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The relationship between malignancy and Behçet's disease features

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ABSTRACT

Introduction: Behçet's disease (BD) is an autoimmune, multisystemic vasculitis characterized by chronic inflammation. Autoimmune responses in BD could drive chronic inflammation which is a risk for malignant transformation. Some genetic, environmental, clinical features and immunosuppressive treatments in BD may increase the risk of malignancy. Common genetic factors and similar environmental factors play a role in the pathogenesis of some autoimmune diseases and malignancies. We hypothesized that the frequency of comorbidity and clinical features of BD may differ in BD patients with a family history of malignancy. So, we aimed to compare the demographic and clinical characteristics features of the BD patients with and without a family history of malignancy.

Material and Method: The BD patients who admitted the rheumatology outpatient clinic consecutively were included in the study. The demographic and clinical characteristics, comorbidities including malignancy in BD patients and malignancies in their family were questioned. The acute phase reactant elevation of at least two follow-ups was accepted as chronic inflammation.

Results: A total of 98 patients (57% male) were included. Mean age was 43.5±12.3 years. The frequency of comorbidity was 60% and malignant/premalignant lesions were seen in 5% of the patients. All lesions were solid organ related and all of them were in women. History of BD and malignancy in patients' families was found 28% and 38%, respectively. The patients with and without malignancy in their family were compared. Female gender and the frequency of erythema nodosum were higher in the patients with malignancy in their family. The other demographic and clinical characteristics, chronic persistent inflammation and medical treatments were statistically. not different

Conclusion: Frequency of malignancy in BD patients' family was evaluated and to the best of our knowledge, there was no literature data on this subject interestingly. The family history of malignancy in BD patients could be associated with clinical characteristics. Further prospective studies were needed to show the clinical effect of malignancy history in families.

Keywords: Behçet's disease, comorbidity, malignancy, family history

INTRODUCTION

Behçet's disease (BD) is a systemic vasculitis that may involve various organ systems. Its prevalence in Turkey is 240 per 100,000 population, and mostly seen in the Mediterranean region and the Far East (1). Although the pathogenesis of BD is not clear, it is thought to occur in individuals with a genetic predisposition under the influence of environmental factors. HLA-B51 allele, T lymphocyte-mediated immune dysfunction, neutrophilic inflammation, endothelial damage (NETosis) including MHC class I molecules are pathways that play a role in the pathogenesis.. Immunosuppressants are the mainstay treatment agents in BD (2,3).

BD has previously been associated with an increased risk of malignancy, both solid tumours and hematologic malignancies (4-9). Common environmental triggers, altered immune system, genetic factors and long-term use of immunosuppressants may be responsible for development of malignancy in BD (10-13). In addition to the role in BD pathogenesis, the HLA-B51 polymorphism has also been reported to be related with lymphoma, cervical carcinoma, papillary thyroid carcinoma (14-16). In BD long-term ongoing inflammation may cause comorbidities and mortality but whether it provokes malignancy development is yet to be clarified (4).

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Family history of a patient encompasses common genetic, behavioural, and environmental risk factors that can affect health among biological relatives. Likewise, having a family history of malignancy has been established as a risk factor for many types of malignancies (17). Knowledge about family history regarding malignancies helps risk assessment of an individual since 5-10% of cases are inherited (18). The American Cancer Society recommends identifying people with a family history and motivating them to engage in genetic counselling alongside earlier and/or more intensive cancer screening (19). Accordingly, family historiy for malignancy in BD patients can be helpful to identify patients with increased risk for malignancy and to individualize malignancy screening for prevention and early detection.

In our study, we aimed to evaluate the presence of malignancy in BD patients and their families and to compare the demographics, clinical characteristics and medical treatments of BD patients with and without a family history of malignancy.

MATERIAL AND METHOD

The study protocol was approved by Ankara City Hospital No: 1 Clinical Researches Ethics Committee (Date: 01.11.2021, Decision No: E1-21-2125). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this cross-sectional study, patients who were consecutively admitted to our rheumatology outpatient clinic between November and December 2021 and diagnosed with BD according to the 1990 ISGB diagnostic criteria (20) were enrolled. Patients under the age of 18 or who did not agree to participate in the study were excluded. Demographics, smoking status, clinical and laboratory data, comorbid diseases, and family history of malignancy were recorded. A history of malignancy in first and second degree members of the family was considered a positive family history for malignancy. Both malignant and premalignant lesions in BD patients were recorded. In at least two consecutive follow-ups, acute phase elevation without an explanatory reason such as underlying infection was considered as chronic persistent disease. BD was divided into two groups as those with and without a family history of malignancy and compared in terms of clinical features of BD.

For numerical variables their conformity to the normal distribution was evaluated using visual (histogram, normality plots) and analytical (Kolmogorov-Smirnof test, coefficient of variation calculation, skewness/sharpness indices) methods. Comparisons between the two groups were made using Student's t-test for normally distributed numerical variables, Mann-Whitney U test for non-normally distributed numerical variables, and Chi-Square or Fisher's exact tests for categorical variables as appropriate. Statistical significance level was accepted as $p<0.05$.

RESULTS

A total of 98 BD patients were included in the study. The mean age ± SD of the patients was 43.5±12.3 years and 57% were male (n=56). At least one comorbidity was present in 60% (n=59) and the frequency of malignancy was 5% (n=5). In family history; the frequences of BD and malignancy were 28% and 38%, respectively.

Demographic characteristics and comorbidities of BD patients were shown in **Table 1**. In the comparison of BD patients with and without a family history of malignancy, the female sex ratio was found to be significantly higher in patients with a family history of malignancy (65% vs. 29%, p=0.001). Age, smoking history, duration of BD symptoms, duration of BD diagnosis, presence of comorbidities and chronic persistent inflammation parameters were similar between the two groups.

The clinical findings of BD patients and the comparison according to the presence and absence of malignancy in the family were shown in **Table 2**. The frequency of mucocutaneous findings in order was oral ulcer %100, genital ulcer 76%, papulopustular eruption 63%, pathergy test positivity 57%. Except for mucocutaneous findings, arthritis was present in 44%, uveitis in 41%, venous thrombosis in 34%, sacroiliitis in 21%, gastrointestinal system involvement in 9%, central nervous system involvement in 7% and arterial thrombosis in 6%. Renal and cardiac involvement was not present in any of our patients. The incidence of erythema nodosum was significantly higher in the group with a family history of malignancy (60% vs. 33%, p=0.010).

The comparison of the drugs used in the treatment of BD patients according to the presence or absence of malignancy in the family is shown in **Table 3**. Most frequently used drug was colchicine in 91%, followed by conventional disease-modifying antirheumatic drugs (cDMARDs) in 72%, glucocorticoids in 64%, biological DMARDs in 22% and cyclophosphamide in 11%. The frequencies of the immunosuppressive treatments were similar between the groups with and without a family history of malignancy.

Table 1. Demographic and laboratory features of Behçet's disease patients with and without a family history of malignancy

Demographic features	All patients, n=98	Malignancy in family n=37	No malignancy in family n=61	p
Age, year, mean±SD	43.5±12.3	43.9 ±10.4	43.3±13.5	0.802
Male, n (%)	56 (57)	13 (35)	43 (71)	0.001
Smoking, n (%)	41 (42)	14 (38)	27 (44)	0.673
Smoking pack-year, median, IQR	14 (15)	10 (14)	15 (16)	0.868
History of surgery n (%)	53 (54)	19 (51)	34 (56)	0.682
Family history of BD n (%)	27 (28)	10 (27)	17 (28)	0.928
Symptom duration of BD, years, median (IQR)	10.5 (11)	11.0 (14)	11.7 (10)	0.443
Diagnosis time of BD, years, median (IQR)	9 (11)	9 (10)	9 (11)	0.809
Comorbidities and laboratory features				
Any comorbidity, n (%)	58 (59)	23 (62)	35 (57)	0.640
FMF, n (%)	3 (3)	2 (5)	1 (2)	0.555
Thyroid disease, n (%)	9 (9)	4 (11)	5 (8)	0.726
Pre/malignancy, n (%)	5 (5)	3 (8)	2 (3)	0.363
Thrombophilia, n (%)	4 (4)	2 (5)	2 (3)	0.631
Diabetes mellitus, n (%)	17 (17)	8 (22)	9 (15)	0.384
Hypertension, n (%)	28 (29)	12 (32)	16 (26)	0.510
Hyperlipidemia, n (%)	11 (11)	4 (11)	7 (12)	0.919
Asthma/allergic rhinitis, n (%)	10 (10)	4 (11)	6 (10)	>0.999
Ischemic heart disease, n (%)	8 (8)	1 (3)	7 (12)	0.252
Anxiety/depression, n (%)	13 (13)	8 (22)	5 (8)	0.071
Migraine, n (%)	6 (6)	3 (8)	3 (5)	0.670
BMI kg/m2, mean±SD	27.6±5.6	28.2±5.4	27.3±5.4	0.467
Chronic persistent inflammation, n (%)	30 (31)	12 (32)	18 (30)	0.823
HLA-B51 positivity, n (%)	9/26 (35)	3/12 (25)	6/14 (43)	0.429

BD: Behçet disease, FMF: Familial mediterranean fever, BMI: Body mass index

Table 2. Comparison of clinical features of patients with Behçet disease who have a family history of malignancy or not

	All patients, n=98 (%)	Malignancy in family n=37 (%)	No malignancy in family n=61 (%)	p
Oral ulcer	98 (100)	37 (100)	61 (100)	-
Genital ulcer	75 (76)	30 (81)	45 (74)	0.408
Papulopustular eruption	62 (63)	20 (54)	42 (69)	0.141
Erythema nodosum	42 (43)	22 (60)	20 (33)	0.010
Uveitis	40 (41)	11 (30)	29 (48)	0.082
Pathergy positivity	47 (57)	16 (49)	31 (62)	0.224
Arthritis	43 (44)	19 (51)	24 (39)	0.246
Sacroiliitis	21 (21)	8 (22)	13 (21)	0.971
Epididymitis	7/56 (13)	2/13 (15)	5/43 (12)	0.658
Venous thrombosis	33 (34)	10 (27)	23 (38)	0.254
Arterial thrombosis	6 (6)	1 (3)	5 (8)	0.404
Central nervous system involvement	7 (7)	2 (5)	5 (8)	0.707
Gastrointestinal system involvement	9 (9)	2 (5)	7 (12)	0.476

Table 3. Comparison of Behçet's disease treatments in patients with and without a family history of malignancy

Drugs	All patients, n=98 (%)	Malignancy in family n=37 (%)	No malignancy in family n=61 (%)	p
Colchicine	89 (91)	35 (95)	54 (89)	0.476
Glucocorticoid	63 (64)	22 (60)	41 (67)	0.437
NSAID	40 (41)	18 (49)	22 (36)	0.219
cDMARD	71 (72)	25 (68)	46 (75)	0.400
IFN-α	4 (4)	1 (3)	3 (5)	>0.999
Cyclophosphamide	11 (11)	2 (5)	9 (15)	0.199
bDMARD	22 (22)	6 (16)	16 (26)	0.321

NSAID: non steroid antiinflammatory drugs; cDMARD: conventional disease modifying antirheumatic drugs, IFN-α: interferon α; bDMARD: biologic disease modifying antirheumatic drugs

In total, 5 (5%) of 98 patients had malignant or premalignant lesions and all patients were female. The lesions were as follows; two thyroid carcinomas and one renal cell carcinoma, two cervical intraepithelial neoplasia-3 (CIN-3) and one endometrial hyperplasia. Three of them had a family history of malignancy and one had a family history of BD. Time from both symptom and diagnosis of BD onset were over 10 years in all patients except one, and the malignancy diagnosis was made 2-18 years after the onset of BD symptoms. The characteristic features of the patients were shown in **Table 4**.

DISCUSSION

In our study 28% of the BD patients had a family history of BD and 38% had a family history of malignancy. All of the 5 patients who had malignant or premalignant lesions in our study were female and all had solid organ lesions. There was no relationship between the presence of malignancy in the family , the demographic and clinical characteristics, the presence of chronic persistent inflammation and the medical treatments for BD, however a relationship was observed with female gender and incidence of erythema nodosum.

Table 4. Characteristics of 5 Behçet's disease patients with Premalignant/Malignant lesions

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**
Premalignant/Malignant lesion	Thyroid cancer	CIN-3	Renal cell cancer	Thyroid cancer	Endometrial hyperplasia
Duration time, year	7	1	1	10	1
Age, years	45	40	42	53	30
Gender	Female	Female	Female	Female	Female
Smoking history	Yes	Yes	No	No	Yes
Smoking pack-year	30	2	-	-	5
Family history of malignancy	Colon cancer	Lymphoma, gastric cancer	Pharynx cancer	None	None
BD in the family	No	Yes	No	No	Yes
Comorbidities	HT HL HCV	None	HT DM HL	HL IHD Migrain Depression ANH	PCOS Myoma uteri
Symptom duration of BD, years	20	16	3	25	19
Diagnosis timeof BD, years	20	14	0,5	25	10
BMI, kg/m2	32.0	23.5	31.6	28.3	33.2
Chronic persistent inflammation	No	No	No	No	No
HLA-B51 positivity	NA	NA	Positive	NA	Negative
Clinical features					
Oral ulcer	Yes	Yes	Yes	Yes	Yes
Genital ulcer	Yes	Yes	-	-	Yes
Papulopustular eruption	Yes	-	Yes	Yes	-
Erythema nodosum	Yes	Yes	-	Yes	-
Uveitis	-	Yes	-	-	-
Pathergy positivity	NA	NA	Yes	Yes	Yes
Arthritis	Yes	Yes	-	-	-
Sacroiliitis	-	-	Yes	-	-
Venous thrombosis	-	-	-	DVT	-
Arterial thrombosis	-	-	-	-	-
Central nervous system involvement	-	-	-	-	-
Gastrointestinal system involvement	-	-	-	-	-
Medical treatments					
Colchicine	Yes	Yes	Yes	Yes	Yes
Glucocorticoid	Yes	Yes	-	Yes	-
NSAID	Yes	Yes	Yes	-	-
cDMARD	AZA	SLZ MTX AZA	-	AZA	-
IFN-α	-	-	-	-	-
Cyclophosphamide	-	-	-	-	-
bDMARD	Infliximab	Infliximab	-	-	-

BD: Behcet disease, BMI: Body mass index, CIN-3: Cervical intraepithelial neoplasia-3, HT: Hypertension, HL: Hyperlipidemia, DM: Diabetes Mellitus, IHD: Ischemic heart disease, ANH:Adrenal nodular hyperplasia, PCOS: polycystic ovary syndrome, DVT: Deep vein thrombosis, NA: Non-available, NSAID: non steroid antiinflammatory drugs, cDMARD: conventional disease modifying antirheumatic drugs, IFN-α: interferon α, bDMARD: biologic disease modifying antirheumatic drugs, AZA: Azathioprine, SLZ: Sulfasalazine, MTX: Methotrexate

Hematologic and solid organ malignancies may be seen in the course of BD. The autoimmune nature of BD, chronic use of some immunosuppressive drugs and environmental triggering factors are thought to play a role in the development of malignancy (11,21). In the literature, a study (22) comparing BD patients hospitalized in United States (n=2605) and other inpatients (n=37.5 million) in 2016, the incidence of malignancy was found to be significantly higher in BD than other hospitalized patients (3.26% vs 2.74%, respectively, p<0.0001). In a meta-analysis published by Wang et al (23) in 2019, it was found that the frequencies of hematologic cancers and thyroid cancers were increased in BD patients. In the subgroup analysis of this study, cancer risk was found to be higher in women. Kaklamani et al (9) reported approximately 60 cases of BD were associated with various hematologic malignancies in their literature analysis. They also reported that solid tumours were present in only 2 of 128 BD patients in their study. In another study conducted in Korea (24) various solid tumours were detected in 11 (2.2%) of 506 BD. The authors found a low risk of malignancy in BD compared with the general population in Korea. In a cohort of 387 BD patients in Turkey (25), malignancy was detected in 8 patients (all male) during a follow-up of approximately 20 years. Seven were solid organ tumours and one was lymphoma. The incidence of cancer in male BD patients was similar to that observed in the general population. In another retrospective study published in 2020 (12), including Turkey data, 11 cancer cases (3 females, 8 males) were observed during a median follow-up of 124 months in 451 cases with BD. Of these, 10 were solid tumours and 1 was myelodysplastic syndrome. This study revealed that BD patients had an approximately three times greater risk for cancer compared to the respective age and sex groups (standardized incidence rate (SIR) 2.84, 95% CI 1.50–4.94, p < 0.001). These studies lacked details on malignancy related variables, including smoking, alcohol consumption, body mass index, and family history of malignancy. Malignancy development is associated with non-modifiable risk factors such as family history and gender, and modifiable risk factors such as smoking, alcohol, physical inactivity, and obesity. Knowing a person's family history can help determine the risk of hereditary diseases, such as cancer, where 5% to 10% of cases are inherited (18,26). In our study, all malignant and premalignant lesions were solid organ related and were present in female patients. .

Wang et al. (4) reported that malignancies with BD, especially hematologic malignancies, were generally detected within the first year after the diagnosis of BD, and the incidence gradually decreased thereafter. A possible explanation for this may be the increased diagnostic tests performed in these patients during the period when they were diagnosed with BD, and the patients' caring about their own routine follow-ups. This may lead to earlier detection of existing cancer compared to the general population (11,21). In addition, the fact that hematologic malignancy has a similar pathogenesis to BD and that the development of hematologic malignancy is faster may be related to the earlier emergence compared to solid malignancies (4). In our study, the time elapsed between the duration of BD symptoms and the time of detection of malignancy was at least 2 years. All malignancies in our cohort were solid tumours. Due to the absence of hematologic malignancy in our patient group, our malignancy development time was longer according to the literature.

Studies have been conducted on the immunosuppressive therapies used in BD and the development of malignancy. In a retrospective study conducted in Turkey (10), malignancies developed in 15 (8%) cases in a 25-year follow-up of 198 BD patients using cyclophosphamide. Another study (13) evaluating the effect of immunosuppressants used in BD on the development of malignancy showed that thalidomide treatment was an independent protective factor for cancer risk and cyclophosphamide was associated with high cancer risk. The remaining agents, including glucocorticoids, methotrexate, azathioprine and cyclosporine did not significantly correlate with cancer risk. In a study published in 2020 (12), which includes data from Turkey, azathioprine was also found to reduce the risk of cancer. In the present study, there was no relationship between the treatments used and malignancy in BD and malignancy in the family.

There were two findings that caught our attention in our results. First, the female gender had more family history of malignancy and all of our cases with malignant or premalignant lesions were female. As mentioned above, there were conflicting results in terms of gender and malignancy development in studies regarding BD. There was no data in the literature in terms of family history of malignancy and gender. The second important result is that the rate of erythema nodosum was higher in patients with a family history of malignancy. To the best of our knowledge, there is no data related to this issue in the literature. We thought that this result could be an incidental finding.

The major limitation of our study is the small number of patients. In addition, our short working time may cause selection bias. Due to the fact that the information was obtained from the patients and the hospital registry system, there may be lack of some data , especially in terms of family histories. Based on 5 patients with premalignant and malignant lesions,

it is unlikely to draw any statistical conclusions. Due to the fact that our clinic is atertiary center and due to the pandemic conditions, the fact that BD patients with mild symptoms may not come to routine outpatient clinic controls, and the clinical features of the applicant BD are more complicated, preventing our knowledge from being generalized to all BD patients. In the investigation of family history of malignancy, the history of malignancy in first and second degree family members was accepted as positive. Perhaps, in further studies, further differentiation in terms of malignancy as first-degree, second-degree and third degree relatives may lead to better results. Another limitation of our study is that the clinical features of BD patients were not evaluated with an objective scale and the severity of organ involvements was not quantified. Finally, due to the nature of cross-sectional studies, the inability to detect a temporal connection between familial malignancy and BD patients is another limitation of our study, since both were examined simultaneously.

CONCLUSION

It was noteworthy that in our group of BD patients, the family history of malignancy, which was not questioned in previous studies, was quite prominent. The presence of a family history of malignancy in BD should be questioned in larger and more comprehensive studies in order to more accurately evaluate the relationship between certain demographic characteristics, habits, comorbid diseases, clinical findings and the course of the disease. This can help identify people at potential malignancy risk and individualize plans for cancer prevention and early detection.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study protocol was approved by Ankara City Hospital No: 1 Clinical Researches Ethics Committee (Date: 01.11.2021, Decision No: E1-21-2125).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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