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Original Research Article

Evaluation of the spectrum of genetic variations in young cancer patients presenting to the tertiary cancer centre

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ABSTRACT

Background: Aim of the study was to evaluate the spectrum of genetic variations in young cancer patients presenting to the tertiary cancer center
Methods: All newly diagnosed patients with cancer presenting to medical oncology OPD at continental hospitals between November 2021 till July 2023 were analyzed. Multigene panel testing (56 genes) by next-generation sequencing was performed for all patients. Demographics and clinical characters were represented using descriptive statistics. The Chi-square test was used to compare the cohorts of Mutations vs. non mutations.
Results: A total of 130 cancer patients were screened and 70 were recruited in the study, which had complete set of clinical details available. Median age of Cohort is 41.9±6.6 years and for females it is 43.6±6.8 years and males it is 40.5±7.3, with males presenting at approximately 3 years earlier than females (p=0.12), which is not statistically significant. Male female ratio is 1.2:1, which is much less compared to Globocon statistics of cancer in India. A total of 47% (33/70) subjects had some mutation and approximately 16% (11/70) had variance of unknown significance and 32% (22/70) patients had pathogenic variants. The commonest cancer is breast followed by colon and prostate.
Conclusions: Younger cancer patients presenting with atypical symptoms harbor more frequent germ line mutations, than expected. In view of the low cost, standardized and wide availability of the germ line analysis, it's preferred to offer the test, wherever clinically relevant. This can help for better education, screening and early intervention, that ultimately help improve the cancer statistics in healthier directions.

Keywords: Germline, Cancer, Screening, Breast, Ovary

INTRODUCTION

One of the most often posed questions by the patients in oncology practice is "How did the cancer happen? And is it hereditary?" Most of the oncologist used to struggle to answer this question in the past as the availability of genetic screening was limited and prohibitively expensive. The conventional answer used to be that you should suspect a potentially hereditary cancer-if early onset/ young cancer patients (Usually <40 years), multiple cancers in a same patient and multiple family members suffering from same or similar cancers (Breast/vary etc.,).[1]

With the technological advancements, now a day's it's widely available with cost as low as 3000 to as high as 300000 based on complexity.[2] This is making most of the oncologists to prescribe these tests more often in their practice than earlier. Even patients and family members started realizing and asking for the testing in view of

increased awareness. In this context we thought of analyzing initial data from single institute on spectrum of genetic variations observed during the random testing. Therefore, we conducted this study to evaluate spectrum of genetic variations in young cancer patients presenting to the tertiary cancer center and see if there are any new variants, what are the frequency of mutations and demographics of those having mutations vs. no mutations.

METHODS

This is non-randomized, retrospective data analysis conducted on all newly diagnosed patients with cancer presenting to medical oncology OPD at continental hospitals, Hyderabad, India from Nov 2021 till July 2023. Eligibility criteria was-Willing to give informed consent, confirmed diagnosis of cancer, availability of family history of at least 1 generation, no previous genetic testing done and clinical suspicion of hereditary malignancy as per NCCN criteria/ literature cross reference.[3]

Those with inconclusive results and poor-quality controls were rejected from analysis. The sequential patients diagnosed with "young cancer/ atypical presentation" were identified and counseled for the potential genetic screening. Separate sample size estimation was not done as this is a continuous process and all the patients who agreed for the testing in the study period were analyzed. Demographic, clinical information, cancer history (personal and family), other relevant details were obtained from the hospital records and complied in table 1. Multigene panel testing (56 genes) by next-generation sequencing was performed for all patients and we have used three different labs during our study period. Stand life sciences, 4basecare, Neuberg diagnostics. Standard reporting format was followed and the diagnosis is classifiable into-Pathogenic, variance of unknown significance and no pathogenic variants found.

However, at the time of final diagnosis and reporting, we followed American college of medical genetics classification which was into five categories-class 1, benign, class 2 likely benign, class 3 variant of uncertain significance (VUS), class 4 likely pathogenic (LP), and lastly class 5 pathogenic (P). LP and P variants were defined as deleterious variants.[4] As this is a retrospective data analysis, no prior approval as obtained from ethics committee as it was not needed. However, we have notified the study details and the manuscript to the institutional scientific review board/ ethics committee.

Statistical analysis

Analysis was performed using STATA software version 13. Demographics and clinical characters were represented using descriptive statistics. The Chi-square test was used to compare the cohorts of mutations vs. non mutations. A $p<0.05$ was considered significant.

RESULTS

A total of 130 cancer patients were screened and 70 were recruited in the study, which had complete set of clinical details available. Median age of Cohort is 41.9±6.6 years and for females it is 43.6±6.8 years and males it is 40.5±7.3, with males presenting at approximately 3 years earlier than females (p=0.12), which is not statistically significant. The male female ratio is 1.2:1, which is much less compared to the Globocon statistics of cancer in India, which may be due to the selection bias.[5]

Mutation profile

A total of 47% (33/70) subjects had some mutation and approximately 16% (11/70) had variance of unknown significance and 32% (22/70) patients had pathogenic variants. The distribution of same is represented in Figure 1. These numbers are significantly higher compared to any of the reported literature from India. The summary of various mutations were represented in Table 2. Coming to the individual cancers where some mutations were found, breast cancer is commonest 32% (22/70) followed by colon 27% (19/70), prostate 9% (6/70), Stomach 7% (5/70) and other rare cancers. Exact distribution of these cases was represented in Figure 2.

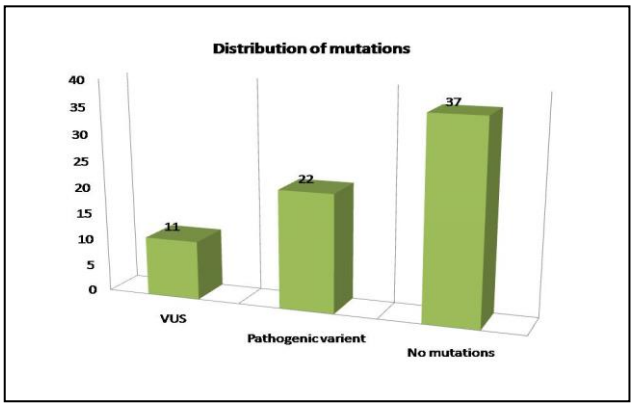

Figure 1: Mutation types and frequency.

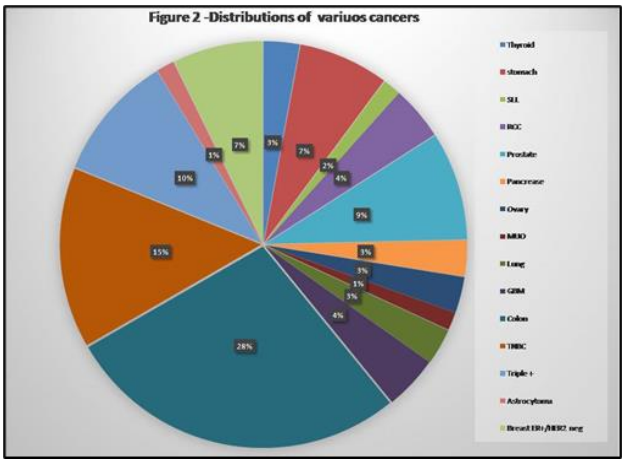

Figure 2: Types of cancers in study population.

Table 1: Demographics.

Details	No mutation	VUS	Mutation±cases
Age (Mean±SD)	40.8±6.2	43.9±7.1	43.1±7.6
Male: female	18:19	3:8	10:12
Type of caner			
Breast	10	5	8
Thyroid	2	0	0
Stomach	3	0	1
SLL	0	0	1
RCC	3	0	0
Prostate	3	2	1
Pancreases	0	0	2
Ovary	2	0	0
MUO	1	0	0
Lung	0	1	1
GBM/astrocytoma	3	1	0
Colon	12	1	8
Stage of the disease, I/II Vs III/IV	**20:17**	**4:7**	**8:14**

Table 2: Detailed description of various mutations.

Type of cancer	Mutation
Breast triple +	VUS in SDHAF2 and PALLD
Lung-Alveloar	VUS in POLE
Breat-TNBC	VUS in EXT2, RAD51C, RB1
SLL	VUS in ERCC4
Prostate	VUS in CHEK2
Breast-TNBC	Variant was detected in exon 2 of the BRCA1 gene.
Colon	Variant was detected in exon 2 of the BRCA1 gene
Colon	Variant was detected in exon 17 of the MLH1 gene
Breast-TNBC	Pathogenic variant in BRCA2
Breast-HER 2 +	Pathogenic variant in BRCA1
Breast-TNBC	Pathogenic variant detected in TP53 gene (c.818G>T, VAF-83.74%), Positive for CCNE1 gene amplification (Copy No: 18), Positive for YWHAE gene rearrangement (SR-16)
Pancrease	Pathogenic variant detected in TP53 gene (c.734G>A, VAF 1.08%)
Pancrease	Pathogenic variant detected in TP53 gene (c.734G>A, VAF- 1.08%)
Stomach	Pathogenic variant detected in TP53 gene (c.202G>T, VAF: 19.72%)
Cervix+ovary	Pathogenic variant detected in KRAS (G13C) gene (c.37G>T, VAF- 10.42%)
Colon	Pathogenic variant detected in KRAS (G12D) gene (c.35G>A VAF- 5.2%)
Colon	Pathogenic variant detected in KRAS (c.35G>T, VAF- 45.06%) and TP53 (c.818G>A, VAF-58.73%)
Lung-Alveloar	Pathogenic variant detected in EGFR (exon19 Indel) (c.2235_2242delinsAATTCCCGTCG) and TP53 (c.45_48del) gene and Positive for MYC gene amplification (Copy No: 9)
Colon	Pathogenic variant detected in CDKN2A (c.238C>T, VAF-39.81%) and TP53 (c.673-1G>A VAF-27.54%) gene
Colon	Pathogenic variant detected in APC (c.4348C>T, VAF- 24.09%, c.2828C>A, VAF-24.63%) PTEN (c.895G>T, VAF- 35.94%) and TP53 (c.817C>A, 15.85%) genes
Colon	Pathogenic variant detected in APC (c.4348C>T, VAF- 24.09%, c.2828C>A VAF:24.63%), PTEN (c.895G>T, VAF 35.94%) and TP53 (c.817C>A, VAF: 15.85%, c.637C>T VAF: 24.12%) genes.
Colon	One 'VUS' was detected in exon 3 and another 'VUS' was detected in exon 8 of the MSH2 gene
Breast-TNBC	One 'VUS' was detected in exon 15 of the ATM gene and another 'VUS' was detected in exon 10 of the BRCA2 gene.
Prostate	One 'VUS' was detected in exon 1 of the MSH2 gene and another 'VUS' was detected in exon 8 of the STK11 gene.
Breast-TNBC	Detected in exon 7 of the PMS2 gene
Prostate	Detected in exon 41 of the TSC2 gene
Breast	Detected in exon 14 of the NBN gene

Continued.

Type of cancer	Mutation
Colon	Detected in exon 13 of the PMS2 gene
Breast	Detected in exon 13 of the CHEK2 gene
Astrocytoma	One 'VUS' was detected in exon 10 of the, ATM gene and another 'VUS' was detected in exon 42 of the NF1 gene.
Breast-TNBC	Variant was detected in exon 7 of the MSH2 gen
Breast-TNBC	One 'VUS' was detected in exon 17 of the, BRIP1 gene and another 'VUS' was detected in exon 9 of the RAD51D gene.
Breast triple +	Detected in exon 12 of the BRIP1 gene

DISCUSSION

Besides the conventional prognostic markers, genetics started to play an important role in determining the disease management options with a huge futuristic impact on the healthcare system. One of the major challenges faced by the healthcare and research community in India is the lack of genotype-phenotype correlations for Indians at a population-wide and an individual level.[7] Studies across the nation found very interesting findings reported in isolations.

The overall incidence of mutations from India varies from 3% to 36% based on the study settings.[7-12] However, in our study we observed a total of 47% (33/70) subjects had some mutation and approximately 16% (11/70) had variance of unknown significance and 32% (22/70) patients had pathogenic variants. These numbers are significantly higher compared to any of the reported literature from India.

In a study evaluating the genetic landscape of TNBC by Koppiker et al, they found 57 pathogenic mutations with a diagnostic yield of 30%.[8] Compared to world literature they observed relatively higher prevalence of BRCA1 (21.24%) and BRCA2 mutations (4.14%). Additionally, 8 pathogenic mutations were also reported in non-BRCA cancer pre-disposing genes associated with the HR pathway like ATM, CHEK2, PALB2. The 10 novel mutations were identified in 3 genes namely BRCA1, BRCA2 and PALB2. Similarly, Basak et al from eastern India observed 5382insC, a BRCA1 mutation, prevalent in Ashkenazi Jews, besides 2 more novel mutations.[8,9] In another study by Soumitra et al "Fifteen (16%) pathogenic mutations (12 in BRCA1 and 3 in BRCA2), of which six were novel BRCA1 mutations were identified."[10] These findings emphasize the need for detailed region-specific analysis.

In our study we have multiple cases of rare unexpected cases showing mutation. Among the individual cancers where some mutations were found, breast cancer is commonest 32% (22/70) followed by colon 27% (19/70), prostate 9% (6/70), Stomach 7% (5/70) and other rare cancers. This emphasizes that we shall have lower threshold for screening the patients with one or more atypical findings. Even in literature, it was reported that these mutations can happen in seemingly "clinically unsuspected" group of patients as well as a reported from TMH by Sudeep Gupta et al-who found that "Indian women with ovarian cancer not selected for study based on clinical factors had a high prevalence of germline pathogenic or likely pathogenic BRCA variants.[11]

In our study as well, most of the observed mutations are there in otherwise non suspected populations. This is quite important to keep the related family members to be kept on selective/ high risk surveillance for the early diagnosis and better management. Tansir et al argued that "The diagnosis of Li Fraumen syndrome (LFS) has socio-economic implications for patients and their families.[12] Delay in genetic testing misses out a crucial window wherein asymptomatic carriers could initiate surveillance in a timely fashion. Greater awareness on LFS and genetic testing in Indian patients is warranted for better management of this hereditary condition."

Limitation

Retrospective nature of the study and the small sample size is a challenge in single institutions studies like this. The high incidence of VUS "variance of uncertain significance" poses a significant clinical dilemma both to the patients and treating physicians.

CONCLUSION

Younger cancer patients presenting with atypical symptoms harbor more frequent germ line mutations, than expected. In view of the low cost, standardized and wide availability of the germ line analysis, its preferred to offer the test, wherever clinically relevant. This can help for better education, screening and early intervention, that ultimately help improve the cancer statistics in healthier directions.

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