Cytotoxic T-Cell Lymphoma Arising in Behçet Disease

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Abstract
The case of a 49-year-old man with peripheral T-cell lymphoma arising in Behçet disease (BD) is reported. A diagnosis of incomplete BD was made, and the patient was treated with immunosuppressive agents for 9 months. A left perirenal mass emerged, and a computed tomography–guided needle biopsy of the tumor revealed the infiltration of small- and medium-sized lymphoma cells. The cells were positive for CD3, CD8, CD45RO, CD43, granzyme B, and T-cell intracellular antigen-1. A diagnosis of non-Hodgkin’s lymphoma (diffuse medium, T-cell) was made. A left orbital mass also appeared. Standard combination chemotherapy diminished the perirenal and orbital lesions. Lymphoma cell infiltration in the esophagus was detected after chemotherapy, and the patient died of massive bleeding from the gastrointestinal tract. Non-Hodgkin’s lymphoma is rarely associated with BD, and only 7 cases have been reported in the literature. We have summarized the published case reports of malignant lymphoma arising in BD. To our knowledge, this case report is the first to describe cytotoxic T-cell lymphoma arising in Behçet disease. Int J Hematol. 2003;77:282-285.

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1. Introduction
Behçet disease (BD) is a multisystem disorder presenting with recurrent oral and genital ulcerations, as well as with a uveitis that often leads to blindness. Involvement of the gastrointestinal tract, the central nervous system, and the large vessels is less frequent, although such involvement can be life threatening. Although the pathophysiology of BD is not well known, susceptibility to BD is strongly associated with the presence of the HLA-B51 allele [1,2].

Malignant lymphomas are neoplastic transformations of cells that reside predominantly in the lymphoid tissues. The classification of lymphomas has been controversial in the past, and establishing an internationally accepted scheme has been difficult, although the World Health Organization (WHO) classification has recently been developed [3]. The WHO classification uses the principles of the Revised European American (REAL) Classification of lymphoid neoplasms, which defines each disease according to its morphologic features, immunophenotype, genetic features, postulated normal counterpart, and clinical features [4]. Among the classified neoplasms of lymphoid tissues, mature or peripheral T-cell lymphomas are uncommon and account for only 10% to 15% of all non-Hodgkin’s lymphomas, and their classification has been controversial. Most extranodal T-cell/natural killer (NK) cell lymphomas have a cytotoxic phenotype [5].

Here, we report a case of extranodal cytotoxic T-cell lymphoma arising in BD. In addition, we summarize the published case reports of malignant lymphoma arising in BD.

2. Case Report
A 49-year-old man was referred to Tsukuba University Hospital in February 2000 with symptoms of swallowing difficulty, penis pain, recurrent oral aphtha, and numbness in both legs that had appeared 7 months before. The major symptoms of recurrent oral aphtha and genital lesions and the minor symptoms of esophageal ulcers and arthritis prompted a diagnosis of incomplete BD disease according to the criteria of the Behçet’s Disease Research Committee of
Japan [6]. After the oral administration of prednisolone (PSL) 60 mg/day was determined to be an ineffective treatment, high-dose pulse glucocorticoid therapy, consisting of methyl-PSL 1 g every 24 hours for 3 doses followed by oral administration of PSL 50 mg/day, was started. Because of inadequate control of the disease with this regimen, treatment with colchicine 1 mg/day was added. The symptoms (fever and swallowing difficulty) subsided, and the serum level of C-reactive protein decreased gradually. The patient was transferred in a stable condition to his previous hospital.

Eight months later, the patient was again referred to our hospital with symptoms of fever and melena. The patient had a spiking body temperature of up to 40°C. On palpation, muscular defense was elicited in the left hypochondriac and epigastric regions. No superficial lymph nodes or skin eruption was observed. The liver and spleen were not palpable. A test for fecal occult blood was positive. Hematologic study showed mild normochromic anemia with a hemoglobin concentration of 10.9 g/dL. The serum levels of lactate dehydrogenase and C-reactive protein were 241 U/L and 7.66 mg/dL, respectively. The level of soluble interleukin 2 receptor was 492 U/mL, which was within the normal range. Tests were negative for the serologic markers of infection with human immunodeficiency virus and human T-lymphotropic virus 1. Titers for Epstein-Barr viral capsid antigen immunoglobulin G (IgG), IgA, and IgM were positive (320×), negative, and negative, respectively. The titer for Epstein-Barr early antigen IgG was positive (1.4), and that for the Epstein-Barr virus nuclear antigen was negative. The concentration of CD4+ cells in the peripheral blood was 189 cells/μL (36.3%). Human leukocyte antigen typing indicated A24/-, B51/62, and Cw3/4. An esophagogastroduodenoscopy demonstrated multiple ulcers in the esophagus. A colonoscopy also revealed multiple ulcers occurring from the distal part of the ileum to the rectum. These findings were compatible with those of the gastrointestinal lesions of BD. Biopsy of the esophageal and intestinal ulcers detected no malignant cells. The same regimen of high-dose pulse glucocorticoid therapy used previously was started and was followed by oral administration of PSL 40 mg/day. Because symptoms were insufficiently controlled, treatment with orally administered cyclosporin A 100 mg was added. The melena discontinued, but the patient was still febrile.

A computed tomography (CT) scan of the abdomen in October revealed hepatosplenomegaly and a space-occupying lesion in the right perirenal space (Figure 1). A CT-guided needle biopsy of the lesion was performed. A histologic examination of the biopsy specimen revealed a diffuse infiltration of small- and medium-sized lymphoid cells (Figure 2A). The tumor cells were positive for CD3, CD8, CD45RO, CD43, granzyme B, T-cell intracellular antigen–1 (TIA-1) (Figure 2B), and Epstein-Barr virus early region protein–1 (EBER-1) but were negative for CD4, CD56, and CD20. Five days after the biopsy, left periocular edema appeared. A CT scan of the face revealed a space-occupying lesion in the left orbit that made the eyeball protrude (Figure 3). A diagnosis of diffuse mixed cell lymphoma (cytotoxic T-cell type), stage IVB, was made. Combination chemo-

Figure 2. A, Biopsy sample of the perirenal tumor demonstrates infiltration of small- and medium-sized lymphoma cells. B, Positive immunohistochemical staining of T-cell intracellular antigen–1 in lymphoma cells.