Cukurova Medical Journal

Araştırma Makalesi / Research Article

Retrospective Analysis of Cancer with Behcet's Disease: Single Center Experience

Behçet Hastalığı ve Kanser İlişkisi: Retrospektif Analiz Tek Merkez Deneyimi

Berna Bozkurt Duman[1], Ismail Oğuz Kara[1], Eren Erken[2]

[1]Cukurova University Medical Faculty Department of Medical Oncology and [2]Department of Rheumatology. ADANA

Cukurova Medical Journal 2014;39(1):19-25.

ÖZET

Amaç: Behçet Hastalığı vaskülitik bir hastalıktır. Behçet Hastalığı ile kanser birlikteliği çok sık değildir. Biz çalışmamızda Behçet Hastalığı kanser ilşkisini araştırdık.

Materyal ve Metod: 2005-2010 yılları arasında takip edilmiş 105 Behçet Hastası çalışmaya alındı. Histopatolojik olarak konfirme edilmiş malignensisi olan hastalar belirlendi.

Bulgular: Bu takip süresinde klavuzlara uygun olarak düzenli taramaları yapılan hastalardan sadece birinde malignensi gözlendi. Bu hasta 55 yaşında meme kanseri tanısı aldı ve 16 yıl kolşisin kullanımı mevcuttu. Meme kanserine yönelik olarak modifiye radikal mastektomi ve 4 kür doksorubisin; siklofosfamid kombinasyonu uygulandıktan sonra tedaviye Tamoksifen ve LHRH anologu ile devam edildi.

Sonuç: Bazı romatolojik hastalıklar kanser gelişimine predispozisyon yaratabilir. Hastalığın natürü ve kullanılan immunsupresif ilaçlar bundan sorumlu olabilir. Bizim çalışmamızda direk böyle bir ilişki gösterilemedi. Ama diğer bir yandan önemle vurgulanması gereken Behçet Hastalığı ile malignensi birlikteliğinde her 2 hastalığın birlikte dikkatlice yönetimidir.

Anahtar Kelimeler: Behçet Hastalığı, kanser, meme

ABSTRACT

Purpose: Behçet's disease (BD) is a vasculitis of unknown origin. In autoimmune and vasculitic disorders the risk of malignancies has been extensively studied. In BD patients more than hundred cases associated with malignancies have been published. However, the direct relationship with BD has not been proved. We aimed to to investigate the incidence of malignancies in BD patients

Material and Methods: Here in we assessed 105 cases retrospectively between 2005-2010 with BD diagnosed according to International Study Criteria (ISG) . The patient's data were reviewed for development of histopathologically confirmed malignancy

Results: One of our 105 patients with BD was found to have solid tumor in the rate of 0.9 %. The remaining 104 patients with BD were in follow up without any malignancy in this period. The malignancy that we reported was invasive right breast carcinoma in a 55-year-old woman with BD. A radically modified right mastectomy and axillary lymphadenectomy were performed and postoperative doxorubicin, cyclophosphamide therapy for four cycles and hormonal therapy with tamoxifen and leuprolide acetate was administered as adjuvant therapy. This patient had a history of 16 years colchicine usage as medication for BD.

Conclusion: The rheumatologic diseases can predispose malignancy, the autoimmune nature of BD or the immunosupressive medicines could be possible causes of this carcinoma. However, in our study only one patient had malignancy. The another point of view; management and also prevention of cancer with BD is important entity.
Key Words: Behcet's disease, cancer, breast

INTRODUCTION

BD was first described in 1937 by Hulusi Behçet[1]. BD is frequently seen in the Middle East; Japan and Mediterranean countries[2]. The first was defined as BD, recurrent aphtous ulcers of the mouth and genitelia and relapsing uveitis was the classical triad[1]. Since then the spectrum of BD has been expanded. It is a multisystem disorder that is characterized by vascular, neurological, ocular, gastrointestinal, mucocutaneous, and articuler abnormalities. The risk of cancer in the presence of connective tissue disease and other vasculitides has shown to be increased however, the association of malignant disease with BD is rare, although there are few case reports in the literature[3].

MATERIAL and METHODS

Patient characteristics

The present study included 105 patients diagnosed with BD that were referred to Cukurova University, Medical Faculty, Medical Rheumatology Department between 2005 and 2010. Inclusion criteria were as follows: BD was diagnosed according to International Study Criteria (ISG) and the patients' data were reviewed for development of histopathologically confirmed malignancy. All of the patients were analysed for their family history of cancer. Active screening was performed for prostate and breast cancer. Prostate spesific antigen levels were assessed for men at age 50 and older than 50 years old.

Mamography was performed anually for the women at age 40 and older than 40. Patients were at follow up every 3 months. Anamnesis, physical examination, systematic evaluation, blood count and biochemistry, erytrocyte sedimantation rate, C-reactive protein were detected. Patients who were not followed up regularly were excluded from study. If suspicious findings were found the patients detected in the guidance of this findings.

Statistical methods

The SPSS 18.0 package program was used for the statistical analysis of data. Categorical measurements were summarised as numbers and percentages, whereas numeric measurements were given as average and standard deviation (SD). The x^2 test was performed to compare categorical measurements between different groups The level of statistical significance was put at 0.05 for all tests.

RESULTS

One hundred and five patients with BD who have admitted to our hospital between 2005-2010 were analyzed retrospectively. The median time for BD diagnosis was 10 months (range 1- 240 months). Median age was 42 (range 21- 63), 66 (62.9%) patients were men and 39 (37.1%) patients were women. All of the patients used colchicine in different periods (range 1-216 months). Azothiopurine, corticosteroid, cylophosphamide and cyclosporine have been used in some patients. Three patients were detected for suspicious mass(2,8%). Only one patient was diagnosed malignancy in this period. The patient whom 55-year-old woman was presented with recurrent painful oral erosive lesions of the oral mucosa, recurrent genital ulcers, acneiform skin lesions and arthritis. Pathergy test was found positive. BD was diagnosed according to International Study Criteria (ISG)[4]. BD had been diagnosed 16 years ago and therefore she had been given 0.5 mg colchicine three times a day since that time. She had any history of another

systemic diease. BD activity have been assessed with Behçet Disease Current Activity Form (BDCAF)[5], disease was inactive.

The patient was administered to our department with right breast mass. Mamography was performed. Breast mass was found on mamography. The biopsy was revealed invasive ductal carcinoma of the breast. A radically modified right mastectomy and axillary lymphadenectomy were performed. Lymph node metastasis was not found on pathology examination so adjuvant radiotherapy was not recomended to the patient. Immunohistochemial staining for estrogen (ER) and progesterone (PR) and HER2-neu were performed. ER and PR were expressed in 80 % and 20 % respectively and HER2-neu was negative. The disease stage was determined to be pathologically T2N0M0. Postoperative doxorubicin, cyclophosphamide therapy given for four cycles and then hormonal therapy with tamoxifen and leuprolide acetate were given as well. Patient is disease free for 16 months. She had any history of trombosis.

DISCUSSION

The risk of cancer in the presence of variety of rheumatic disease and other vasculitides have shown to be increased. A high risk of malignancy has been observed in rheumatoid arthritis, systemic sclerosis, Sjögren's syndrome and systemic lupus erythematosus[6-9]. The relationship between BD and malignancy still remains controversial[10]. It was reported that incidence of malignancy in BD patients was not different from that observed general population [3,11,12]. The underlying cause of BD is unknown. As with other autoimmune diseases, the disorder may represent aberrant immune activity triggered by exposure to an agent, perhaps infectious, in patients with a genetic predisposition to develop the disease and these different factors can cause the cancer occurence[13]. BD is a wide spectrum of vasculitis, BD may also raise the risk of cancer[3]. The autoimmune nature of BD or the immunosuppressive medicines that are used for its management are regarded as probable causes of malignat change in most cases. Most of the patients use colchicine; a medicine that inhibits leukocyte migration and reduces the production of lactic acid by leukocytes[2]. In many of the previous reports authors blamed the use of immunosupressive drugs such as chlorambucil, cyclophosphamide or colchine, for lymphoma transformation in BD[3]. There was also a report that polymorphism of TGF-ß receptor gene in BD may have a protective role in development of malignancy[14]. Recent report suggest that ANCA associated vasculites are associated with an increased risk of malignancy[15].

Presented literature data showed that there is an increased risk of malignancy in connective tissue disorders although there is no exact literature data about BD and malignancy[3,6-8]. Solid tumors with BD presented in the world literature showed that in most intances the authors considering their cases to be incidental. There is no clear evidence that autoimmune disorders or immunosuppresive drugs cause epithelial cancer or sarcoma, Cengiz M. et al have considered malignancies as sporadic concurrent with BD, excluding the patient with bladder cancer with history of prolonged use of cyclophosphamide in their review[3].

Kyong Jet al. had reported 32 patients who had malignancy with BD there were no significant differences in the clinical charateristics between patients with or without malignancy for their report[10].

On the other hand the autoimmune nature of BD or the immunosupressive medicines that are used for its management were regarded as probable causes of malignant change in most cases[10]. The present patient was also treated with for 16 years colchicine, a drug that inhibits leukocyte migration and reduces the production of lactic acid by leukocytes[10]. This drug might have contributed to the development of malignancy in this patient. Further studies will be required to

ascertain the pathogenetic relation between BD and malignancy and the prevalence of malignancy in BD.

Management of malignancies in these patients is an important issue because of reported high complication rate after surgery like wound infection[3], and lack of knowledge about the morbidity of radiation therapy and chemotherapy[3].

Management of breast cancer with BD is important. Five cases of breast cancer with BD reported in the literature to date[2,3,10] (Table1). Surgery, chemotherapy, radiotherapy, endocrine therapy are the important compenents of breast cancer treatment. There are some reports of high surgical morbidity in BD[16,19]. Cengiz M.et al. have reported 13 cases with BD, 7 of them underwent surgery; the surgical treatment of malignancies in the presence of BD seems to be safe for their report[3]. Kammori et al. reported a case with wound infection and skin necrosis over a wide area after mastectomy but no progression of the BD symptoms. The wound morbidity after mastectomy might have been related to BD and/or prednisolone therapy according to their report[3]. In our case there was no complication after surgery and no progression of the BD symptoms. BD was inactive; and under control with colchicine treatment in our patient ; because of this reason any complication(delay of the wound healing, wound infection ext.) has been occurred after surgery.

Most cases of BD associated with malignancies were treated with cytotoxic chemotherapy regimens and no authors suggested any increase in chemotherapy toxicity. Cengiz et al. reported 9 cases treated with chemotherapy by different schedules and agents. Toxicity of chemotherapy was similar to the patients not bearing such a risk factor in their report. The authors agree that chemotherapy can be administered without any increase in morbidity in BD patients[3]. In our present case; toxicity of chemotherapy was similar to the other patients without BD.

There were some reports about collagen vascular disease, especially in rheumatoid arthritis, predisposes patients to increased toxicity from therapeutic irradiation but there was no data about increased radiation therapy morbidity in the presence of BD with malignancy in the literature respectively[3,18,19]. Radiotherapy was not given to the our patient.

On the other side tamoxifen therapy was given to our patient. A number of studies, including the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview analysis and the large Breast Cancer Prevention Trials, have demonstrated that tamoxifen use is associated with an increased rate of venous thromboembolic events, especially within the first two years[16]. In the five-year, randomized, double-blind, placebo-controlled International Breast Cancer Intervention Study (IBIS-1), involving 7139 patients, use of tamoxifen was associated with an increased risk of developing a major venous thromboembolic event (odds ratio 2.1, 95% CI: 1.1-4.1) [21]. However, venous disease is more common than arterial in BD. Superior and inferior vena cava occlusion, Budd-Chiari syndrome, dural sinus thrombosis, and other venous obstructive lesions can occur in addition to the more common superficial and deep vein thrombosis. Venous thrombosis is often an early feature of BD. Recurrent thrombosis of the lower extremities may lead to a post-thrombophlebitic syndrome [22]. In one study of 493 cases of BD, 53 were found to have one or more large vessel thrombosis[19]. A case-control study of 73 Behcet's patients found a 14-fold increased risk of venous thrombosis compared to controls [24].Venous disease may also be more common in patients with a positive pathergy test or ocular involvement. A study of 2319 Turkish patients with BD's found a prevalence of vascular disease of 14.3 percent[25]. In our case tamoxifen therapy was given to the patient. Pathergy test was found positive . Venous disease may also be more common for our patients for these reasons . We found no data about prophylaxis for this patients in

the literature. We aimed to follow up the patient carefully about this side effects and informed the patient, and its the first case that emphasize the affinity of trombotic events with usage of tamoxifen in breast cancer with BD. Her disease was inactive for BDCAF and there was any trombosis and history of trombosis because of this reason any prophylaxis for trombosis was not given to the patient.

BD and malignancy could be coincedental. The mortality rate from cancer in BD is not very low. Saadoun et al., have reported main causes of death from BD included major vessel disease (mainly, arterial aneurysm and Budd-Chiari syndrome) (43.9%), cancer and malignant hemopathy (14.6%), central nervous system involvement (12.2%), and sepsis (12.2%) from the cohort of 817 patients in their study[26]. At the same time its important to know the management of cancer in patient with BD. We suggest that oncologists should be aware for screening of cancer and all complications while using chemotherapy, radiotherapy, endocrine therapy and targeted therapies in patient with BD.

Table 1:Breast Cancer with BD.

Age (years)	Sex	BD Symptoms	Interval Months	Drug used for BD	Management of cancer	References
43	F	O,G,S	120	Colchicine Prednisolone	MRM+AD CTx,RT,Tmx	3
47	F	O,P,S,A	45	Colchicine Prednisolone	MRM CTx	10
38	F	O, G, P	0	Colchicine	MRM CTx	10
34	F	O, G, S	38	Colchicine	Partial mastectomy CTx	10
72	F	O, G, S	528	Colchicine	MRM+AD Anastrazol	2
55	F	O, G, S, A	180	Colchicine	MRM+AD TMX, Leuprolide acetate	Our case

F:Female, O: Oral ulcer, G: Genital ulcer, S: Skin lesions, A: Arthritis, MRM: Modified radicallly mastectomy AD: Axillary dissection, CTx: Chemotherapy

REFERENCES

1. Behçet H. Uber rezidivierende aphtose, durch ein virus verursachte Geschwure am Mund; am Auge und an den Genitalien. Dermatol Wschr. 1937;105:1152
2. 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.
3. Cengiz M, Altundağ MK, Zorlu AF, Güllü IH, Özyar 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.
4. International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's disease.Lancet. 1990;335;1078-80.
5. Hamuryudan V, Fresko I, Direskeneli H et al. Evaluation of the Turkish translation of a disease

activity form for Behçet's syndrome. Rheumatology. 1999;38:734–6.

6. Black KA, Zilko PJ, Dawkins RL, Armstrong BK, Mastaglia GL. Cancer in connective tissue disease. Arthritis Rheum. 1982;5:1130-3.

7. Barnes BE, Mawr B. Dermatomyositis and malignancy. A review of the literature. Ann Intern Med. 1976;84:68-76.

8. Canoso JJ, Cohen AS. Malignancy in a series of 70 patients with systemic lupus erythematosus.Arthritis Rheum.1974;17:383-90.

9. Abu-Shakra M, Guillemin F, Lee P. Cancer in systemic sclerosis. Arthritis Rheum. 1993;36:460-4.

10. 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. Epub 2009 Dec 17.

11. 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;23:35-41.

12. 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.

13. Direskeneli, H. Behçet's disease: infectious etiology, new autoantigens, and HLA-B51. Ann Rheum Dis. 2001;60:996.

14. Kaklamani VG, Sadim M, Koumantaki Y, Kaklamanis P, Pasche B. Role of polymorphisms in Adamantiades-Behçet's disease.J Rheumatol. 2008;35:2376-15. Epub 2008 Oct 15.

15. Pankhurst T, Savage CO, Gordon C, Harper L. Malignancy is increased in ANCA-associated vasculitis. Rheumatology (Oxford). 2004; 43(12):1532-5.

16. Sayek I, Aran O, Uzunalimoglu B, Hersek E. Intestinal Behçet's disease: surgical experience in seven cases. Hepatogastroenterology. 1991;38:81-3.

17. Paccagnella A, Turolla LM, Zanardo G, Cipolotti G, Rocco F, Salandin V, et al. Fatal progression of Behçet's disease after cardiac surgery.Thorac Cardiovasc Surg. 1989;37:320-1.

18. Fleck R, McNeese MD, Ellerbroek NA, Hunter TA, Holmes FA. Consequences of breast irradiation in patients with pre-existing collagen vascular diseases. Int J Radiat Oncol Biol Phys. 1989;17:829-33.

19. Ross JG, Hussey DH, Mayr NA, Davis CS. Acute and late reactions to radiation therapy in patients with collagen vascular diseases. Cancer. 1993;71:3744-52.

20. Hernandez, RK, Sorensen, HT, Pedersen, L, et al. Tamoxifen treatment and risk of deep venous thrombosis and pulmonary embolism: a Danish population-based cohort study. Cancer. 2009;115:4442.

21. Vogel, VG, Constantino, JP, Wickerham, DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes. JAMA. 2006;295:2727.

22. Seyahi, E, Melikoglu, M, Yazici, H. Clinical features and diagnosis of Behcet's syndrome. Int J Adv Rheumatol. 2007;5:8.

23. Bayraktar Y, Balkanci, F, Bayraktar, M, Calguneri M,et al. Budd-Chiari syndrome: A common complication of Behcet's disease. Am J Gastroenterol. 1997;92:858.

24. Ames, PR, Steuer, A, Pap, A, Denman, AM. Thrombosis in Behcet's disease: a retrospective survey from a single UK centre. Rheumatology (Oxford). 2001;40:652.

25. Sarica-Kucukoglu R., Akdag-Kose A, Kayabal M, Disci R et al. Vascular involvement in Behcet's disease: a retrospective analysis of 2319 cases. Int J Dermatol. 2006;45:919.

26. Saadoun D, Wechsler B, Desseaux K, Le Thi Huong D, Amoura Z, Resche-Rigon M, Cacoub P. Mortality in Behçet's disease. Arthritis Rheum. 2010;62: 2806-12.

Yazışma Adresi / Address for Correspondence:
Dr. Berna Bozkurt Duman
Çukurova University Medical Faculty,
Department of Oncology,
01330 Balcalı / ADANA
e mail: berboz@hotmail.com

geliş tarihi/received :27.09.2013
kabul tarihi/accepted:14.10.2013