Original Article

http://dx.doi.org/10.3349/ymj.2013.54.4.895
pISSN: 0513-5796, eISSN: 1976-2437

Yonsei Med J 54(4):895-901, 2013

YMJ

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

So Young Na, Jaeyoung Shin, and Eun-So Lee

Department of Dermatology, Ajou University School of Medicine, Suwon, Korea.

Received: May 15, 2012
Revised: September 7, 2012
Accepted: September 10, 2012
Corresponding author: Dr. Eun-So Lee,
Department of Dermatology,
Ajou University School of Medicine,
164 World cup-ro, Yeongtong-gu,
Suwon 443-721, Korea.
Tel: 82-31-219-5190, Fax: 82-31-219-5189
E-mail: esl@ajou.ac.kr

· The authors have no financial conflicts of interest.

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

with malignancy and analyzed the cancer morbidity of BD compared to that of the general population of Korea.

MATERIALS AND METHODS

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 BD[9] 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).

The standardized morbidity rate (SMR) was used to compare the observed and expected morbidities. In this study, the SMR was the ratio of the observed morbidity in BD patients to the morbidity in the total age- and sex-matched Korean population. The expected number of malignancies was determined from the statistical data of the National Cancer Information Center (http://www.cancer.go.kr/ncic/cics_f/04/041/index.html) in 2008. The results are expressed as SMRs and 95% confidence intervals.

RESULTS

Of the 506 BD patients from our hospital, 11 (2.17%) developed malignancies. The clinical findings and other characteristics of these 11 patients are summarized in Table 1. Nine patients were women, and 2 patients were men. The mean±standard deviation (SD) ages at diagnosis of BD and malignancy were 35.4±7.4 years and 44.2±7.7 years, respectively. The mean±SD follow-up duration for our patients was 76.4±53.2 months (range, 12-174 months). BD preceded the malignancy in 9 patients (81.8%), concurrently developed in 1 patient (9.1%), and developed after malignancy in 1 patient (9.1%). The median duration between BD and malignancy was 6 years (range, 0-26 years).

Solid cancers were diagnosed in all patients without hematologic disease. The various types of solid cancers identified included lung, breast, ovary, cervical, and colon cancer in 2 patients each, and gastric cancer in 1 patient.

Among the BD-related symptoms, all 11 patients presented with oral ulcers, followed by genital ulcers (90.9%),

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	Ovary cancer	RSO	Alive

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

Table 2. Case Reports of Solid Cancer Associated with Behçet's Disease in the Literature

No.	Author	Age*	Sex	Interval†	Malignancy
1	Tagami, et al.[11]	24	F	2 months	Malignant granuloma of pharynx
2	Tamaoki, et al.[12]	35	M	7 months	Thyroid carcinoma
3	Tamaoki, et al.[12]	28	F	2 yrs	Thyroid carcinoma
4	Cengiz, et al.[33]	42	F	6 yrs	Gastric carcinoma
5	Hamza[13]	42	M	9 yrs	Metastatic adenocarcinoma of unknown primary
6	Hamza[13]	44	M	3 yrs	Lung cancer
7	Kamata, et al.[14]	45	M	5 yrs	Colon carcinoma
8	Oishi, et al.[15]	32	M	At diagnosis	Pheochromocytoma
9	Murata, et al.[16]	31	M	9 yrs	Hepatocellular carcinoma
10	Kaklamani, et al.[8]	62	M	13 yrs	Rectal carcinoma
11	Muramatsu, et al.[17]	51	M	6 yrs	Malignant rhabdoid tumor
12	Bethea and Khan[18]	46	F	NA	Pheochromocytoma
13	Celik, et al.[19]	43	M	17 yrs	Bladder carcinoma
14	Akpolat, et al.[20]	49	M	At diagnosis	Lung cancer
15	Kötter, et al.[21]	32	M	3 yrs	Kaposi's sarcoma
16	Baltaci, et al.[22]	51	F	19 yrs	Bladder carcinoma
17	Nishimura, et al.[23]	52	M	At diagnosis	Hilar bile duct cancer
18	Satolli, et al.[24]	67	M	8 yrs	Merkel cell carcinoma
19	Kwon, et al.[25]	40	F	7 yrs	Hepatic leiomyosarcoma
20	Lee, et al.[26]	40	M	12 yrs	Colon carcinoma
21	Kammori, et al.[27]	72	F	15 yrs	Breast carcinoma
22	Mezalek, et al.[28]	44	M	10 months	Kaposi's sarcoma
23	Meyer, et al.[29]	52	M	-32 yrs	Lung cancer
24	Chargari, et al.[30]	61	F	NA	Breast carcinoma
25	Yamada, et al.[31]	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.[35] 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 maligancy	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.[32] 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.[8]

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.[31] 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.[26] 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.[37] Therefore, the possibility of cancer development from an ulcer scar due to intestinal BD should be carefully considered.[31]

Long-term cyclophosphamide therapy is reported to be associated with the development of anaplastic bladder carcinoma in BD patients.[19,33] It is well known that the risk of bladder carcinoma increases with cumulative doses of cyclophosphamide and that the histology is always high grade.[19] 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.[21,28,34] 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.[38] 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,[39,40] which may be a consequence of therapeutic immunosuppression.[41] 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.[33] Similarly, a study from Korea, compared the characteristics of treatment including immunosuppressants but found no significant difference between BD patients with or without malignancy.[32] 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.[42] 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 TFGBR1*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.

Our study has several limitations. Since it was conducted in a single center in Korea, the sample size was relatively small. The data in our study were obtained only from the Department of Dermatology despite the fact that BD patients usually visit several departments due to their various symptoms. This could lead to possible recruitment bias. Moreover, the selection bias could have been amplified by the fact that the comparison was not performed on a case-to-case basis between BD patients and the corresponding normal population in terms of the period that the malignancy developed. Although 1 patient had severe BD with symptoms including gastrointestinal and neurological involvement, the symptoms of other patients were mild and did not require immunosuppressive therapy. Furthermore, only 27% of our BD patients associated with malignancy had ocular involvement, which is reported in approximately 70% of BD patients.[1] The methodology of our study is limited by its retrospective nature and lack of a genetic analysis. Further studies about other candidate genetic polymorphisms may be required to clarify the mechanism of carcinogenesis in BD.

In conclusion, cancer morbidity is significantly lower in BD patients than the general Korean population. However, further investigation, particularly multicenter surveys, are nec-

essary to verify the correlation between BD and malignancy.

REFERENCES

1. Sakane T, Takeno M, Suzuki N, Inaba G. Behçet's disease. N Engl J Med 1999;341:1284-91.
2. Direskeneli H. Autoimmunity vs autoinflammation in Behcet's disease: do we oversimplify a complex disorder? Rheumatology (Oxford) 2006;45:1461-5.
3. Pankhurst T, Savage CO, Gordon C, Harper L. Malignancy is increased in ANCA-associated vasculitis. Rheumatology (Oxford) 2004;43:1532-5.
4. Szekanecz Z, Szekanecz E, Bakó G, Shoenfeld Y. Malignancies in autoimmune rheumatic diseases - a mini-review. Gerontology 2011;57:3-10.
5. Liang JA, Sun LM, Yeh JJ, Lin WY, Chang SN, Sung HC, et al. Malignancies associated with systemic lupus erythematosus in Taiwan: a nationwide population-based cohort study. Rheumatol Int 2012;32:773-8.
6. Abu-Shakra M, Guillemin F, Lee P. Cancer in systemic sclerosis. Arthritis Rheum 1993;36:460-4.
7. So MW, Koo BS, Kim YG, Lee CK, Yoo B. Idiopathic inflammatory myopathy associated with malignancy: a retrospective cohort of 151 Korean patients with dermatomyositis and polymyositis. J Rheumatol 2011;38:2432-5.
8. Kaklamani VG, Tzonou A, Kaklamanis PG. Behçet's disease associated with malignancies. Report of two cases and review of the literature. Clin Exp Rheumatol 2005;23(4 Suppl 38):S35-41.
9. Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's Disease. Lancet 1990;335:1078-80.
10. Mizushima Y. [Revised diagnostic criteria for Behçet's disease in 1987]. Ryumachi 1988;28:66-70.
11. Tagami H, Makimoto K, Yamazaki M, Kodera M. [Unusual case of malignant pharyngeal granuloma--with symptoms resembling Behcet's syndrome]. Hifuka Kiyo 1970;65:253-61.
12. Tamaoki N, Habu S, Yoshimatsu H, Tsuchiya M, Watanabe H. Thymic change in Behçet's disease. Keio J Med 1972;21:201-13.
13. Hamza MH. Cancer complicating Behçet's disease treated with chlorambucil. Ann Rheum Dis 1986;45:789.
14. Kamata T, Yamaguti A, Fusida S, Ishida T, Katou M, Sekino H, et al. A case report of the development of intestinal Behcet disease immediately after sigmoidectomy for sigmoid cancer. Jpn J Gastroenterol Surg 1988;21:2331-4.
15. Oishi S, Koga B, Sasaki M, Umeda T, Sato T. Pheochromocytoma associated with Behçet's disease. Jpn J Clin Oncol 1989;19:283-6.
16. Murata I, Omagari K, Nishihata S, Kamiya T, Imanishi T, Tanaka Y, et al. [A case of Behçet disease associated with hepatocellular carcinoma]. Gan No Rinsho 1989;35:625-31.
17. Muramatsu M, Kotake S, Yoshikawa K, Sasamoto Y, Matsuda H, Yamawaki S. The development of malignant rhabdoid tumor in a patient with Behçet's disease treated with ciclosporin. Graefes Arch Clin Exp Ophthalmol 1998;236:798-9.
18. Bethea L, Khan S. Behçet's disease and pheochromocytoma. J S C Med Assoc 1999;95:295-8.
19. Celik I, Altundağ K, Erman M, Baltali E. Cyclophosphamide-associated carcinoma of the urinary bladder in Behçet's disease. Nephron 1999;81:239.
20. Akpolat T, Yildiz L, Akpolat I, Bekir Selcuk M, Ozbek N, Yücel I. Small-cell carcinoma as a cause of superior vena cava syndrome in a patient with Behçet's disease. Respiration 2000;67:593.
21. Kötter I, Aepinus C, Graepler F, Gärtner V, Eckstein AK, Stübiger N, et al. HHV8 associated Kaposi's sarcoma during triple immunosuppressive treatment with cyclosporin A, azathioprine, and prednisolone for ocular Behçet's disease and complete remission of both disorders with interferon alpha. Ann Rheum Dis 2001;60:83-6.
22. Baltaci S, Gögüs C, Karamürsel T, Tulunay O. Invasive bladder carcinoma in a patient with Behçet's disease. Int J Urol 2003;10:669-71.
23. Nishimura K, Fujiki R, Hirotsu J, Ueda T, Nakamura E, Yoshidomi M, et al. A case of hilar bile duct cancer with intestinal Behçet's disease. Kurume Med J 2004;51:169-73.
24. Satolli F, Venturi C, Vescovi V, Morrone P, De Panfilis G. Merkel-cell carcinoma in Behçet's disease. Acta Derm Venereol 2005;85:79.
25. Kwon KM, Jang BK, Chung WJ, Park KS, Cho KB, Hwang JS, et al. [A case of primary hepatic leiomyosarcoma with intrahepatic and abdominal subcutaneous metastasis in Behcet's disease]. Korean J Hepatol 2005;11:386-91.
26. Lee JE, Sohn JW, Lee KH, Park YS, Kim KH, Choi JW, et al. Colon Cancer in Behcet's Disease. Yeungnam Univ J Med 2006;23:124-30.
27. Kammori M, Tsuji E, Ogawa T, Takayoshi N, Kurabayashi R, Takubo K, et al. The pathological findings of vasculitis simultaneously occurring with carcinoma, invasive breast carcinoma in a patient with Behçet's disease. Breast Cancer 2006;13:378-81.
28. Mezalek ZT, Harmouche H, Attar NE, Serraj K, Aouni M, Adnaoui M, et al. Kaposi's sarcoma in association with Behcet's disease: case report and literature review. Semin Arthritis Rheum 2007;36:328-31.
29. Meyer J, Wahidi M, Shofer S, Evans J, Crawford J, Kelsey CR. Formation of a bronchoesophageal fistula following concurrent radiation and chemotherapy for lung cancer in the setting of Behçet's disease. J Thorac Oncol 2008;3:1361-2.
30. Chargari C, Kirova YM, Fourquet A, Campana F. Severe acute radiation-related skin toxicity in a breast cancer patient with Behçet's disease. Radiother Oncol 2009;91:139.
31. Yamada M, Shiroeda H, Nomura T, Hayashi R, Sato K, Tsutsumi M, et al. Colon cancer arising in an ulcer scar due to intestinal Behçet's disease. Intern Med 2011;50:429-32.
32. Ahn JK, Oh JM, Lee J, Koh EM, Cha HS. Behcet's disease associated with malignancy in Korea: a single center experience. Rheumatol Int 2010;30:831-5.
33. Cengiz M, Altundag MK, Zorlu AF, Güllü IH, Ozyar E, Atahan IL. Malignancy in Behçet's disease: a report of 13 cases and a review of the literature. Clin Rheumatol 2001;20:239-44.
34. Shahram F, Daneshmandi S, Bayan N, Nadji A, Akbarian M, Davatchi F. Behcet's disease and malignancy, report of 11 cases. In: Bang D, Lee E-S, Lee S, editors. Behcet's disease. Seoul: Design Mecca Publishing Co.,; 2000. p.515-9.
35. Kural-Seyahi E, Fresko I, Seyahi N, Ozyazgan Y, Mat C, Hamuryudan V, et al. The long-term mortality and morbidity of Behçet syndrome: a 2-decade outcome survey of 387 patients followed at a dedicated center. Medicine (Baltimore) 2003;82:60-76.
36. Bang D, Lee J-H, Lee E-S, Lee S. Ten Cases of Behcet's disease associated with Tumor. In: Bang D, Lee E-S, Lee S, editors. Behcet's disease. Seoul: Design Mecca Publishing Co.; 2000. p.526-8.
37. Rubin DC, Shaker A, Levin MS. Chronic intestinal inflammation:

inflammatory bowel disease and colitis-associated colon cancer. Front Immunol 2012;3:107.
38. Lioté F, Pertuiset E, Cochand-Priollet B, D'Agay MF, Dombret H, Numéric P, et al. Methotrexate related B lymphoproliferative disease in a patient with rheumatoid arthritis. Role of Epstein-Barr virus infection. J Rheumatol 1995;22:1174-8.
39. Harada M, Kumemura H, Fujita A, Yanagimoto C, Harada R, Hashimoto O, et al. A human T-cell lymphotropic virus type-1 (HTLV-1) carrier complicated with various autoimmune diseases including primary biliary cirrhosis. Hepatol Res 2005;31:116-9.
40. Chen MR. Epstein-barr virus, the immune system, and associated diseases. Front Microbiol 2011;2:5.
41. Zandman-Goddard G, Shoenfeld Y. Infections and SLE. Autoimmunity 2005;38:473-85.
42. Kaklamani VG, Sadim M, Koumantaki Y, Kaklamanis P, Pasche B. Role of polymorphisms in Adamantiades-Behçet's disease. J Rheumatol 2008;35:2376-8.