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ORIGINAL ARTICLE

Cancer incidence in Behçet's disease

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Abstract

Background Previous studies demonstrated an increased cancer risk in autoimmune diseases. Behçet's disease (BD) was also reported to be associated with an increased risk of cancer, although the data is limited.

Aims In this study, we aimed to assess cancer incidence in a large cohort of BD patients and to compare with the data of the same age and gender groups.

Methods The study cohort consisted of BD patients of > 18 years of age who were prospectively recorded in the Hacettepe University Vasculitis Center. Data on any cancer was collected from the patient files. Cancer incidence was compared with age- and gender-specific cancer incidence rates of the normal population retrieved from the 2014 Turkish National Cancer Registry (TNCR) data using standardized incidence rates (SIR).

Results Totally, 451 adult cases with BD were included. The median age of the cohort was 43 (20–75), and 52.5% of the patients were males. Eleven cancer cases were observed during a median of 124 months follow-up. Behçet's disease was associated with an increase in cancer risk compared with expected counts in the corresponding age and sex group (SIR 2.84, 95% CI 1.50–4.94, $p < 0.001$). Patients with papulopustular lesions had a trend toward a decreased risk of cancer ($p = 0.060$), and patients using azathioprine had a significantly decreased cancer risk ($p = 0.031$).

Conclusion This study revealed BD patients had approximately three times increased cancer risk compared with corresponding age and sex groups. Besides the routine care, increased attention for cancer surveillance is required in the follow-up of BD patients.

Keywords Behçet's disease · Cancer risk · Inflammation

Introduction

Behçet's disease (BD) is an immune-mediated multisystem vasculitis affecting the blood vessels of any size and type [1]. Almost every system can be affected by the disease and the damage generated by the chronic inflammation during the disease course including the skin, joints, gastrointestinal system, and central nervous system [2]. The disease presentation has been regarded as the outcome of an autoimmune process that is triggered by infectious and environmental factors in genetically predisposed individuals [3–5].

Although the immune system has protective roles against cancer, chronic uncontrolled inflammation is among the main causes of cancer development as seen in chronic infections and rheumatic diseases [6]. The microenvironment in chronic inflammation leads to changes in cytokine and chemokine profiles of inflammatory cells which normally have roles in anti-cancer immunity [7–9]. After the development of an immune-exhausted milieu in chronic inflammatory conditions, these immune cells and mediators take roles in the tumor initiation, progression, angiogenesis, and metastases [10, 11]. After the establishment of the tumor, this vicious cycle further perpetuates itself due to chronic antigenic stimuli and immune evasion [12, 13].

Not surprisingly, multiple wide-scale studies demonstrated the increased risk of malignancy in systemic autoimmune diseases [14]. Behçet's disease was also reported to be related to

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an increased risk of malignancy in multiple studies, although differences in designs were an important issue [15–18]. While earlier studies were mostly consisted of case series with a modest number of patients and mostly stated an increased risk of hematologic malignancies [19, 20], recent studies from the Far East used larger cohorts and reported the increased risk of solid tumors in addition to hematological malignancies although data on the disease involvement and medications were mostly lacking due to use of administrative data rather than individual patient files [15–17]. From this point, in this study, we aimed to assess the cancer risk in a large cohort of well-followed BD patients and compared them with the data of the Turkish National Cancer Registry (TNCR) in the same age and gender groups [21].

Patients and methods

Patient selection

This is a retrospective cohort study conducted in the Hacettepe Vasculitis Center and Hacettepe Oncology Hospital, Ankara, Turkey. The study cohort consisted of BD patients who were prospectively recorded since October 2014 in Hacettepe Vasculitis Center, which is one of the referral centers for BD in Turkey [22]. Patients younger than 18 years of age ($n = 12$) were excluded from the study.

The confirmation of BD diagnosis by an experienced rheumatologist according to the Behcet's Syndrome International Study Group Criteria [23] is mandatory for recording in the Hacettepe Vasculitis Center database. Besides the baseline demographics and the extent of disease, treatment medications (colchicine, steroids, and immunosuppressives), smoking habits, and family histories were recorded for most patients. Data on any cancer was collected from the patient files, and hospital registries were available. Age- and sex-specific cancer incidence rates of the normal population were retrieved from the 2014 Turkish National Cancer Registry (TNCR) data [21].

The study was approved by the Ethics Committee of Hacettepe University with an approval number GO 18/1043.

Statistical analysis

Standardized incidence rates (SIR) were calculated after adjustment for age and sex and compared with age- and sex-specific incidence rates abstracted from the 2014 TNCR data [21]. The observed number of cases is all individuals diagnosed with cancer on follow-up after the diagnosis of BD. Expected cases represent the total number of patients that would have been reported to the cancer registry within the same period of follow-up as per the TNCR rates under the null hypothesis of no increased risk, given the age and sex structure. A ratio greater than 1.00 indicates that there were more cases observed than expected. The SIR and the 95% confidence interval (CI) for the SIR were calculated using OpenEpi version 3.01 software. Statistical Package for Social Sciences 20 program was used for the baseline descriptive features and for the evaluation of variables that may have affected cancer risk. $P < 0.05$ was considered statistically significant.

Results

A total of 451 adult cases with BD were recorded in the Vasculitis Center database and included in the analyses. The median age of the cohort was 43 (20–75), and 52.5% of the patients were males. The median age of diagnosis was 30 (18–59) for females and 29 (18–53) for males. Most of the cases were diagnosed between 20 and 35 years of age (64.1%). The median follow-up of all groups was 124 months with a slightly longer follow-up for the female group (132 months) compared with the male group (121 months). Oral aphthous ulcers were present in almost all patients (450/451) followed by genital ulcers (322/451) and skin involvement (295/451). The patient cohort was characterized by a rather aggressive disease as evidenced by the high usage rate of regular steroid use (238/451) and other immunosuppressives like azathioprine (186/451) and interferon (151/451).

Eleven cancer cases were observed on follow-up. The types of cancers and interval between BD diagnoses and cancer are summarized in Table 1. Behçet's disease was associated with an increased cancer risk compared with expected counts in the corresponding age and sex group (SIR 2.84, 95% CI 1.50–4.94, $p < 0.001$). Overall cancer risk was not increased in women (SIR 1.22, 95% CI 0.31–3.33, $p = 0.68$), while in men with BD, increased cancer risk was statistically significant (SIR 5.63, 95% CI 2.62–10.70, $p < 0.001$). Patients with papulopustular lesions had a trend toward a decreased risk of cancer (x^2: 3.82, $p = 0.060$), while other clinical features did not have a significant relation with cancer risk including family history. When looking at the effects of specific treatments, patients using azathioprine had a significantly decreased cancer risk (x^2: 4.809, $p = 0.031$). Due to the low number of index cases, SIR values were not calculated for cancer subgroups.

Discussion

This study revealed an increased cancer incidence among a prospective BD cohort compared with corresponding age and sex groups of TNCR data. When considering specific treatment agents, patients treated was azathioprine had a decreased risk of cancer.

Table 1 Cancer cases after the diagnoses of BD and the interval between two diagnoses

Cancer type	Age at cancer diagnosis	Sex	Time interval (years)	Clinical manifestations	Treatments ever used
Breast cancer					
#1	54	Female	23	OU, GU, EN, cutaneous lesions, uveitis, arthritis	Colchicine, sulfasalazine
#2	53	Female	28	OA, GU, uveitis	Colchicine
Colorectal cancer					
#1	51	Male	6	OU, GU, cutaneous lesions, EN	Colchicine, sulfasalazine
#2	62	Male	32	OU, GU	Colchicine, steroid
Lung cancer					
#1	51	Female	6	OA, GU, cutaneous lesions, EN	Colchicine
#2	61	Male	21	OU	Colchicine
Cholangiocellular carcinoma	53	Male	30	OU, uveitis, arthritis, enterobehcet	Colchicine, interferon
Thymoma	56	Male	18	OU, GU, EN, cutaneous lesions, uveitis, arthritis	Colchicine, sulfasalazine
Renal cell carcinoma	54	Male	5	OU	Colchicine
Myelodysplastic syndrome	55	Male	24	OU, GU, EN, cutaneous lesions, uveitis	Colchicine, steroid, azathioprine
Oligodendroglioma	38	Male	6	OU, GU, uveitis	Colchicine

BD Behçet's disease, *OU* oral ulcer, *GU* genital ulcer, *EN* erythema nodosum

Inflammation is an important factor in carcinogenesis [6], and even the remote inflammation in chronic periodontitis seems to be related with the increased cancer risk [24, 25]. Behçet's disease is considered as a mixed disease with features of both autoimmune and autoinflammatory spectrum [26]. Although clinical features seem to be related to autoinflammatory processes, autoimmune features are prominent in disease pathogenesis lead by T-cells of adaptive immunity [27, 28]. Similar to the other autoimmune diseases, BD is related to specific class I major histocompatibility complex molecules with HLA B-51 being most common [3, 4, 29]. T-helper and T-helper 17 cells are among the main mediators of inflammatory process participating in both mucocutaneous and visceral inflammation, with neutrophils and natural killer cells that are also accompanying, while anti-inflammatory mediators like IL-10 and regulatory T-cells are decreased in abundance leading to uncontrolled inflammation in multiple systems [4, 30–32].

Considering BD as an autoimmune disease, cancer risk is expected to increase in BD, as we found in our study (SIR 2.84). Our results are consistent with the population-based studies from Taiwan [16] and Korea [17], albeit lower SIR values (1.5 and 1.13, respectively) were reported in these studies. Another nationwide study from Korea reported a higher risk of cancer than our study (SIR 3.54), with a rather short follow-up time of 2.34 years [15]. All three studies reported a similarly increased cancer risk in both men and women with BD [15–17], while the cancer risk was significantly increased in males but not in females in our study. Mechanisms of this association may include the more aggressive BD course in the young male patients as a general feature of BD [2] and more frequent smoking in the men, or it may just be due to the low number of cases precluding the demonstration of a minor increase.

In our study, both men (60%) and women (26.1%) with BD had higher rates of smoking compared with the general population [33]. It is a known tendency possibly due to decreased mucocutaneous disease activity in smokers with BD [34, 35]. Surprisingly, the increased risk of smoking-related cancers was not evident in the previous cohort studies [15–17] and also in our study. Whether it is due to short-follow up times or the presence of a disease-specific effect or the beneficial effects of colchicine is an important issue, which needs further evaluation.

Due to the nature of population-based studies using administrative data, the effects of disease characteristics and

treatments on the cancer risk could not be further evaluated in most of the previous studies [15–17, 36]. In our study, there was a trend toward decreased cancer risk in patients with papulopustular lesions, which may be simply due to the benign course of the BD in these patients when compared with patients with visceral organ involvement. Increased interleukin (IL) 17 and 22 levels were reported to be associated with mucocutaneous lesions [37]. These interleukins were reported to have dual roles in both promotion and suppression of cancers [38], making mechanistic implications of this finding difficult.

Other system involvements did not have a significant effect on cancer risk, although chronic inflammation is expected to increase the cancer risk in affected organs. Also, family history did not affect the results significantly in our study. Behçet's disease is associated with specific genetic polymorphisms lead by HLA-B51 and IL23R-IL12R [39], although their association with cancer risk is unknown. HLA-B51 polymorphisms were reported in the lymphoma [40], cervical carcinoma [41], and papillary thyroid carcinoma [42] and can be relevant in the BD and cancer link.

Almost all medications used in BD treatment can affect the cancer risk although in different directions. Cyclophosphamide was reported to increase bladder cancer and hematological cancers [43, 44], while methotrexate was reported to increase the risk of lymphoproliferative disorders [45]. Colchicine is an anti-microtubule agent similar to vinca alkaloids [46] and was reported to inhibit tumor growth in human cancer cell lines [47, 48]. It has been reported that colchicine use was related to a decreased cancer risk in gout patients compared with colchicine non-users [49]. Almost all patients used colchicine in our patient cohort, rendering the analyses of the effect of colchicine use on cancer risk not possible. Cyclophosphamide use was not associated with cancer risk in our study, which may be explained with the intravenous use of the drug with a cumulative dose limit of 6 g in our center. The cancer risk was similar in the interferon user and non-user groups (Table 2), although decreased cancer risk can be expected in users due to the anti-tumor properties of the drug [50]. Most of interferon-treated patients had also other immunosuppressives in previous lines of therapy, which may preclude the cancer risk reduction with the use of interferon.

Patients using azathioprines had a decreased risk of cancer which was statistically significant in our study (Table 2) similar to a recent study from Korea in BD [15]. A similar finding was found in a meta-analysis of the inflammatory bowel disease patients treated with azathioprine [51]. The authors proposed that suppression of inflammation by azathioprine may lead to this risk decrease [51] which may have been the underlying mechanism of decreased risk in BD also. However, the absence of a similar risk reduction with other immunosuppressives lessens the probability of inflammation suppression as the sole mechanism of cancer protection with azathioprine. Most of our cancer patients were treated with a weak immunosuppressive regimen (only colchicine or colchicine and sulfasalazine in 8/11 cases) which hinted the possible role of inflammation suppression for cancer protection in BD.

Table 2 Comparison of disease and treatment characteristics and cancer risk in BD

Factor		Cancer present, n	Cancer absent, n	*p* value
Smoking	Present, n	6	165	0.546
	Absent, n	5	213	
Uveitis	Present, n	6	202	0.525
	Absent, n	4	234	
Papulopustular lesions	Present, n	2	220	0.060
	Absent, n	8	209	
Enterobehçet	Present, n	1	19	0.396
	Absent, n	10	421	
Vascular involvement	Present, n	1	91	0.457
	Absent, n	8	258	
Steroids	Present, n	3	235	0.125
	Absent, n	8	205	
Azathioprine	Present, n	1	185	0.031
	Absent, n	10	255	
IFN	Present, n	1	150	0.109
	Absent, n	10	290	
Anti-TNF	Present, n	0	42	0.610
	Absent, n	11	398	

**BD* Behçet's disease, *IFN* interferon, *TNF* tumor necrosis factor

Our study has several limitations. The number of patients is relatively low, precluding SIR calculations for specific cancers difficult. Also, the relatively young age of our cohort led to a low number of observed and expected cases, which made the confidence intervals of SIR wide. The cancer data were taken from the patient files and hospital records, so cancer cases diagnosed out of our hospital may have been missed. This factor may drive the results toward to null hypothesis. However, we still found an increased cancer risk in BD; other cancer risk factors were lacking in most patients precluding further adjustments. The increased medical contact during the follow-up BD can be also a confounder for increased cancer risk, but most of our cancer cases were symptomatic on the presentation that lessens this possibility. Finally, our study did not have a control group; therefore, we used the data of TNCR for comparisons.

Conclusion

In conclusion, we found that the cancer risk was increased in a well-followed cohort of patients with BD. Besides the routine care, increased attention for cancer surveillance is required in the follow-up of BD patients.

Availability of data and material Not applicable.

Code availability Not applicable.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Approved by the Ethics Committee of Hacettepe University with an approval number GO 18/1043.

Consent to participate Not applicable.

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