Solid Tumors other than Breast Cancer are Associated with Germ-line *ATM* Heterozygosity

Meme Kanseri Dışındaki Solid Tümörler, Germ-line ATM Heterozigotluğu ile İlişkilidir

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ABSTRACT

Objective: It is known that *ATM* heterozygosity is associated with increased risk of cancer, especially for breast cancer. This report reveals the characteristics of the patients with solid tumors other than breast cancer, associated with Germ-line *ATM* heterozygosity.
Methods: Patients with germline ATM heterozygous mutation, admitted to the Department of Medical Genetics between January 2020 to 2023 were evaluated retrospectively. Patients with a diagnosis of solid tumors other than breast cancer, being followed up for at least 6 months were included in the study. Data of the patients were examinated using the SPSS software version 23.
Results: Median aged at cancer diagnosis of 36 patients were 52.5 (23-65) years. The median follow-up period was 29.5 (11-283) months. Colorectal cancer was the most common diagnosis (30.6%). At follow-up, second primary solid malignancy was diagnosed in 27.8% (10 patients) of the patients. The median time for development of second primary malignancy were 9 (3-156) months. Most common diagnosis of these 10 patients were breast cancer (80%-8 patients).
Conclusion: Development of various solid tumors other than breast cancer related to Germ-line *ATM* heterozygosity highlights the importance of *ATM* linked to cancer susceptibility.

Keywords: Germ-line *ATM* heterozygosity, solid malignancy, other than breast cancer

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ÖZET

Amaç: ATM heterozigotluğunun özellikle meme kanseri olmak üzere kanser riskinin artmasıyla ilişkili olduğu bilinmektedir. Bu rapor, Germline ATM heterozigotluğu ile ilişkili, meme kanseri dışında solid tümörleri olan hastaların özelliklerini ortaya koymaktadır.
Yöntem: Tıbbi Genetik Anabilim Dalı'na Ocak 2020- Ocak 2023 tarihleri arasında başvuran germline ATM heterozigot mutasyonu olan hastalar retrospektif olarak değerlendirildi. Çalışmaya meme kanseri dışında solid tümör tanısı olan ve en az 6 aydır takip edilen hastalar dahil edildi. Hastaların verileri SPSS 23 programı kullanılarak analiz edildi.
Bulgular: 36 hastanın, kanser tanısı anında median yaşı 52,5 (23-65) idi. Median takip süresi 29,5 (11-283) aydı. Kolorektal kanser en sık görülen tanıydı (%30,6). Takipte, ikinci primer solid tümör tanısı, hastaların %27,8'inde (10 hasta) konuldu. İkinci primer malignitenin gelişmesi için median süre 9 (3-156) aydı. Bu 10 hastanın en sık tanısı meme kanseriydi (%80-8 hasta).
Sonuç: Germline ATM heterozigotluğuna bağlı olarak meme kanseri dışında çeşitli solid tümörlerin gelişmesi, ATM'nin kanser duyarlılığı ile bağlantılı önemini vurgulamaktadır.

Anahtar Sözcükler: Germline ATM heterozigotluğu, solid malignite, meme kanseri dışı

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INTRODUCTION

Homologous DNA repair and checkpoint arrest are two important landmarks of stable genome during DNA replication (1). Ataxia telangiectasia mutated (*ATM*) gene, located on chromosome 11q 22–23 plays a crucial role in the repair of DNA double-strand breaks (2). ATM gene mutations, occurs in each functional domain of the gene, are known to be characterized as the autosomal recessive ataxia telangiectasia syndrome (3, 4). As germ-line mutations of the ATM gene may manifest with many phenotypic characteristics, such as neurodegeneration, cerebellar ataxia, hypogammaglobulinemia, immunodeficiency, gonadal dysgenesis, or radiosensitivity, A-T syndrome is also associated with cancer such as breast, lymphoid, gastric, central nervous system, skin, and other cancers (1, 5).

In the literature, it is known that being heterozygous for *ATM* gene is associated with 2- to 3-fold risk of cancer, and also 5- to 9-fold risk of breast cancer in women (6, 7). Dombernbowsky et al showed that approximately 20% of the patients with ATM mutation developed cancer during follow-up (8). ATM mutation was found to be associated with an increased incidence of melanoma, prostate cancer, and oropharyngeal cancer in this study (8). Also, it was found to be associated with thyroid or endocrine cancers (8). In other studies, identified functional variants were demonstrated and they were associated with lung cancer or thyroid cancer risk (9, 10). Grant et al, Roberts et al and Rustgi et al showed that inherited *ATM* mutations may play role in familial pancreatic ductal adenocarcinoma (11-13). Furthermore, ATM gene mutations are demonstrated to be the mechanisms of lymphocyte infiltration in breast and ovarian cancer (14).

Beyond playing an role as a biomarker, *ATM* status may give information for prognosis and may be crucial for novel targeted therapies (15, 16). Pitter et al analyzed 357 advanced cancer patients with a somatic or germline *ATM* mutation, who received radiotherapy (15). They emphasized that somatic *ATM* inactivation is related to reduced tumor volume following radiotherapy. Also, loss of ATM protein expression in colorectal cancer was found be associated with worse prognosis (17). So, getting information about ATM status may enlighten the clinicians for follow-up and treatment.

This report aimed to analyze the patients with solid tumors other than breast cancer which are associated with Germ-line *ATM* heterozygosity.

METHODS

Study population and data collection

Patients with germline ATM heterozygous mutation, admitted to the Department of Medical Genetics between January 2020 to 2023 were examined retrospectively. Patients with a diagnosis of solid malignancy other than breast cancer, being followed up for at least 6 months were included in the study.

Cancer patients with pathogenic variant (PV), likely pathogenic variant (LP), or variants of uncertain significance (VUS) of ATM gene were evaluated. Patients younger than 18 years of age, diagnosed with carcinoma in situ, or with breast cancer were excluded from the study. Thirty-six patients meeting these criterias were included in the study. The data of the patients was taken from hospital data system and evaluated retrospectively.

Mutation classification

Variants of ATM mutation have been reported in 5 classes (PV, LP, VUS, Likely Benign, and Benign) in accordance with international standards (18). PV, LP and VUS variants of these variants were included in the study.

The study protocol was approved by the ethics committee of Gazi University Faculty of Medicine (2023-397).

Statistical analysis

Data of the patients were examinated retrospectively using the SPSS software version 23. The variables were analyzed with visual and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk test) to find out the normal distribution. While the quantitative variables such as the age of the patients was stated using medians, the categorical data such as gender, presence of family history and types of the cancer were shown in numbers and percentages.

RESULTS

A total of 36 patients, met the criteria of the study were evaluated in the study. Median aged at cancer diagnosis of the patients were 52.5 (23-65) years. Most of the patients were female (77.8%) and median follow-up period was 29.5 (11-283) months. Baseline characteristics of the patients were demonstrated in Table 1. While pathogenic variant of ATM gene was seen in 19.4% (7 patients), likely pathogenic variant was seen in 5.6% (2 patients) and variants of uncertain significance of were demonstrated in 75% (27 patients).

Twenty-seven patients (75%) had the family history of cancer. Colorectal cancer was the most common diagnosis (30.6%), others were as follows; ovarian, thyroid, pancreatic, endometrial, prostat cancer, intrahepatic cholangiocarcinoma. Two patients were diagnosed with both rectum and endometrial cancer at the time of diagnosis. Fifty percent of 8 male patients were diagnosed with colorectal carcinoma and they were being followed-up.

At the follow-up period, 27.8% of the patients (10 patients) were diagnosed with second primary solid malignancy. All of these patients were female and the median time for development of second primary malignancy were 9 (3-156) months. Most common diagnosis of these 10 patients were breast cancer (80%-8 patients). Endometrial and colon carcinoma were developed in other 2 patients.

During follow-up, 2 of 36 patients died due to causes secondary to cancer. The follow up of the other patients is still continuing by our clinic.

Table 1. Baseline characteristics of the patient population

Parameters		Results
Age (years)		57.5 (31-68)
Gender (n-%)	Female	28 (77.8)
	Male	8 (22.2)
Follow up period (months)		29.5 (11-283)
Presence of cancer in family history (n-%)		27 (75)
Diagnosis (n-%)	*Colorectal cancer*	11 (30.6)
	Ovarian cancer	8 (22.2)
	Thyroid cancer	5 (13.9)
	Pancreatic cancer	4 (11.1)
	Endometrial cancer	3 (8.3)
	Prostate cancer	2 (5.6)
	*Others**	3 (8.3)

Others*: *Intrahepatic cholangiocarcinoma: 1 (2.8%),*
Rectum and endometrial cancer: 2 (5.6%)

DISCUSSION

This original article aimed to reveal the patients with solid tumors other than breast cancer that are associated with Germ-line *ATM* heterozygosity. Nowadays, ATM inhibition is attractive issue as a cancer therapy in combination with radiotherapy or some chemotherapeutics.

As data have showed that knockdown of ATM is associated radiosensitization, in some studies it is suggested that ATM alterations in tumor cells may sensitize to platinum drugs (19-22). Zhang et al showed in their study that ATM inhibition induces innate immune response in pancreatic cancer. They emphasized that this phenomenon is further enhanced by radiation and results in increased sensitivity to anti–PD-L1 therapy (23). Also, Yi et al showed in their study of bladder cancer patients that ATM may have impact on the immune checkpoint inhibitors by acting on the tumor immune microenvironment (24). These findings are encouraging for further ATM targeted therapies (25). In this report, we demonstrated that 36 patients with Germ-line *ATM* heterozygosity were diagnosed with solid tumors other than breast cancer, so getting information about ATM heterozygosity may lead to decreased mortality and morbidity.

The ATM gene product is one of large proteins that plays an important role in the cell cycle and also DNA damage. Heterozygosity for this gene is associated with an increased risk of malignancies, mostly female breast cancer (26). In our study, we analyzed the cancer patients other than breast cancer to notice ATM-associated other malignancies. ATM is a well known tumour suppressor that is usually mutated in many solid malignancy such as lung, colorectal, breast and haematopoietic cancers (27-31). In our study, colorectal cancer was the most common diagnosis. Other ATM related solid malignancies were ovarian, thyroid, pancreatic, endometrial, prostat cancer, intrahepatic cholangiocarcinoma in the study. Two patients with ATM mutation were diagnosed with both rectum and endometrial cancer at the time of diagnosis. The number of patients diagnosed with prostate cancer was very small in our study due to small size of our study but in the literature, ATM heterozygosity has been associated with excess risk of prostate cancer (32). Furthermore, Kimura et al emphasized in their study that ATM is independent prognostic factor of the short duration of response to hormonal therapy in advanced prostat cancer (33).

Many mutations in the ATM gene are associated with a moderately increased risk of breast and other cancers (34). Klavanian et al. evaluated a total of 114 patients, positive for a pathogenic/likely pathogenic *ATM* mutation. This study described the association of pancreatic cancer and pathogenic *ATM* mutations. In this study, 19.3% of the patients had a family history of pancreatic cancer in a close relative. In our report, 27 patients (75%) had the family history of cancer. Furthermore, in their study it was seen that the mean age of diagnosis was found be younger than the average age. Our study population was heterogenous so that median aged at cancer diagnosis of the patients were 52.5 (23-65) years.

Another remarkable issue in our study was the development of second primary cancer in 27.8% of the patients during follow-up. The most common diagnosis was breast cancer in these patients. In addition, a second primary cancer developed in these patients in a short median time of 9 months. It should be highlighten that the frequency of breast cancer may be high in the follow-up of patients with ATM mutations.

The most common diagnosis of our study population was colorectal cancer and the most common second primary diagnosis was breast cancer that developed in the follow-up. These are important findings our report.

In conclusion, wide range of solid tumors other than breast cancer may be associated with *ATM* heterozygosity. Genetic counseling and population screening are important for such a wide range of malignancy-related gene. Due to playing an role as a biomarker and giving information for prognosis, getting information about ATM status may give direction to the clinicians for follow-up and treatment.

Our study population was heterogeneous and had small size. There were deficient data due to its retrospective design. Also, the majority of our study population was patients with VUS variants. Further evaluation with larger study population may reveal important information.

Conflict of interest

No conflict of interest was declared by the authors.

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