Morbidity of Solid Cancer in Behçet’s Disease: Analysis of 11 Cases in a Series of 506 Patients

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Purpose: Behçet’s disease (BD) is rarely reported to be associated with malignancies in the literature. However, the frequency of cancer in BD patients remains unknown. This study evaluated cancer morbidity in BD patients compared with that in the general population of Korea. Materials and Methods: A retrospective chart review was performed on 506 patients visiting our hospital from 1994 to 2011 for BD. We analyzed the standardized morbidity rate (SMR), which is the ratio of observed to expected malignancies. Furthermore, we reviewed cases of solid cancer in BD patients in the literature. Results: Of the 506 patients with BD, 11 (2.17%) developed cancer. We found a variety of solid cancers without predominance and no hematologic malignancies. The total number of cancers observed was less than expected, which was determined from the statistical data of the National Cancer Information Center of Korea, with an SMR of 0.023 (95% confidence interval, 0.012-0.039). Conclusion: BD may be associated with a lower cancer-related morbidity compared with the general population of Korea.

Key Words: Behçet’s disease, malignancy, morbidity, solid cancer

INTRODUCTION

Behçet’s disease (BD) is a chronic relapsing systemic vasculitis, characterized by diverse manifestations including recurrent orogenital ulcers, uveitis, skin lesions, and arthritis, as well as the involvement of the gastrointestinal tract, central nervous system and blood vessels.1 The pathogenesis of BD is regarded to be partially associated with autoimmunity on the basis of the evidence of effective immunosuppressive treatment and detected auto-antibodies.2 The risk of malignancy is higher in patients with antineutrophil cytoplasmic antibody-associated vasculitis and Henoch-Schönlein purpura than in controls.3 A high risk of malignancy is also reported in autoimmune rheumatic diseases such as systemic lupus erythematosus, systemic sclerosis, and dermatomyositis.4-7 These characteristics are assumed to be possible causes for the development of malignancies in patients with BD.

However, there are only a few case reports and case series regarding the association between malignant diseases and BD in the literature.8 Due to the scant evidence of the relationship between BD and malignancy, the prevalence of malignancy in BD patients remains unclear. Here we report 11 cases of BD patients associated...
A total of 506 BD patients, who visited the Department of Dermatology of Ajou University Hospital between 1994 and 2011, were included in this study. All patients fulfilled either the International criteria for the diagnosis of BD9 or the revised criteria of the Behçet’s Disease Research Committee of Japan.10 To identify which BD patients were associated with malignancy, the medical charts were reviewed retrospectively. The following data were collected: the age at diagnosis of BD and malignancy, type of malignancy, sex, duration of disease, clinical features of BD, and treatment regimens for BD and the malignancy. The Institutional Review Board approved this study (IRB number: AJIRB-MDB-12-007).

Table 1. Characteristics of the 11 Behçet’s Disease Patients Who Developed Solid Cancer

| Case no. | Age (yrs) | Sex | Interval* (yrs) | BD symptoms | Drugs used for BD | Type of malignancy | Management of malignancy | Clinical status |
|----------|-----------|-----|----------------|-------------|------------------|--------------------|------------------------|----------------|
| 1        | 41        | F   | 3              | O, G, S, A  | Colchicine       | Cervical cancer (CIS) | Conization            | Alive          |
| 2        | 49        | F   | 12             | O, G, S, A  | Colchicine, Minocycline, Pd | Breast cancer | MRM+CTx+RTx | Alive          |
| 3        | 52        | M   | 20             | O, G, S     | Colchicine, Sulfasalazine | Rectal cancer | Neoadjuvant CCRT+LAR | Alive          |
| 4        | 31        | F   | 4              | O, G, S     | Colchicine, Sulfasalazine, Minocycline, HCQ | Cervical cancer (CIS) | Conization            | Alive          |
| 5        | 44        | F   | 6              | O, G, S     | Colchicine, Minocycline | Lung cancer | CTx           | Dead           |
| 6        | 45        | F   | 18             | O, G, S     | Colchicine, Minocycline, Pd | Ovary cancer | TAH c LSO | Alive          |
| 7        | 40        | M   | 6              | O, U        | Colchicine, Minocycline | Gastric cancer | Subtotal gastrectomy | Alive          |
| 8        | 55        | F   | 26             | O, G, S, U  | Colchicine, Minocycline | Lung cancer | CTx           | Dead           |
| 9        | 42        | F   | 2              | O, G, S     | Colchicine, Minocycline, Sulfasalazine, Pd | Breast cancer | MRM+CTx | Alive          |
| 10       | 53        | F   | 2              | O, G, U     | Colchicine, Sulfasalazine | Colon cancer | Neoadjuvant CCRT+LAR | Alive          |
| 11       | 33        | F   | 0              | O, G, I, N  | Pd, Sulfasalazine | Colon cancer | Ovary cancer | RSO            |

BD, Behçet’s disease; O, oral ulcer; G, genital ulcer; S, skin lesions; A, arthritis; U, uveitis; I, intestinal involvement; N, neurologic involvement; Pd, prednisolone; HCQ, hydroxychloroquine; CIS, carcinoma in situ; MRM, modified radical mastectomy; CTx, chemotherapy; RTx, radiation therapy; CCRT, concurrent chemoradiotherapy; LAR, lower anterior resection; TAH, total abdominal hysterectomy; LSO, left salphingo-oophorectomy; RSO, right salphingo-oophorectomy.

*Interval between Behçet’s disease and cancer.
skin lesions (72.7%), and uveitis (27.3%). A young female patient (case, 11) experienced severe BD symptoms with the simultaneous involvement of the nervous and gastrointestinal systems. No patient was treated with immunosuppressive agents except corticosteroids before the diagnosis of the malignancy. Colchicine was used as the main treatment in most patients, and corticosteroids, sulfasalazine or antibiotics were administered in some cases.

Surgery was the preferred treatment option in 9 BD patients although surgical procedures were different. Among them, only 1 patient (case, 6) developed wound dehiscence as a postoperative complication, which was well controlled by secondary suture. She was negative for the pathergy reaction. Chemotherapy was used in 6 patients and radiation therapy was performed in 3 patients without complication. During the follow-up period, 2 patients (case, 5 and 8) died from tumor progression and the others are still alive without recurrence of cancer.

The expected number of BD patients associated with cancers was 485.12, which was calculated by the indirect standardized method from Korean data of 10-year prevalence rate of malignancy in 2008. This expected number was 44.10 times more than the observed number of patients-11 in our study. According to SMR analysis, BD patients exhibited a lower malignancy-related morbidity (SMR 0.023, 95% CI 0.012-0.039), than the general population of Korea. Male (SMR 0.024, 95% CI 0.002-0.048) and female (SMR 0.014, 95% CI 0.011-0.044) patients showed similar results.

**DISCUSSION**

The frequency of malignancy, especially solid cancers associated with BD, was low compared with those of other autoimmune diseases with less than 100 cases in the world literature.8,11-36 We summarized the case reports for only solid

| No. | Author         | Age* | Sex | Interval† | Malignancy                                      |
|-----|----------------|------|-----|-----------|-------------------------------------------------|
| 1   | Tagami, et al. | 24   | F   | 2 months  | Malignant granuloma of pharynx                  |
| 2   | Tamaoki, et al.| 35   | M   | 7 months  | Thyroid carcinoma                               |
| 3   | Tamaoki, et al.| 28   | F   | 2 yrs     | Thyroid carcinoma                               |
| 4   | Cengiz, et al. | 42   | F   | 6 yrs     | Gastric carcinoma                               |
| 5   | Hamza          | 42   | M   | 9 yrs     | Metastatic adenocarcinoma of unknown primary    |
| 6   | Hamza          | 44   | M   | 3 yrs     | Lung cancer                                     |
| 7   | Kamata, et al. | 45   | M   | 5 yrs     | Colon carcinoma                                 |
| 8   | Oishi, et al.  | 32   | M   | At diagnosis | Pheochromocytoma                           |
| 9   | Murata, et al. | 31   | M   | 9 yrs     | Hepatocellular carcinoma                       |
| 10  | Kakamani, et al.| 62  | M   | 13 yrs    | Rectal carcinoma                               |
| 11  | Muramatsu, et al.| 51  | M   | 6 yrs     | Malignant rhabdoid tumor                        |
| 12  | Bethea and Khan | 46  | F   | NA        | Pheochromocytoma                               |
| 13  | Celik, et al.  | 43   | M   | 17 yrs    | Bladder carcinoma                              |
| 14  | Akpolat, et al.| 49   | M   | At diagnosis | Lung cancer                         |
| 15  | Kötter, et al. | 32   | M   | 3 yrs     | Kaposi’s sarcoma                                |
| 16  | Baltaci, et al.| 51   | F   | 19 yrs    | Bladder carcinoma                              |
| 17  | Nishimura, et al. | 52  | M   | At diagnosis | Hilar bile duct cancer                        |
| 18  | Satoli, et al. | 67   | M   | 8 yrs     | Merkel cell carcinoma                          |
| 19  | Kwon, et al.   | 40   | F   | 7 yrs     | Hepatic leiomyosarcoma                         |
| 20  | Lee, et al.    | 40   | M   | 12 yrs    | Colon carcinoma                                 |
| 21  | Kammmori, et al.| 72  | F   | 15 yrs    | Breast carcinoma                               |
| 22  | Mezalek, et al. | 44  | M   | 10 months | Kaposi’s sarcoma                                |
| 23  | Meyer, et al.  | 52   | M   | -32 yrs   | Lung cancer                                     |
| 24  | Chargari, et al.| 61   | F   | NA        | Breast carcinoma                               |
| 25  | Yamada, et al. | 77   | M   | 5 yrs     | Colon carcinoma                                 |

NA, not available.

*Age at diagnosis of malignancy.

†Interval between Behçet’s disease and cancer.
cancers associated with BD in Table 2. In the literature, the average age of malignancy diagnosis was 46.48±13.47 years, and the median duration between BD and malignancy was 6 years; these values are similar to those of the present study despite the male predominance. Malignancy was diagnosed after BD was diagnosed in most patients in both our study and the literature.

Only a few clinical researchers have made efforts to determine the incidence rate of malignancy in BD. Cengiz, et al.33 reported 13 cases of malignancies in 400 BD patients with a median follow-up of 10 years; however, they did not find any significant difference from the incidence of malignancies in the general population of Turkey. In another study from Turkey, they observed 8 patients with cancer among 387 BD patients with a 20-year follow-up.34 The estimated annual incidence rate of malignancies in BD patients is 103 in 100000, which is similar to the crude yearly cancer incidence of 90 in 100000 among the general population of Turkey in 1995.35 In 2005, Kaklamani, et al.8 found that among 128 BD patients, 2 developed malignancies since 1990. They also calculated the age-standardized rate (ASR) for cancer cases in their population as 1600 per 100000 in 10 years. This rate is lower, although not significantly, than the ASR of 2725 per 100000 in 10 years in the general population of Greece. In Korea, a country known for having a high prevalence of BD, a single-center study on the association between BD and malignancy has been performed. Among 1769 BD patients, 32 (1.8%) developed cancer in a 12-year period.32 However, the incidence rate was not compared to that of the general population in that study. In the present study, we analyzed the SMR to compare the cancer morbidity in BD patients with that of the general population of Korea. The morbidity of malignancies was significantly lower in BD patients after adjusting for age and sex.

According to a literature review, BD is predominantly associated with hematologic malignancies, especially myelodysplastic syndrome.32,36 In their case series in Korea, Ahn, et al.32 also reported that myelodysplastic syndrome is the most common associated disease (21.9%), followed by thyroid cancer (12.5%). They stated that the types of solid cancers in BD patients are presumed to be similar to those of the general population on the basis of the 2002 annual report of the Korean Central Cancer Registry program.32 However, we did not find any hematologic malignancies among the present 506 BD patients, and no particular type of solid cancer was predominant (Table 3). The difference in frequencies of hematologic malignancies between the study by Ahn, et al.32 and our study may result from the difference of recruitment group for BD patients. They recruited the BD patients from the department of rheumatology, whose patients usually present more internal involvement such as intestinal or vascular manifestations, and have tendency to

| Table 3. Comparison of Malignancy in Behçet’s Disease Reported as Case Series in Korea with Our Study |
|---------------------------------------------------|---------------------------------------------------|
| Ahn, et al.32 | Our study |
| Age at diagnosis of BD | 39.8±11.7 | 35.4±7.4 |
| Age at diagnosis of malignancy | 42.7±11.1 | 44.2±7.7 |
| Malignancy at first 5 yr of BD Dx | 17 (53.1) | 5 (45.4) |
| Female | 23 (71.9) | 9 (81.8) |
| Type of malignancy | | |
| Solid cancer | 21 (65.6) | 11 (100) |
| Thyroid cancer | 4 (12.5) | 0 (0) |
| Lung cancer | 0 (0) | 2 (18.2) |
| Breast cancer | 3 (9.4) | 2 (18.2) |
| Hepatoma | 3 (9.4) | 0 (0) |
| Gastrointestinal cancer | 6 (18.8) | 3 (27.3) |
| Renal cell cancer | 1 (3.1) | 0 (0) |
| Female organ cancer | 4 (12.5) | 4 (36.4) |
| Hematologic malignancy | 11 (34.4) | 0 (0) |
| Myelodysplastic syndrome | 7 (21.9) | 0 (0) |
| Lymphoma | 1 (3.1) | 0 (0) |
| Aplastic anemia | 3 (9.4) | 0 (0) |

BD, Behçet’s disease.

Unless otherwise indicated, values are frequency (percentage) or mean±standard deviation.
administer more immunosuppressive agents including cyclosporine and/or azathioprine. These drugs have been implicated in the development of hematologic malignancies by the direct effect of the drugs on DNA replication and indirect effect on cellular regulation.

Previous research has tried to determine the cause of solid cancers in BD cases in the literature. Colon carcinoma confined to the ileocecal region with histopathological evidence of transmural ulcer scarring has been reported; in addition, the ileocecal region is the most commonly involved region in cases of BD with gastrointestinal involvement. Recently, the biology of chronic inflammation was determined to play a major role in cancer development. Chronic inflammation, which can induce attenuated local cell-mediated immunity and elevated angiogenesis, may provide an ideal environment to nurture mutated cells and help them evade immune surveillance. The fact that inflammatory bowel diseases share some clinical features with rheumatic diseases, and the well-known association between colorectal cancer and inflammatory bowel diseases, support the role of inflammation in cancer development. Therefore, the possibility of cancer development from an ulcer scar due to intestinal BD should be carefully considered.

Long-term cyclophosphamide therapy is reported to be associated with the development of anaplastic bladder carcinoma in BD patients. It is well known that the risk of bladder carcinoma increases with cumulative doses of cyclophosphamide and that the histology is always high grade. Accordingly, the possibility of bladder cancer development should be considered in long-term cyclophosphamide treatment, particularly in young patients with long life expectancies. Several cases of Kaposi’s sarcoma after immunosuppressive therapy in BD patients have been also documented in the literature. The causative immunosuppressive drugs of this disease alone or in combination therapy include corticosteroids, azathioprine, methotrexate, cyclophosphamide, and cyclosporin A. The association between Kaposi’s sarcoma and immunodeficiency induced by cytotoxic drugs had been established. Use of immunosuppressive agents is also associated with lymphoproliferative disorders, as shown in methotrexate-related lymphoma in patients with rheumatoid arthritis. Furthermore, reactivation or de novo infection of various pathogens, such as Epstein-Barr virus and human T-lymphotropic virus-1, are involved in not only hematological malignancies but also in several autoimmune and rheumatic diseases, which may be a consequence of therapeutic immunosuppression. The relationships between solid cancers, excluding the aforementioned cancers, and BD seem to be incidental. Although most authors consider autoimmune-related or immunosuppressive drugs as risk factors for carcinogenesis in BD, there is no clear evidence that these factors induce carcinoma or sarcoma. Similarly, a study from Korea, compared the characteristics of treatment including immunosuppressants but found no significant difference between BD patients with or without malignancy. In addition, we did not find any BD cases treated with immunosuppressants before the development of cancer. Therefore, we think the incidence of cancer was coincidental.

Studies on the possible genetic mechanism of solid cancer in BD patients are rare. We found only one article mentioning transforming growth factor-β (TGF-β), which is a potent cell growth inhibitor. Kaklamani, et al. showed that not only is the risk of malignancy in BD patients lower (albeit not significantly) than that of the general population, but also that TGFBR1*6A, a variant of the type I receptor of TGF-β, is implicated in breast, ovarian, and colon cancers. Based on these findings, they found that the allelic frequency of TGFBR1*6A is lower than that of the general population; possibly indicating a protective mechanism against the development of malignancy in BD patients.

In conclusion, cancer morbidity is significantly lower in BD patients than the general Korean population. However, further investigation, particularly multicenter surveys, are nec-
essay to verify the correlation between BD and malignancy.

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