CASE STUDY

Preventable Breast Cancer: Early Genetic Testing Advisable In High Risk Families

Gender: Female

Age: 30 years

Location: Delhi, NCR

Diagnosis: Breast Cancer

Strand Test: Germline

Conclusion:

- Eligibility for PARP inhibitor therapy established.

  Awareness of hereditary breast and ovarian cancer, amongst family members increased.

Patient Profile

Sumana Chakraborty* was 21 years old when her mother Madhumita Chakraborty*, age 45 years, was diagnosed with ovarian cancer. Sumana's mother was referred to a prominent oncologist at Sir Gangaram Hospital in Delhi.

Madhumita was advised to undergo genetic analysis of her blood sample. With uncanny premonition, she suggested that Sumana should also get her DNA tested to understand her own risks of suffering from ovarian cancer, in future. At the age of 21, no one is inclined to take such suggestions seriously and that is exactly what Sumana also did.

As fate would have it, Sumana was diagnosed with breast cancer, at the age of 30 years. In India, the number of cases of breast cancer being diagnosed at a young age is significantly higher than that in Western countries and this is an alarming fact.

Family History

Owing to Sumana's family history, she was asked to consult a genetic counsellor to record and analyze information about incidence of cancer in her family. In addition to her mother, Sumana's grandmother had also suffered from breast cancer at the age of 35 years and was subsequently lost to the disease.

Sumana's paternal aunt (father's sister) was suspected to have had colon cancer, although the family could not confirm this information. Additionally, Sumana's mother's sister had been diagnosed with breast cancer at the age of 36 years, and subsequently cancer in the contralateral breast at the age of 55 years. Sumana's maternal uncle had been diagnosed with lung cancer at the age of 60 years.

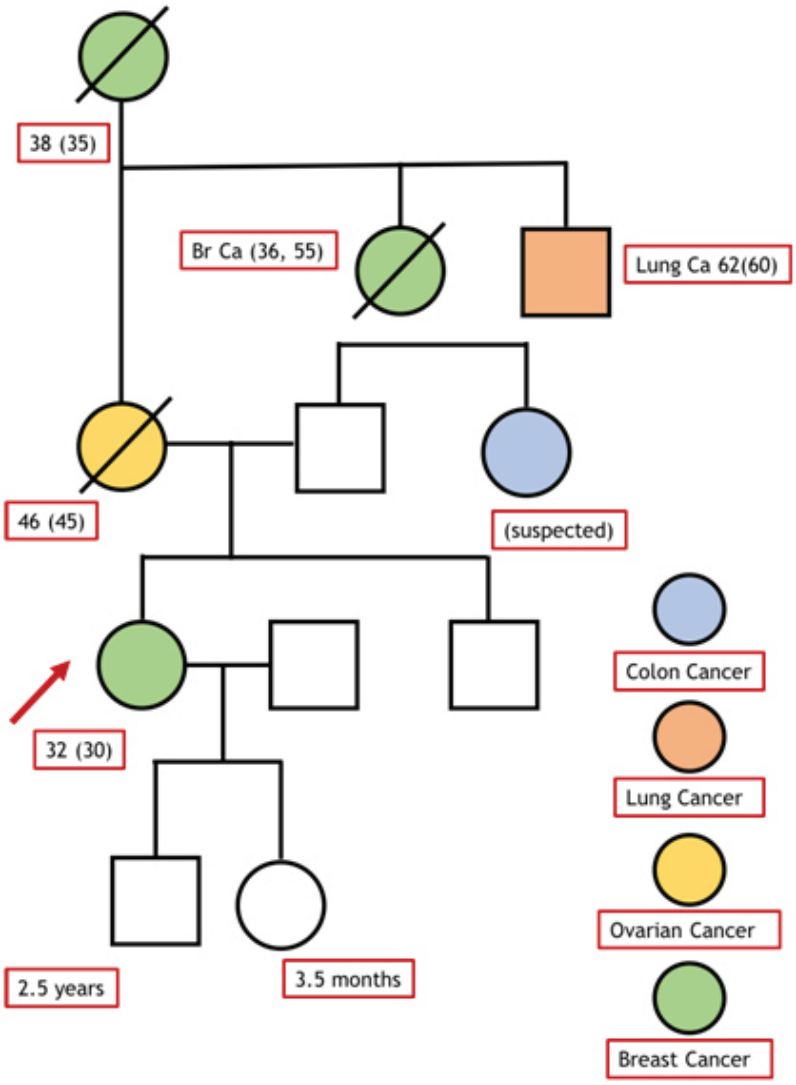
Considering the high prevalence of breast, ovarian, lung and possibly colon cancer amongst Sumana's first- and second- degree relatives, she was advised to undergo germline testing to understand the nature of heritable mutations in the family.

Therapy Recommendations

Sumana had undergone modified radical mastectomy in the left breast and nipple-sparing mastectomy in the right breast, as the first stage of treatment. Following these surgeries, she had received 12 cycles of carboplatin + paclitaxel chemotherapy to tackle residual disease. Bilateral whole-breast radiation (50Gy/ 25 fractions / 31 days) was also prescribed for her. She was able to resume her daily life, after these treatments. The identification of a BRCA1 mutation in her genome has also established her eligibility for receiving PARP inhibitor therapy (1,2), if her cancer should recur in the future.

** Name changed to protect patient privacy*

Family Tree - Pre-Genetic Testing



Results of Genetic Testing

The Strand Germline Test was advised to Sumana. This test is designed to identify mutations in 19 genes that have been linked with hereditary breast and ovarian cancer.

RESULT **Positive** for a heterozygous '**pathogenic**' mutation in exon 13 of the *BRCA1* gene

Results

Positive for a heterozygous **'pathogenic'** (disease-causing) variant, which was detected in the splice donor site at the junction of exon 13-intron 13 of the *BRCA1* gene.

Key Findings

Gene	Variation	Zygosity	Clinical significance
BRCA1	chr17:41228504C>T c.4484+1G>A	Heterozygous	Pathogenic

Sumana was found to be heterozygous for a pathogenic mutation in the *BRCA1* gene (*BRCA1* c.4484+1 G>A).

Key Findings

- The identified variant bears a mutation in an essential splice donor site downstream of exon 13 in the *BRCA1* gene.
- In *silico* splice prediction tools (NNSPLICE and ASSP) predict that this variant is likely to disrupt the splice site at the junction of exon 13 and intron 13 of the *BRCA1* gene. This could lead to a frameshift, which will probably result in truncation of the protein.
- The resultant protein is likely to lack a functional BRCT domain (1650-1863 amino acids), which is required for the DNA repair pathway, therefore will likely result in loss-of-function.
- Moreover, due to the introduction of a premature stop codon, this aberrant transcript will likely be targeted by the nonsense mediated mRNA decay (NMD) mechanism.
- The resultant deficiency in the DNA repair mechanism is likely to have caused the breast and ovarian cancers in the proband as well as her first-degree relatives.
- The identified variant has been classified as 'pathogenic' variant in the ClinVar database (RCV000031177.5).

Conclusions

- Sumana Chakraborty is a representative case of the current trend observed in hereditary breast and ovarian cancer in India: Women younger than 40 years of age are getting diagnosed with breast and/ or ovarian cancer (3).
- Early review of Sumana's family history might have led to earlier discovery of the prevalence of cancers amongst her relatives thereby leading to ad hoc discovery of the heritable BRCA1 mutation.
- Preventive screening of genomic mutations can possibly enable young (20-45 year age group) women to plan their families and avail of risk reduction salpingo-oophorectomy (RRSO) that confers protection from breast and ovarian cancer (4–6).
- Risk assessment for hereditary breast and ovarian cancer and increased awareness about the protective benefits of RRSO could possibly be integrated in gynaecology practice, in order to pre-empt the incidence of cancer in individuals bearing inherited *BRCA1* and *BRCA2* pathogenic mutations.

Strand® Germline Test

The Strand Germline Cancer Test is designed to identify genes that are involved in several inherited cancers. The following genes are analyzed in samples from breast and ovarian cancer patients, as per international genetic testing guidelines.

ATM, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, NBN, NF1, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11, TP53

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