Behçet's disease associated with malignancies. Report of two cases and review of the literature

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Received on September 30, 2004; accepted in revised form on April 1, 2005.

Clin Exp Rheumatol 2005; 23 (Suppl. 38): S35-S41.

Key words: Behçet's disease, malignancies.

ABSTRACT

Objective. *To investigate the incidence of malignancies in a cohort of Behçet's disease patients and review the world literature.*

Methods. *Our database of 128 patients was searched and the age standardized rate (ASR) for cancer was calculated. Furthermore, we performed a MEDLINE search from 1970 through 2003, as well as, a search in the proceedings of international conferences for cases of malignancies associated with Behçet's disease.*

Results. *Two of our 128 patients with Behçet's disease were found to have solid tumors. One male had lung cancer and the other female had kidney cancer. The ASR for cancer cases in our population was investigated and it was found to be 1,600 per 100,000 in 10 years. The ASR for cancer cases in Greece according to WHO is 272.51 per 100,000 per year and therefore 2,725 per 100,000 in 10 years.*

In the world literature 112 cases of malignancies associated with Behçet's disease were found: Sixty five cases were of male patients and 46 of female with 1 case of unknown gender. The solid malignancies associated with Behçet's disease included cases of bladder, breast, uterus, thyroid and stomach cancer, whereas haematological malignancies included leukemia, myelodysplastic syndrome, lymphoma, multiple myeloma, Hodgkin's disease and lymphosarcoma. The treatment administered in these patients with their disease is also reported.

Conclusion. *The age standardized rate of cancer in our population was lower than that of the general population in Greece, although the difference was not statistically significant. However, there is discrepancy in the world literature and the possibility of development of malignancies in Behçet's disease patients should not be ignored.*

Introduction

Behçet's disease (BD) is a chronic, relapsing multi-system disorder. The principal manifestations are: oral aphthous ulcers, genital ulcers, skin lesions, eye, joint, neurological and vascular manifestations (1-3). Rare clinical findings include: cardiac, pulmonary and renal disorders (1-3), as well as, epididymoorchitis (4). The epidemiology of BD in most parts of the world has recently been reviewed (5-7). The pathogenesis of the disease has not been elucidated (1,2,8), although genetic factors, environmental agents and immune aberrations have been implicated (1, 2, 9). Immune abnormalities, particularly increased production of some antibodies have been reported in patients with BD (9). However, Raynaud's phenomenon, polyserositis, Sjögren's syndrome, neutrophil, antiphospholipid and antinuclear antibodies, which characterize an autoimmune disease, have not been associated with BD (10,11). Several studies have shown that arterial and venous involvement of all size vessels are characteristic findings of the disease (12-16). Given the above vasculitic manifestations, BD is classified among the wide spectrum of systemic vasculitides (14).

In autoimmune and vasculitic disorders the risk of malignancies has been extensively studied. In patients with rheumatoid arthritis (RA), both solid and haematopoietic malignancies have been reported (17,18). In Western Europe and in the United States the risk is related primarily to the development of haematopoietic neoplasms, whereas in Japanese patients oropharyngeal malignancies are more commonly seen (19). The discrepancy may have to do with environmental and dietary differences between the different regions. Patients with systemic lupus erythematosus (SLE) have increased risk of developing both solid tumors and haematologic

malignancies (19-23). In patients with progressive systemic sclerosis (scleroderma) increased risk of malignancy was found (24), particularly bronchoalveolar carcinoma (23). The incidence of malignancy in dermatomyositis and polymyositis (DM,PM) has been the subject of multiple publications (25-29). Among 618 patients with DM and PM, 198 cases of cancer were reported (26), pointing toward a predisposition to the development of malignant disorders in such patients. Wegener's granulomatosis (30), Henoch-Schönlein purpura (31) and other vasculitides (32) have also been associated with increased risk of malignancies. In BD patients more than hundred cases associated with malignancies have been published. However, the direct relationship with BD has not been proved.

The development of malignancies in autoimmune diseases and vasculitides could be related to abnormalities in immune regulation, T cell deficiency, or the overproliferation of B cells, which may trigger a malignant transformation of cells (33). The association of malignancies with BD may represent a paraneoplastic syndrome (34) or may be related to the above mentioned disturbances (33). Furthermore, medications that BD patients are chronically on may also predispose to the development of neoplastic diseases.

Our primary aim in this report is to share our own experience on the association of malignant neoplasms and BD by searching our database of 128 patients with a median follow up of 10 years. Furthermore, we will review the cases of malignancies associated with BD present in the scientific literature.

Material and methods

Our BD patient cohort has been prospectively collected since 1990, during which time we have enrolled 128 patients. All patients met the International Study Group (ISG) criteria for BD (35). In 2000, two of our patients died.

Case 1

A 44-year-old man at the age of 34 developed oral aphthous ulcers and pseudofolliculitis. Four weeks later anterior uveitis was diagnosed and two genital ulcers appeared. These lesions were recurrent. Pathergy test was positive and the diagnosis of BD was established. He was treated with colchicine and prednisolone 30 mg/d which was tapered slowly to 7.5 mg/d. Since then every 3-4 months most of the clinical manifestations would recur and the dose of prednisolone would be increased. The time of cancer diagnosis he presented with small oral aphthae, one genital ulcer and arthritis of the right knee. In March 1999 he presented with neurological symptoms and a brain MRI showed a solid mass measuring 3.5 cm at the lower left parietal area. This was a metastatic tumor originating from his lung and a biopsy of the lung tumor showed to be a microcytic type adenocarcinoma with large cells. The patient was treated with carboplatin, paclitaxel and radiotherapy. Several months later he died. The patient developed lung cancer 10 years after the diagnosis of BD. He had a 40 pack/year smoking history.

Case 2

A 60-year-old housewife at the age of 17 developed oral and genital ulcers. They were followed by arthritis of the lower extremities. At the age of 20 those symptoms recurred several times and anterial uveitis was diagnosed. Five years later erythema nodosum and recurrences of oral and genital ulcers developed. Pathergy test was negative and she had HLA B5 (51). The diagnosis of BD was established and began treatment with prednisolone 30 mg/d and chlorambucil 6-10 mg/d for 3 years. Two years later hypopyon iritis was diagnosed and received prednisolone 20 mg/d and azathioprine 100-200 mg/d for 8 years. At the time of diagnosis of cancer she suffered from chronic uveitis, recurrent erythema nodosum and oral aphthae. At the age of 59 she developed haematuria and an infiltrating carcinoma of the left kidney stage IV was diagnosed 43 years after the diagnosis of BD. She had a 30 pack/year smoking history. She refused any treatment and died two months later with multiple metastases.

In addition, a MEDLINE search from 1970 to 2003 was performed by the use of search headings of «Behçet's disease», «Behçet's syndrome», «Adamantiades-Behçet's disease», «cancer» and «malignancy». Cases from proceedings of international conferences in BD were also included in the analysis.

Statistical section

We wanted to determine whether the incidence of malignancy in our BD population was similar to that of the general population. For this we had to standardize our population since the age distribution of our population was not similar to that of the general population. We calculated the age standardized rate (ASR) for cancer cases in our population which was 1,600 per 100,000 in 10 years. We used the following formula for calculating ASR: ASR = Σ cases (age group)/population (age group) x 100,000 world standard population (age group)/world standard population. According to the WHO the ASR for cancer cases in Greece is 272.51 per 100,000 per year and therefore 2.725 per 100,000 in 10 years (36). After performing a χ^2 test to assess the significance, we found that there was no statistically significant difference between the two populations. Furthermore, we calculated the annual incidence of malignancy in our population of 128 patients with BD and found it to be 156 in 100,000.

Review of the literature

A variety of solid tumors have been reported in the world literature including two of our own. The diagnosis of BD was established according to the criteria reported (96). In a few cases the disease onset was defined as the time when the patient developed the first symptom, while in others when the diagnostic criteria were fulfilled.

1. *Solid tumors (references: (33, 34, 37, 39, 46, 51, 56-58, 61, 62, 65, 73, 82, 85-88, 92, 94)*

Among the 54 cases, 33 were male and 21 female with a median age of 38.9 years (range 13-69). In 51 out of 54 cases BD preceded the diagnosis of solid tumor with a median duration of 9.5 years (range 2 months-43 years). In only two patients malignancy preceded

Table I. Immunosuppressive drugs administered for BD before the diagnosis of solid tumors and heamatological malignancies.

Drug	No of patients
Cyclophosphamide	17
Cyclophosphamide + cyclosporine A	1
Chlorambucil	3
Chlorambucil + cyclosporine A	1
Chlorambucil + azathioprine	3
Azathioprine + cyclosporine A + Interferon–a	1
Cyclosporine A+ azathioprine	2
Cyclosporine A	2
Chemotherapy	3
Interferon–a	3
Azathioprine + interferon–a	1

the diagnosis of BD, by 4 and 5.6 years respectively. In one patient both diseases developed nearly simultaneously.
A great variety of solid tumors were reported: bladder (7), breast (5), thyroid (4), stomach (4), uterus (3), liver (3), lung (3), colon (3), pancreas (2), ovary (2), basal cell cancer (2), Kaposi sarcoma (2), renal (2), malignant histiocytoma (2) and pheochromocytoma (2). Furthermore, other malignancies such as pharyngeal, malignant rhabdoid tumor, seminoma, teratoma of the uterus, adenocarcinoma of unknown origin, mesenchymal tumor, small cell carcinoma of the lung and cancer of the testis have been reported. The majority of these cases (44/54) were published within the past 13 years (1991-2003).
Thirteen BD patients who developed solid tumors were treated with cyclophosphamide. Among them 5 had bladder cancer and the other a variety of other tumors (malignant granuloma of pharynx, malignant histiocytosis, pancreas adenocarcinoma, rectum adenocarcinoma, breast cancer, thyroid cancer and seminoma, malignant mesenchymal tumor (the last one received also IFN-α). Two patients, one with adenocarcinoma of unknown origin and the other with pulmonary cancer were treated with chlorambucil. Renal carcinoma was diagnosed in a patient treated with chlorambucil and azathioprine. Kaposi sarcoma was diagnosed in a patient who received azathioprine, cyclosporine A and interferon-α. Malignant rhabdoid tumor, and pancreas adenocarcinoma were found in 2 patients treated with cyclosporine A. Chemotherapy was administrated in two patients with BD who developed bladder cancer and malignant histiocytosis. Uterine adnexia teratoma was found in a patient who was treated with IFN-a. Colchicine and corticosteroids each one alone or in combination with other medications in 30% and 43% respectively was administrated in patients who developed various malignancies. A variety of tumors were diagnosed in 10 patients in whom the treatment was not reported. Furthermore, two more patients with solid tumors (ovarian cancer, breast cancer) did not received any drug.
The drugs given for BD before the development of solid tumor are reported (Table I).

2. *Haematological malignancies (references: 33, 38, 40-45, 47-50, 52-54, 55, 59, 60, 62-64, 66-72, 74-81, 83, 84, 87, 89-94)*

Sixty cases of BD associated with haematological malignancies were reported in the world literature of which 32 males and 27 females, whereas in one patient age and sex were not reported. Their median age was 44.1 years (range 21-72 years).
Behçet's disease was associated in 24 cases with leukemia, 18 with myelodysplastic syndrome (MDS) and 13 with lymphoma. Multiple myeloma (2), Hodgkins disease (2) and lymphosarcoma (1) were also reported. In 39 cases, BD preceded the diagnosis of malignancy with a median duration of 6.1 years (range 3 months-41 years). Malignancy preceded the diagnostis of BD in 18 cases, 9 with MDS and 9 with leukemia with a median duration of 6.5 years (range 3 months–20 years). In 3 cases both diseases were diagnosed nearly simultaneously.
When examining the different haematological malignancies separately, we found that leukemia was diagnosed in 24 patients, 11 male and 12 female. In 1 patient the sex was not available. The median age was 40.1 years (range 21-62 years). In 14 patients BD preceded the diagnosis of malignancy with a median duration of 3.8 years (range 3 months to 10 years), while in 9 the development of malignancy preceded the diagnosis of BD with a median duration of 4.1 years (range 4 months-6 years). In 1 patient both diseases were diagnosed simultaneously.
Myelodysplastic syndrome was diagnosed in 18 patients associated with BD 11 of which were male and 7 female with a median age of 49.1 years (range 34-72 years).
Behçet's disease preceded the MDS in 7 patients with a median duration of 5 years (range 5 months-8 years) and the malignancy preceded the diagnosis of BD in 9 patients with a median duration of 3.33 years (range 4 months-13 years). In 2 cases both diseases were diagnosed simultaneously.
Malignant lymphoma associated with BD was reported in 13 patients, 7 of which were male and 6 female. Their median age was 7.57 years (range 4 months-20 years) and the locations of the lymphoma were: nasal, intracranial, gastric and intestinal. One patient with lymphosarcoma was also reported. Most of these cases are from Japan and in all patients BD preceded the development of lymphoma.
The treatment administered for BD before the development of neoplasia is reported (Table I).
Four patients with BD were treated with cyclophosphamide and developed acute leukemia, chronic myeloid leukemia, non Hodgkins lymphoma, Hodgkins disease. One patient was treated with cyclophosphamide and cyclosporine A and developed non-Hodgkins lymphoma. Chlorambucil was administrated in a patient who developed MDS. Two patients one with acute leukemia and another with high grade lymphoma were treated for their BD with chlorambucil and azathioprine. Another one on chlorambucil and cyclosporine A developed MDS. Two patients treated with azathioprine and cyclosporine A developed MDS. Azathioprine and interferon-a was given in a patient who developed chronic myeloid leukemia. Two patients with chronic myeloid leukemia were treated with interferon-α. Another with acute myeloid leukemia was treated with chemotherapy. Levamisole, busulfan, hydroxyur-

Table II. Cases of Behçet's disease associated with malignancies in the world (country, year and number of cases).

Years	Japan	Turkey	Iran	Korea	China	USA	Greece	Tunisia	France	Spain	Germany	Italy	England	Total
1961-1970	1													1
1971-1980	3					3			1					7
1981-1990	13	1			3	1		2	1				1	22
1991-2000	13	7	11	10	6	1	4	1	1	3	3	1		61
2001-2003		21				1		1						23
Total	30	29	11	10	9	6	4	4	3	3	3	1	1	114

References: **Japan:** 37, 39, 40, 44, 46, 53-59, 61, 63, 66, 68-70, 74-79, 82. **Turkey:** 47, 73, 80, 85, 88, 92, 94. **Iran:** 87. **Korea:** 33. **China:** 45, 50, 52, 62. **USA:** 38, 41, 42, 49, 86, 91. **Greece:** 81, 90. **Tunisia:** 51, 71, 93. **France:** 35, 43, 60. **Spain:** 64,67,72. **Germany:** 65, 84, 89. **Italy:** 83. **England:** 48.

ea were given in other patients with malignancies. Corticosteroids and colchicine each one alone or in combination with other medications, were administrated in 38% and 25% of patients respectively who subsequently developed various malignancies. In 18 patients with various haematological malignancies the treatment given for BD was not reported by the investigators. Combination of treatment with corticosteroids and or colchicine was very frequent.

The countries and the year of publications of BD associated with malignancies are presented in Table II.

Discussion

We have presented 114 cases of malignancy- associated BD. This is, to the best of our knowledge, the most complete review. A recent review article included at total of 40 cases of malignancies in patients with BD (92). The onset of malignancy may precede, coincide with, or follow the diagnosis of BD.

So far most of the data on malignancies in patients with BD come from case reports. In our patient population of 128 BD patients, 2 developed solid tumors during a 10-year follow up. In other studies the frequency of malignancy in BD varied. In 100 patients with BD from China 6 developed malignancies (62). In 4,130 patients with BD from Iran only 11 cases were associated with malignancies (87). Similarly, a study from Korea including 5,000 patients with BD reported only 10 cases of malignancies (33). Furthermore, in a more recent study of 387 patients with BD, followed-up for 20 years, 8 cases of malignancy were reported (2%) (94) and in 400 patients with BD from Turkey with a 15 year follow up there were no reported malignancies (95). The authors stated that BD may be protective against the development of malignancy and hypothesized that BD patients may possess a protective HLA subtype against malignant transformation (95). However, in another study from Turkey, which included 400 patients followed-up for a median of 9.8 years, 13 cases of malignancy were reported (3.25%) (92).

The incidence of malignancy in BD patients compared with the general population has been reported in only 2 studies. Cengiz *et al.* (92) found 13 cases of malignancies in 400 BD patients, with a median follow up of 9.8 years, which did not differ statistically (x^2test) from the crude annual incidence of malignancies in the general population in Turkey. In the second study (94), among 387 BD patients 8 developed malignancies, in a 20-year follow up period. This gives the annual incidence rate of 103 in 100,000 with a crude yearly cancer incidence of 90 in 100,000 among the general population in Turkey in 1995. None of these studies however have taken into account the age difference between the BD population and the general population. In our study of 128 patients with BD and a 10-year follow up period, 2 of our patients developed a malignant disorder and therefore the annual incidence in our population was 156 in 100,000. In Greece according to the WHO, in the year 2000 there were 36,747 incidence cases of malignancy, making the incidence rate of malignancy in Greece 345 per 100,000. When standardizing our population for age we also found the incidence of malignancy to be lower than in the standardized general population. However, our results did not reach statistical significance.

A factor, which may be associated with neoplasia in BD, is trisomy 8. In 9 out of 14 patients with BD-associated neoplasia, trisomy 8 was found (79). This chromosomal abnormality is found in 8.9-18.4% of patients with MDS (77, 96,97). Thus, the percentage of chromosomal abnormalities in patient with BD associated MDS is markedly higher than in those with MDS alone (77). Trisomy 8 has not been associated with BD. However, in 9 of 18 patients in the literature MDS preceded the development of BD with a median period of 3.3 years (range 4 months-13 years), whereas in 7 patients BD preceded the development of MDS and in two cases both diseases were diagnosed simultaneously (79). Therefore, there is an indirect evidence that trisomy 8 may predispose to BD in a subgroup of MDS patients (79).

Immune mechanisms may also contribute in the development of malignant disorders in patients with BD. More specifically it has been shown that during the course of BD there is an increased number of $\gamma\delta+$ and $\alpha\beta+$ T cells, probably due to a microbial agent, which induces the expression of heat shock protein 65 (HSP65) (98). Lymphocytes, macrophages and neutrophils are activated, and therefore may be responsible for the abnormal clones and the development of B-cell lymphoma (93).

Patients with BD are treated, particularly the refractory cases, with immunosuppressive drugs (99) most of them have been implicated in the development of malignancies. However, there

are several cases of BD associated malignancies in patients who had never received immunosuppressive therapy. In a patient with pheochromocytoma, corticosteroids were administered, while in another patient with the same malignant disorder, there was no history of use of immunosuppressive agents. Both cases may represent a coincidental finding whereas it is plausible that some basic pathophysiologic connection between the two disorders may exist (86). Furthermore chlorambucil and cyclophosphamide, may perhaps be the only drugs used in patients with BD, with convincing evidence for the development of neoplasia.

Immunosuppressive drugs can induce malignancy by two possible mechanisms (84).

1. By the direct effect of the drug on DNAreplicatation.
2. By an indirect effect on cellular regulatory effects.

Other investigators (47, 48) consider that the carcinogenicity of immunosuppressive drugs can be linked to many factors such as: the role of marrow aplasia, chromosomal abnormalities, the potential activation of a leukemogenic virus and the effect of repeated antigen stimulation in the immunosuppressive state.

Conclusion

We have presented two cases with BD-associated malignancy and have summarized the cases reported in the scientific literature. There is limited data on the incidence of malignancy in BD patients; some studies have suggested an increased rate, whereas our study suggests a decrease incidence compared with the general population, although our results did not reach statistical significance. Our small sample size may account for this. Both of our patients who developed malignant disorders had been exposed to environmental carcinogens (cigarette smoking) making it difficult to form assumptions on the association of BD and malignant disorders. Furthermore, few other studies have addressed this topic, and it is unclear whether the incidence of malignancy in BD is greater than that seen in the general population. In patients with BD, treatment with immunosuppressive drugs may coincide with the development of malignant disorders although there is no convincing evidence for this. Another implicating factor may be the immune mechanism behind the pathogenesis of BD.

Since most cases of BD associated with malignancies were reported in the last 13 years, it is unclear whether this represents a true increase in the incidence or whether there has been increased awareness, leading researchers to report such cases. As more potent agents are being used in the treatment of BD, it is possible that those patients live longer than before, making the development of malignant disorders more likely. However, our observations do not support the hypothesis that BD predisposes to malignancy. Large prospective international studies will be able to answer this question.

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