Research Article / *Araştırma Makalesi*

Ege Journal of Medicine / *Ege Tıp Dergisi* 2024; 63 (3): 390-395

A novel challenge in elderly people with hemophilia: Cancer

Yaşlanan hemofilik bireylerde yeni bir problem: Kanser

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ABSTRACT

Aim: Our study is aim to evaluate the prevalence of cancer in patient with hemophilia (PWH) and describe the demographic and clinical features of hemophilia patients with cancer.

Materials and Methods: The data of PWH who were followed our center between 2010-2020 were analyzed retrospectively. Among them, patients who were diagnosed with any type of cancer were evaluated. Clinical characteristics such as hemophilia type (A and B) and severity (severe, moderate and mild), inhibitor status, factor replacement strategy (prophylaxis or on-demand) of patients with and without cancer were recorded.

Results: Totally, 447 patients with hemophilia A (n =355) and B (n =92) were included and median age was 40 years (range, 19-86). Fifteen (3.4%) patients had a history of cancer. There is no significant difference between patients with and without cancer about hemophilia type, hemophilia severity, factor replacement therapy and inhibitor status. Hemophilia patients with cancer were older than without cancer. Colorectal carcinoma (n=3) and lung cancer (n=3) were most common types of cancer among patients. Two patients infected with hepatitis C had virus related cancer, hepatocellular carcinoma. All the patients treated with adequate treatment modality for their malignancies and hemostasis was effectively established during the chemotherapy and/or radiotherapy and/or surgery.

Conclusion: Nowadays cancer is expected to be commonly seen in elderly PWH. The adequate treatment strategies like as general population and personalized comprehensive hemophilia care with factor replacement should be provided for them.

Keywords: Hemophilia, cancer, prevalence, comorbidity.

ÖZ

Amaç: *Çalışmamızda hemofilik bireylerde kanser prevalansının değerlendirilmesi ve kanserli hemofili hastalarının demografik ve klinik özelliklerinin tanımlanması amaçlanmıştır.*

Gereç ve Yöntem: *Merkezimizde 2010-2020 yılları arasında takip edilen hemofilik bireylerin verileri geriye dönük olarak analiz edildi. Bunlar arasında herhangi bir tipte kanser tanısı konulan hastalar ayrıca değerlendirildi. Kanser tanısı olan ve olmayan tüm hemofilik bireylerin hemofili tipi (A ve B) ve hastalık şiddeti (ciddi, orta ve hafif), inhibitör durumu ve faktör tedavisi stratejisi (profilaksi veya kanadıkça) gibi klinik özellikleri kaydedildi.*

Bulgular: *Ortanca yaşı 40 (aralık, 19-86) olan toplamda 447 hasta (Hemofili A =355 ve B =92) çalışmaya dahil edildi. On beş (%3,4) hastanın en az bir kanser tanısı vardı. Kanser tanısı olan ve olmayan hastalar hemofili tipi, hemofili şiddeti, faktör replasman tedavisi ve inhibitör durumu açısından karşılaştırıldığında hastalar arasında anlamlı bir fark yoktu.*

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Application date: 17.01.2024 Accepted: 06.03.2024

Kanser tanısı olan hemofili hastaları kanser olmayanlara göre daha yaşlıydı. Hastalarda en sık görülen kanser türleri kolorektal karsinom (n=3) ve akciğer kanseri (n=3) idi. Hepatit C ile enfekte olan iki hastada virüsle ilişkili kanser, hepatoselüler karsinom vardı. Tüm hastalar kanserleri için yeterli ve uygun olan tedavi yöntemleriyle tedavi edildi. Hastaların tamamında kemoterapi ve/veya radyoterapi ve/veya cerrahi sırasında hemostaz etkin bir şekilde sağlandı.

Sonuç: *Günümüzde, yaşlı hemofilik bireylerde kanser tanısının daha sık görülmesi beklenmektedir. Bu hastalara kişiselleştirilmiş kapsamlı hemofili bakımı ve faktör replasmanları ile birlikte genel popülasyona benzer şekilde uygun kanser tedavilerinin verilmesi sağlanmalıdır.*

Anahtar Sözcükler: *Hemofili, kanser, prevalans, komorbidite.*

INTRODUCTION

There has been significant improvement in life expectancy in patient with hemophilia (PWH) over the past few decades as a result of increased safety and accessibility of recombinant and plasma-derived coagulation factor products, highly effective antiviral medications, establishment of comprehensive hemophilia care centers and specialized treatment strategy (1, 2). Today, longevity is becoming the most important issue in PWH because of the age-related chronic diseases in addition to the comorbidities of hemophilia (arthropathy, complications of viral infections). Most common age-related comorbidities are cardiovascular diseases (such as coronary artery and cerebrovascular atherothrombotic disease), arrhythmia, heart failure, diabetes, chronic kidney disease, degenerative arthritis, dementia and cancer (3). Besides, there is still limited data about the prevalence and management of age-related comorbidities in PWH. The subject of malignancies in hemophilia is especially noteworthy due to the hypothesis of protective effect of impairment of coagulation factors from the progression of cancer (4). Activated coagulation factors can activate endothelial cells and/or platelets, leading to the release of many mediators including growth factors and proliferation of tumor cells. The tumor cell can evade the immune system because of the tumor cell-platelet-fibrin complex that is created by this mechanism. Additionally, the complex sticks to the endothelium in the vascular wall and leads to tumor-associated angiogenesis (5). Based on in vitro research, factor VIII deficiency and reduced thrombin activity inhibit angiogenesis and prevent metastases of solid tumors (6). However, currently there is no clinical evidence endorsing this hypothesis.

Between early 1970s and mid-1980s, the substitution of plasma-derived factors resulted in a significant increase in the spread of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infections (7). In this regard, virus-associated malignancies such as non-Hodgkin's lymphomas, Kaposi sarcoma and hepatocellular carcinomas (HCC) have been seen more common in PWH (8, 9). Either HCV infection alone and concomitant HCV and HIV infections increased risk of end-stage liver disease and HCC (10). After improvement of the effective viricidal techniques and development recombinant factor concentrates, the mortality rates because of virus-associated malignancies have been decreased significantly (11). Nevertheless, epidemiologic data about non-virus-associated malignancies in PWH is very limited and controversial. Therefore, we aim to determine the prevalence of cancer in patients with hemophilia who were followed in our center. Our secondary objective is to define our experience of cancer management in PWH.

MATERIAL and METHODS

Study Design

This was an observational retrospective study conducted with hemophilia patients treated at *European* Hemophilia Comprehensive *Care* Centre (EHCCC) certificated Ege Adults Hemophilia and Thrombosis Center. A total of 447 patients with a previous diagnosis of hemophilia A (*n* =355) and B (*n* =92) aged higher than 18 years were included. Clinical and socio-demographic information was collected from the hospital's electronic databases included hemophilia type and severity [hemophilia is classified into severe (<0.01 IU/ml FVIII or FIX), moderate (0.01–0.05 IU/ml FVIII or FIX) or mild (0.05–0.40 IU/ml FVIII or FIX) hemophilia], inhibitor status, viral infections [hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV)]. Type of cancer, the date of diagnosis and management

(chemotherapy, radiotherapy, or invasive surgery), hemophilia treatment strategy (prophylaxis and on-demand, both at diagnosis and during cancer management), bleeding complications, cancer progression or recurrence, and outcome (alive or dead) were documented for each case.

Statistical Analysis

Statistical data analysis was carried out using SPSS version 16.0 (2007, SPSS for Windows, SPSS Inc., Chicago, IL, USA) package. Exploratory analysis was carried out to describe the study population where categorical variables were summarized using frequency tables and continuous variables were summarized using measures of central tendency and dispersion such as mean ± standard deviation (SD) and median (range). Qualitative or categorical variables were described as frequencies and proportions. Chi-square test and Fisher's exact test were used to determine association between categorical variables. Mann–Whitney U test was used to analyze quantitative data with skewed distribution. A level of p-value < 0.05 was considered statistically significant.

Ethical Considerations

During the planning of the study, necessary permissions were obtained from a Ege University Department of Hematology where the study was carried out. The study was approved by Ege University, Clinical Research Ethics Committee (Date: 08.07.2021, Decision No: 21-7T/47). Written and verbal consent of the individuals included in the study was taken.

RESULTS

A total of 447 PWH (355 with hemophilia A and 92 with hemophilia B) were evaluated and the median age 40 (range 19-86) years. Severe hemophilia was seen in 51.9% (n=232) patients and moderate and mild hemophilia was seen in 29.3% (n=131) and %18.3 (n=32) patients, respectively. Most of the patients (64.7%, n=289) were on prophylactic factor replacement therapy. Inhibitor positivity was detected in 4.3% (n=19) patients. Among 447 patients, 15 (3.4%) PWH had a history of cancer. Comparison of the characteristics of patients with and without cancer were summarized in Table-1. There was no difference of hemophilia type, severity and factor replacement strategy between two groups. Nevertheless, hemophilia patients with cancer were significantly older than without cancer group [63 (range, 44-72) vs 40 (range, 19-86) years, respectively and p=0.002]. Inhibitor status was negative in all PWH with cancer group however the prevalence of inhibitor was 4.4% (19/432) in PWH without cancer.

Table-1. Characteristics of patients.

Variables	Total (n= 447, 100%)	Patients without cancer (n= 432, 96.6%)	Patients with cancer (n= 15, 3.4%)	P value
Age in years, median (range)	40 (19-86)	40 (19-86)	63 (44-72)	**0.002***
Hemophilia type				
Hemophilia A	355 (79.4)	343 (79.3)	12 (80)	0.62**
Hemophilia B	92 (20.6)	89 (20.6)	3 (20)	
Disease severity, n (%)				
Severe	232 (51.9)	223 (51.6)	9 (60)	0.77**
Moderate	131 (29.3)	128 (29.6)	3 (20)	
Mild	82 (18.3)	79 (18.3)	3 (20)	
Factor VIII treatment, n (%)				
Prophylactic treatment	289 (64.7)	281 (65)	8 (53.3)	0.48**
On-demand treatment	155 (34.7)	148 (34.3)	7 (46.7)	
Presence of inhibitor, n (%)				
Yes	19 (4.3)	19 (4.4)	0	0.51**
No	427 (95.5)	412 (95.4)	15 (100)	

*Mann–Whitney U test; **Chi-square test

Table-2. Clinical features and cancer types of hemophilia patients with cancer.

Case No	Age, years	Hemophilia type, severity	Factor therapy	Comorbidity	Viral serology	Cancer type	Treatment	Outcomes
1	63	B, Mild	On- demand	DM	Negative	Colorectal ca	Surgery CT	Alive
2	50	B, Mild	On- demand	None	Negative	Nasopharynx ca	Surgery CT	Alive
3	52	A, Severe	On- demand	None	Negative	Acute myeloid leukemia	CT	Alive
4	64	A, Severe	Prophylactic	Cirrhosis	HCV	HCC	None	Dead
5	51	A, Mild	On- demand	None	Negative	Colorectal ca	Surgery CT	Alive
6	67	A, Severe	Prophylactic	DM, Hypertension	Negative	Gastric ca	Surgery	Alive
7	67	A, Mild	On- demand	None	Negative	Lung ca brain metastasis	Surgery	Dead
8	71	A, Moderate	Prophylactic	DM, Hypertension	HCV	HCC	None	Alive
9	63	A, Severe	Prophylactic	None	Negative	Lung ca	CT/ RT	Alive
10	72	B, Moderate	On- demand	Hypertension	Negative	Prostate ca	Surgery	Alive
11	44	A, Severe	Prophylactic	None	Negative	Pancreas ca	CT	Alive
12	47	A, Severe	Prophylactic	None	HCV	Nasopharynx ca	CT/ RT	Alive
13	68	A, Mild	On- demand	None	Negative	Colorectal ca	Surgery CT/ RT	Alive
14	48	A, Severe	Prophylactic	None	HCV	Bone tumor	CT	Alive
15	60	A, Severe	On- demand	None	Negative	Lung ca	CT	Dead

CA, cancer; HA, hemophilia A; HB, hemophilia B; HCV, hepatitis C; CT, Chemotherapy; RT, Radiotherapy; DM, diabetes mellitus; HCC, hepatocellular carcinoma

Table-2 summarizes the characteristics of fifteen hemophilia patients with cancer. In patients with cancer group 12 patients were hemophilia and 3 were hemophilia B. When eight patients of 15 had severe disease, moderate and mild hemophilia were seen in 2 and 5 patients, respectively. Other than one patient, all patients with severe hemophilia were treated with prophylactic factor replacement 3 times in a week. In total, 7 patients with cancer were treated with prophylactic factor replacement therapy. Lung (n=3) and colorectal cancers (n=3) are the most common types of malignancy. However, four patients were HCV infected, only 2 patients had virus related cancer and both of them had end stage liver disease and HCC. The patients infected with HCV were on antiviral therapy. Nasopharynx carcinoma was seen in 2 patients and acute myeloid leukemia (AML), bone tumor, gastric, prostate and pancreas cancer were detected in one patient each. Diabetes and hypertension are commonly seen comorbidities in PWH with cancer group and they were seen in 4 patients each.

All patients received the same recommended treatment modality as patients who do not have coagulation disorder for their cancer**.** Other than 2 patients with HCC, all patients treated with chemotherapy and/or radiotherapy and/or surgery. The patient (number #3) with AML were diagnosed when he was 7 years old. The hemostasis was successfully controlled even he had severe thrombocytopenia during the induction and consolidation chemotherapy. Major surgery was performed in 7 patients and hemostasis was effectively established in every invasive procedure. Twenty percent of patients with cancer (n=3) were dead. One of them (number #4) had HCC and he died from liver failure. One patient (number #7) had cranial surgery for the resection of brain mass and diagnosed with metastasis of non-small cell lung cancer. Although he had a successful surgery without any bleeding complication, he died from sepsis 2 weeks after the operation. The other one (number #15) died because of pneumonia.

DISCUSSION

Hemophilia was thought to provide a barrier of cancer spread due to lower thrombin generation (4, 6) however, observational studies could not offer conclusive evidence that hemophilia patients had decreased incidence or mortality rates from non-virus-related cancers compared to general population (12-15). On the other hand, extended life expectancy in PWH, typical aging-related diseases such as lung, colon, and prostate cancer have become more prevalent and cause morbidity and death in this population (16). To our knowledge, this is the first and largest study which investigated the cancer prevalence in adult patients with hemophilia.

We reported that cancer prevalence is 3.4% in our study group. As expected, hemophilia patients with cancer were older than patients without cancer in our cohort (median age was 63 and 40 years, respectively). However, this prevalence rate is very low when compare to a previous study from Germany (17). It was reported that five times higher prevalence of cancer in PWH than in the age-matched general population (28% vs. 5.2%). In this study, patients who were at least 60 years of age at their last visit were included and the median age was 64 years (range, 60-85) (17). We thought that this finding is resulted from relatively younger median age of our cohort (median age was 40 years for all patients). Median age was higher in the studies from in industrialized countries since the expected life time for PWH is probably longer in developed countries. So far, increased incidence of virus-related malignancies such as HCC and non-Hodgkin's lymphoma due to HCV and/or HIV in PWH are well known. However, there have been few studies comparing PWH's incidence or prevalence of cancer to that of the general population, with inconsistent findings (12, 18, 19). It is anticipated that PWH will experience a rise in virally linked tumors, but not other cancer types, such as lymphoma and hepatocellular carcinoma. In comparison to controls, a study from Canada showed a significantly increased occurrence of malignancies in hemophilia (20). Additionally, Miesbach et al. reported PWH had a greater cancer prevalence than the overall population in both virus-related and non-virus-related cancers (14, 17). Lung and colorectal cancers were common cancer types in our study group like as the distribution of cancer type in general population. It is noteworthy that conclusions could not be made due to the small number of patients. Virus-related cancers were detected in only 2 patients and both of them had HCC.

The management of cancer in PWH is very complex because they are supposed to receive the same chemotherapy, examinations and invasive procedures as general population without hemophilia (21). All the patients in our study received the appropriate treatment for their cancer without any bleeding complication. Death from bleeding- related complications in hemophilia patients with cancer was not commonly reported in some of the studies so far (12, 22), somehow the survival rate was not longer than in general population with cancer (12). The cancer management of PWH should be individualized in order to balance the bleeding risk with the chemoradiotherapy, the severity of factor deficiency and/or bleeding phenotype and increased cancer related thromboembolism. Especially severe hemophilia patients should get factor prophylaxis during the cancer treatment due to increased bleeding risks other than factor deficiency such as thrombocytopenia and/or frequent invasive procedures (21). Prior to invasive operations such prostate biopsies and colonoscopies, patients should get factor replacement up to 80–100 U/dL, with a trough above 50 U/dL. Therefore, in order to enable early detection and management, older PWH should continue to get routine, age-appropriate screenings. For example, PSA screening, digital rectal examination and transrectal prostate biopsy are necessary for the diagnosis of prostate cancer and fecal occult blood testing and colonoscopy should be done for colorectal carcinoma.

Even though our study has some limitations. It is a retrospective analysis with a relatively small number of patients. We could not compare the prevalence rate of cancer with general population since we do not have any control group. Our study highlights that cancer is a growing problem in adult PWH. Besides, most substantial epidemiological studies document cancer mortality retrospectively but not incidence. Regarding potential links between cancer and hemophilia, surveillance of cancer occurrences and metastases appears to provide more accurate data than mortality rates. We need more prospective data to evaluate the relationship between hemophilia and cancer incidence.

CONCLUSION

The aging of PWH has revealed the need for more prospective research to help with the appropriate delivery of care to this unique population, as well as the necessity for data regarding their treatment and age-related comorbidities. There is still a debate about the incidence and prevalence rate of cancer in PWH comparing to general population. According to our research, PWH who are older have a higher risk of developing any type of cancer. Although longevity is one of the most important issues in PWH even in developing countries, any consensus and guidelines on the management of cancer in PWH have not been established yet.

Conflict of interest: The authors declare no conflict of interest.

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