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Is There A Genetic Predisposition for Transitional Cell Carcinoma of the Bladder at a Young Age?

Genç Yaşta Görülen Transizyonel Hücreli Mesane Karsinomunda Genetik Yatkınlık Var Mıdır?

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ÖZET

Amaç: Bu çalışmada genç yaşta görülen mesane transizyonel hücreli karsinomlu (TCC) hastalarda genetik yatkınlığın olup olmadığı belirlenmeye çalışıldı.

Gereç ve Yöntemler: Ocak 2010-Ocak 2021 tarihleri arasında transüretral mesane tümörü rezeksiyonu (TUR-MT) yapılan total 652 hastanın verileri incelendi. Verilerine ulaşılabilen 40 yaş altında, sigara kullanmayan ve üriner sistem TCC açısından mesleki predispozan faktörü olmayan 7 hasta çalışmaya dahil edildi. Hastaların yaşı, vücut kitle indeksi (VKİ), cinsiyeti, meslekleri ve beş yıllık takipleri geriye dönük kayıt edildi. Hastaların kan örneklerinden toplam 403 kanserle ilgili gen çalışıldı. Genetik mutasyonları belirlemek için Clinical Exom Sequencing testi kullanıldı.

Bulgular: Hastaların 6'sı erkek 1'i kadındı. Ortalama yaş ve VKİ sırasıyla 31,42 ± 2,12 (22-39) yıl ve 21,72 ± 33,14 (22-27,7) kg/m2 idi. Hastaların hiçbirinin birinci derece akrabalarında üriner sistem TCC özgeçmişi yoktu. Tüm hastaların içinde sadece 1 hastada kesme noktası küme bölgesi geninde ekson 1-17 delesyonu vardı.

Sonuç: Genç yaşta görülen mesane TCC'de genetik predispozan faktörler henüz net ortaya konulamamıştır. Çalışmamız sınırlı sayıda hastayı içermekle birlikte, sonuçlarımıza göre mesane kanseri aile hikayesi olmayan genç yaşta görülen mesane TCC'li hastalarda genetik predispozan saptanmamıştır. Net ilişkinin değerlendirilebilmesi için daha büyük hasta sayılı prospektif randomize kontrollü çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Mesane Kanseri, gen değişimleri, transizyonel hücreli karsinom, genç hasta.

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ABSTRACT

Objective: The aim of this study is to determine whether there is a genetic predisposition in young patients with transitional cell carcinoma (TCC) of the bladder.

Material And Methods: Data were collected from a total of 652 patients who underwent transurethral resection of bladder tumor (TUR-BT) between January 2010 and January 2021. Seven patients under the age of 40, non-smokers, and without occupational predisposing factors to urinary tract TCC were included in the study. Age, body mass index (BMI), sex, occupation, and five-year follow-up were collected retrospectively. A total of 403 cancer-related genes were analyzed from the patients' blood samples. The Clinical Exome Sequencing test was used to identify genetic mutations.

Results: Six of the patients were male and one patient was female. The mean age and BMI were 31.42 ± 2.12 (22-39) years and 21.72 ± 33.14 (22-27.7) kg/m2, respectively. None of the patients had a first-degree relative with urinary tract TCC. Of all the patients, only one patient had a deletion of exons 1 to 17 in the breakpoint cluster region gene.

Conclusion: Genetic predisposing factors in young bladder TCC have not been clearly identified. Although our study included a limited number of patients, our results showed no genetic predisposition in young patients with bladder TCC without family history of bladder cancer. To evaluate the exact relationship, prospective randomised controlled trials with larger numbers of patients are needed.

Keywords: Bladder cancer, gene alterations, transitional cell carcinoma, young patient.

INTRODUCTION

Bladder cancer (BCa) is a common malignancy and is four times more common in men than in women. Mortality in men is also four times higher than in women (1). BCa is predominantly a disease of older adults, and in the United States, 90% of diagnoses are made in people over 55 years of age and 80% in people over 65 years of age. The average age at diagnosis of BCa in the US is 73 years (2). Transitional (urothelial) cell carcinoma (TCC) accounts for 90% of BCa cases worldwide and is particularly common in developed countries. Tobacco smoking is by far the largest risk factor for BCa, accounting for approximately 50-65% of new cases each year (3). The second largest preventable risk factor for BCa is occupational exposure to chemicals (4). A linear relationship has been shown between BMI and the risk of developing BCa. A meta-analysis study showed that pre-obesity and obesity increased the risk of BCa by 7% and 10%, respectively (4).

A large number of genetic loci have been found to be moderately associated with an increased susceptibility to BCa by means of genome-wide association studies (5). Several oncogenes and tumour-suppressing genes have been studied in BCa. There are ongoing clinical trials targeting the HER2/neu and EGFR pathways. The UroVysion BCa test is based on FISH for the detection of genetic alterations in this disease. Studies are underway to answer questions about the genetic aetiology of BCa (6).

Bladder TCC is diagnosed between 1.0% and 2.4% in patients <40 years (7). Studies have shown that younger patients with urinary tract TCCs are more likely to have positive outcomes than older patients (8). Although bladder TCC in younger patients lack some of the genetic alterations often observed in older patients, genetic factors are likely to play an important role in the early onset of TCCs in younger patients (9, 10).

Main Points:

- There is a lack of research regarding hereditary transition of transitional cell carcinoma of the bladder in the literature
- A total of seven patients were analyzed. Only one male patient has exon 1-17 deletion of the breakpoint cluster region (BCR) gene.
- Our finding support there is no hereditary transition of transitional cell carcinoma of the bladder.

This study aimed to show the effect of genetic factors in young patients diagnosed with bladder TCC.

MATERIAL AND METHODS

After approval of the local institutional review board (Antalya Education and Research Hospital Human Ethics Committee, no: 19/18, date: 10/12/2020), Patients under 40 years of age who underwent transurethral resection of bladder tumours (TUR-BT) at the Urology Department of Antalya Training and Research Hospital between January 2010 and January 2021 and were diagnosed with TCC were studied. Patients with risk factors such as family history, smoking, occupational exposure (poly-aromatic hydrocarbons), obesity, chronic bladder infection (except chronic human papillomavirus infection) and sedentary lifestyle (lifestyle with no or irregular physical activity) were excluded. Only patients who were followed up for five years were analyzed.

We used 1973 WHO pathology staging and 2004 WHO grading system to BCa classification of the patients (11).

Genetical Analysis

Blood samples were collected from all patients and sent to the laboratory for analysis. Laboratory analyzes include amplification of disease-associated gene region(s) by polymerase chain reaction (PCR) and sequencing of this region using next-generation sequencing technology. For this purpose, Clinical Exome Solution kit (Sophia Genetics) was used. The sequencing reaction was performed using the Illumina NextSeq® system and compatible reagent kits. Raw data were analyzed via the Sophia DDM® data analysis platform. Sequence alignment and variant calling were performed by Pepper®, a proprietary base algorithm from Sophia Genetics, based on the hg19 human genome reference. Variant annotation was performed with Sophia Genetics› MOKA® software. Moreover, for each variant, data such as the effect of the variant on the protein sequence (missense, stop gain etc), the incidence in various populations (1000G, ESP, ExAC, gnomAD), prediction algorithms (SIFT, PolyPhen) and the destructive effect of the variant were added. A total of 403 cancer related genes were studied for each patients (Table 1).

Table 1. Demographic data of the patients

Patients	Age	BMI	Gender	Co-morbidity
1	36	27.7	♂	No
2	39	26.2	♂	No
3	33	23.7	♂	No
4	29	25.2	♂	No
5	33	22	♂	No
6	22	24.5	♀	No
7	28	22.6	♂	No
	Mean: 31.42	Mean: 21.72		

BMI: Body Mass Index

RESULTS

We found 652 patients who underwent TUR-BT in our database. After exclusions, we found that seven patients were eligible for the study. Six of the patients were male and one was female. Six of the patients were office workers and one was a student.

The mean age was 31.42 ± 2.12 (22-39) years, and the mean BMI was 21.72 ± 33.14 (22-27.7) kg/m^2. Demographic and characteristic features of the patients were recorded. The risk factors of the patients for BCa were determined. Pathological examination of all patients resulted in TCC. Demographic characteristics of the patients are given in Table 1.

All pathological examinations yielded a result that did not require cystectomy. The ratio to all patients was 1.07%. Initial pathological diagnosis and other features are given in Table 2.

Hereditary cancer gene panels were examined in 7 patients included in our study. One male patient has exon 1-17 deletion of the breakpoint cluster region (BCR) gene. Pathological examination of the patient with hereditary transmission resulted in PUNLMP Grade 2. No recurrence was observed in this patient. The detected hereditary parameters are given in Table 3.

Table 2. The first symptom, peroperative and postoperative findings of the patients.

Patients	First Symptom	Tumor Number	Size	Pathological Diagnosis	Relapse
1	Painless hematuria	1	< 3 cm	PUNLMP G2	No
2	Painless hematuria	2	< 3 cm	PUNLMP G2	Chronic cystitis
3	Painless hematuria	1	< 3 cm	PUNLMP G2	No
4	Painless hematuria	1	< 3 cm	PUNLMP G3	No
5	Painless hematuria	3	>3 cm	HG-PUC G2	pTa
6	Painless hematuria	1	< 3 cm	PUNLMP G3	No
7	Painless hematuria	1	< 3 cm	PUNLMP G3	No

G1, grade 1(well differentiated) ; G2 , grade 2: moderately differentiated ; G3, grade 3 (poorly differentiated); HG-PUC, high-grade papillary urothelial carcinoma; PUNLMP, papillary urothelial neoplasm of low malignant potential.

Table 3. Status of hereditary parameters of the patients after genetical analysis.

Patients	1	2	3	4	5	6	7
Gene name	-	-	CASP8	-	-	-	-
Chromosome-position	-	-	2: 202137619	-	-	-	-
Pattern of inheritance	-	-	AR AD SMu	-	-	-	-
hgvs.c hgvs.p	-	-	c.728-2A>G p.(?)	-	-	-	-
RS ID / NM	-	-	rs755309536 NM_001080125.1	-	-	-	-
Variation type	-	-	splice_acceptor_-2 pathogenic heterozygous	-	-	-	-
Clinical manifestation	-	-	Hepatocellular carcinoma, somatic {Lung cancer, protection against} {Breast cancer, protection against} ?Autoimmune lymphoproliferative syndrome, type IIB	-	-	-	-

AD, autosomal dominant; AR,autosomal recessive; NM_001080125.1, the RefSeq number of CASP8 gene; rs, reference SNP; SMu, somatic mutation; SNP, single nucleotide polimorphism

DISCUSSION

Hereditary transmission in young patients with bladder TCC has not been clearly demonstrated in the literature. Although there is no clear oncogenesis of TCC in young patients, many environmental and genetic factors may contribute to the etiology of the disease. Smoking is known to be a major risk factor for BCa in older patients, and the risk increases with the duration of smoking. One study showed that patients younger than 30 years with a history of smoking had an increased risk of invasive BCa (12). Occupational exposure is an another known risk factor for BCa. Although bladder TCCs in younger patients lack some of the genetic alterations often observed in older patients, genetic factors are likely to play an important role in the early onset of bladder TCCs (9, 10). Today, the existence of a genetic predisposition for the emergence of superficial and slowly progressing bladder tumors has been considered. Although BCa is not typically considered to have an inherited pattern, some cancer symptoms highlight the risk of bladder cancer. Riegert-Johnson et al. demonstrated Cowden Syndrome, an inherited defect in the tumor suppressor gene PTEN, which predisposes to a wide variety of neoplasms, including transitional and squamous cell urothelial cancer. In their study, the age of the patients was over 40 years, and no classification was made for etiological risks (13) . In another study, Van der et al. systematically questioned carriers and first-degree relatives of 95 families for the occurrence of carcinoma. The cumulative risk of cancer (CR70) occurring before age 70 years was compared with the CR70 of the general Dutch population. They performed microsatellite instability testing and/or immunohistochemistry (IHC) for mismatch repair proteins on bladder tumor tissue. In addition, they showed that patients with Lynch syndrome carrying the MSH2 mutation are at high risk for urinary tract cancer, including bladder cancer, and therefore they reported that surveillance program should be considered in these cases (14).

In our study, patients younger than 40 years of age had no family history at the time of diagnosis. There was no significant etiological risk of bladder cancer. Only one patient had exon 1-17 deletion of the BCR gene. The patient had a good prognosis, with absence of recurrence at 5-year follow-up. This result was 0.15% of the 652 patients screened**.** There was no study in the literature that included a young patient with hereditary transition. Therefore, we were unable to make any comparisons.

BCa has better prognosis in young patients (12, 15, 16) . Elderly patients had a higher incidence of invasive disease, which was reported by some studies to occur due to mutations in chromosomes 8, 9, 11, and 17, and often presented in elderly patients with a longer time to carcinogenesis (17, 18). Fine et al reported that all of the < 20 years patients with bladder TCCs had no recurrence within a mean follow-up of 4.5 years (19). However, another study reported that there is no difference on prognosis between young and elder patients with superficial bladder TCC. The population of the study has a tendency of developing TCCs, and, in terms of grade and stage, they have been found similar to older patients rather than the younger ones. It has been reported that TCC has an excellent prognosis in younger patients, especially in patients younger than 20 years, but with a decrease in favorable prognosis with increasing age (20).

Carcinogenesis of BCa is a complex interaction between genetic and environmental factors. The urinary bladder is significantly exposed to many mutagenic environmental substances as they are excreted in the urine (21). In our study, all patients had no etiological risk factors, except for dietary factors, analgesic use, and environmental factors. All patients had a lower grade tumor that did not require radical cystectomy. All patients were alive after 5 years of follow-up. This has been interpreted as the presence of mutations with a more aggressive course resulting from long-term exposure to etiological risk factors that are more important than the genetic transmission of bladder cancers.

There are some limitations in our study. First, the number of the patient is the most important limitation of the study. Second, chronic bladder infection of human papilloma virus cases were not excluded. Third, in our study occupational exposure of the patients were questioned but other environmental exposure of chemical materials were not excluded.

CONCLUSION

Although the number of patients in this study is limited, we believe that this study will make a scientific contribution to the literature. Prospective randomized controlled trials with larger numbers of patients are needed to investigate whether genetic factors affect patients who were diagnosed with bladder TCC under aged 40 years old. In addition, unexplained environmental factors may also have an effect on the development of bladder TCC at a young age.

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