food and Drug Administration (FDA) approved selpercatinib for use in adults and pediatric patients (aged ≥2 years) with advanced or metastatic medullary thyroid cancer with an FDA-approved RET mutation, based on findings from the LIBRETTO-531 trial (NCT04211337) [24-26]. The patient was suggested for monitoring annual serum calcitonin and carcinoembryonic antigen (CEA), along with neck ultrasounds, screening for pheochromocytomas through annual testing of plasma-free metanephrines or 24-hour urinary fractionated metanephrines, with imaging studies like CT or MRI if results are abnormal. Monitoring for parathyroid adenoma/hyperplasia with annual serum calcium and Parathyroid Hormone (PTH) testing was also recommended.

Follow-up appointments of the patient with us were limited and could not be assessed for long-term outcomes and effectiveness of treatments. This hinders the generalizability of the case to other patients with similar conditions.

Conclusion

This case underscores the importance of the rare presentation of 2 pathogenic mutations in the same patient with clinical presentation of only FMTC associated with RET. While BRCA 1 gene complicates the clinical picture, emphasizing the need for personalised management plans in patients with pathogenic variants. The family history of cancer raises concerns about a potential genetic component, necessitating further exploration and genetic counselling for at-risk family members. The present case also highlights the significance of using a broader panel in identifying hereditary cancer predisposition. Further research and collaboration between oncologists and genetic counsellors are essential to understand the implications of these genetic findings and optimize patient care. Personalised genetic counselling based on the 5Ps is a way forward in better patient treatment. The current condition of the patient remains unknown due to the

absence of follow-up. As a result, we were not able to determine the long-term effects or progression of the condition.

Ethical statement

Informed Consent for Hereditary Germline cancer testing and future research and publication was taken from the patient (KDAH/MPG/R-142 and KDAH/MPG/R-139). The test conducted was necessary for clinical purposes, so ethical approval was not requested.

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