Tuberculous Lymphadenitis and the Appearance of Behçet’s Disease-like Symptoms

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Abstract

A 48-year-old man visited our hospital complaining of a tender mass in the left side of the neck. He was diagnosed with tuberculous lymphadenitis based on the results of a biopsy. Shortly after the diagnosis, oral aphthae, erythema nodosum-like lesions on the lower legs and genital ulcers developed. A diagnosis of cutaneous tuberculosis was ruled out according to a negative mycobacterial culture of tissues obtained from stained smears and lesional biopsy specimens. The patient’s symptoms remitted following the introduction of antituberculous therapy. We assume that tuberculous lymphadenitis was strongly associated with the appearance of Behçet’s disease-like symptoms in this case.

Key words: tuberculosis, Behçet’s disease, tuberculous lymphadenitis, aphthous stomatitis, scrotal ulcer, vasculitis

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Introduction

Behçet’s disease (BD) is an inflammatory disease of unknown etiology. The criteria for a diagnosis of BD consist of recurrent oral aphthae in addition to at least two of the following findings: recurrent genital ulceration, characteristic eye or skin lesions or a positive pathergy test (1). The etiology of BD is thought to be related to genetic and environmental factors. Human leukocyte antigen (HLA)-B51 is a well-known genetic factor in patients with BD (2), while microbial infections [e.g., oral anaerobes (3), herpes viruses (4) and tuberculosis (5)] are considered to be environmental triggers of BD. The present report describes a case of BD-like symptoms that may have been triggered by tuberculosis.

Case Report

A 48-year-old Japanese man visited our hospital complaining of a mass in the left side of his neck that he had first noticed two years earlier. The patient also had been suffering from recurrent aphthous stomatitis for approximately 10 years. At the initial examination, the patient’s body temperature was 37°C. A hard 2×5-cm nodule was present along the left sternocleidomastoid muscle, accompanied by tenderness and restricted mobility. Lymphadenopathy was noted in the left submandibular and left occipital areas. Oral aphthae were observed on the tongue, and small areas of erythema were found irregularly distributed on both lower legs.

A laboratory examination revealed no leukocytosis (white blood cells: 8,400/μL, neutrophils: 68.6%, lymphocytes: 17.8%, monocytes: 9.8% and eosinophils: 3.0%); however, elevated serum levels of C-reactive protein (6.06 mg/dL; normal range <0.3 mg/dL) and soluble interleukin-2 receptor were observed (1,110 U/mL; normal range <519 U/mL). No other abnormalities were detected on laboratory testing, which included assessments of the levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and ferritin. A chest X-ray was normal. A sputum smear and culture were negative for...
mycobacterium. A serological test ruled out acute infection with Epstein-Barr virus (EBV), human immunodeficiency virus (HIV), hepatitis B and C viruses and human T-cell leukemia virus 1 (HTLV-1). However, QuantiFERON testing was positive. An ultrasonographic examination for cervical masses revealed multiple round and hypoechoic lymph nodes containing hyperechoic lesions.

Malignant lymphoma, Kikuchi disease and tuberculous lymphadenitis were included in the differential diagnoses. We performed a biopsy of the neck mass in order to distinguish between these diseases.

The histopathology of the neck mass showed a caseous epithelioid granuloma with Langhans-type giant cells (Fig. 1). Acid fast-positive rods were also observed (Fig. 2). Malignant lymphoma and Kikuchi disease were ruled out. Subsequently, a lymph node culture grew *Mycobacterium tuberculosis*. Based on these results, the patient was diagnosed with tuberculous lymphadenitis.

Three days prior to the start of treatment for tuberculous lymphadenitis, aphthae on the hard palate and genital ulcers emerged (Fig. 3). In addition, the small erythematous lesions on both lower legs expanded and became erythema nodosum-like lesions (Fig. 4). At that time, we suspected BD. We performed a biopsy of the scrotal skin in order to evaluate potential cutaneous tuberculosis. A specimen of the scrotal skin with ulceration showed vasculitis of a small-sized artery with a thrombus, neutrophilic infiltration and fibrinoid necrosis of the vascular wall (Fig. 5). In addition, infiltration of neutrophils was observed in the extravascular soft tissue, which formed neutrophilic abscesses. Elastica van Giessen staining showed disruption of the internal elastic lamina. There were no tuberculoid granulomas, and the skin culture did not grow *Mycobacterium tuberculosis*. This finding was compatible with a diagnosis of cutaneous polyarteritis nodosa (cPN). Nevertheless, we considered that this result was more likely consistent with the features of BD, according to the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides (6).

Because pathergy testing was positive and the patient had three symptoms (recurrent aphthous stomatitis, erythema nodosum-like lesions on both lower legs and genital ulcers), the criteria for BD were fulfilled. No ophthalmological problems were noted. A serum examination revealed antinuclear antibodies, while anti-neutrophil cytoplasmic autoantibodies with myeloperoxidase and proteinase 3 specificity were negative. HLA typing revealed that the patient was
HLA-A*24:02, HLA-B*07:02 and HLA-B*52:01. Because the BD-like symptoms were localized to mucocutaneous lesions, we administered only symptomatic treatment, including nonsteroidal anti-inflammatory drugs and topical corticosteroids, then proceeded with antituberculous therapy. The patient was treated with rifampicin, isoniazid, ethambutol and pyrazinamide. As the neck lymph nodes shrank, the genital ulcers scabbed over, and the erythema nodosum-like lesions disappeared. The oral aphthae gradually improved with occasional recurrence.

Discussion

The patient in the present case was diagnosed with tuberculous lymphadenitis and experienced BD-like symptoms. As the tuberculous lymphadenitis worsened, the BD-like symptoms emerged. Furthermore, the BD-like symptoms improved immediately as a consequence of treatment for tuberculous lymphadenitis. It is therefore unlikely that each disease appeared incidentally and independently of one another.

Some case reports have suggested a relationship between BD and infection with Mycobacterium tuberculosis. Efthimiou et al. described a patient in whom BD developed following antituberculous treatment for erythema induratum Bazin, a type of cutaneous tuberculosis (7). Coelho et al. described a case of pulmonary tuberculosis that was diagnosed three days after the diagnosis of BD (8). Hamill et al. reported two cases of tuberculosis diagnosed several months after the diagnosis and treatment of BD (9). The present case is the first to suggest a possible relationship between tuberculous lymphadenitis and BD.

Various skin eruptions can be caused by tuberculosis. These eruptions generally stem from two causes: 1) cutaneous tuberculosis, which is caused by the direct entry of Mycobacterium tuberculosis into the skin from an exogenous or endogenous focus of tuberculosis, and 2) tuberculid, which is caused by hypersensitive reactions to Mycobacterium tuberculosis antigens.

Histopathologically, cutaneous tuberculosis represents a tuberculoid granuloma, which involves the accumulation of epithelioid histiocytes and Langhans-type giant cells that demonstrate a variable degree of central caseous necrosis and a peripheral rim composed of numerous lymphocytes. The gold standard for diagnosis is a positive mycobacterial culture of tissues obtained from stained smears and lesional biopsy specimens (10). A diagnosis of cutaneous tuberculosis was ruled out in the present case due to the negative mycobacterial culture and histopathological findings described above.

Tuberculid is an immunological reaction to dead bacilli or antigenic fragments that have been deposited in the skin and subcutis (11). In patients with tuberculids, mycobacterial cultures and stained smears are negative. The presence of tuberculids was ruled out in the present case due to the morphological findings and distribution of the skin eruptions.

Several cases of vasculitides with fibrinoid necrosis associated with BD have been reported (12-16). As stated above, when small-sized vasculitides with fibrinoid necrosis of the skin are observed, cPN should be considered in the differential diagnosis. The possibility of cPN cannot be entirely discounted histopathologically in the present case; however, cPN generally occurs in the legs or arms (17) and scrotal ulcers are not characteristic of cPN. Moreover, infiltration of neutrophils and neutrophilic abscesses in the extravascular soft tissue is atypical in patients with cPN (18).

Previous reports have documented the occurrence of various-sized vasculitides in the context of BD (6). In the present case, the patient’s symptoms and cutaneous histopathological findings were consistent with a diagnosis of BD. These observations suggest that tuberculous lymphadenitis acted as a trigger of the BD-like symptoms in this case of recurrent aphthous stomatitis.

In this case, the criteria for BD were fulfilled. Nevertheless, we were unable to diagnose BD because the patient’s symptoms remitted following treatment with antituberculous therapy and were thought to be associated with tuberculous lymphadenitis. We can only conclude that the patient’s symptoms were BD-like symptoms.

HLA-B51 and HLA-A26 are known to be associated with BD (2, 19). Because the present patient exhibited neither HLA-B51 nor HLA-A26, we cannot discuss the relationship between genetic factors and the appearance of BD-like symptoms.

Microbial infection can trigger the onset of BD. Pervin et al. mapped T cell epitopes of heat shock protein (HSP) in patients with BD by stimulating T cells with overlapping synthetic peptides derived from gene sequences of Mycobacterium tuberculosis HSP (5). Mycobacterium tuberculosis HSP displays molecular mimicry to human HSP, resulting in an immunologic cross-reaction and the subsequent development of BD.

Furthermore, genome-wide association studies have identified IL23R-IL12RB2 and IL-10 to be BD susceptibility genes.
loci (20, 21). IL23R-IL12RB2 is a cytokine that mediates the differentiation and activation of Th1 and Th17 cells. The production of the inhibitory cytokine, IL-10, is lower in the context of BD-associated alleles compared with that associated with alleles from healthy donors, which results in excess inflammation as a result of the unrestrained activity of Th1 and Th17 cells. Active BD is characterized by an increased level of IL-17, which is produced by Th17 cells (22). In addition, a genome-wide association study showed that the upregulation of the STAT4 expression and the subsequent STAT4-driven production of inflammatory cytokines, such as IL-17, constitute a potential pathway leading to BD (23).

Th17 cells, defined by the production of IL-17A and IL-17F, play an important role in immunity against tuberculosis (24). Nathella et al. reported that tuberculous lymphadenitis is characterized by elevated levels of Th1 and Th17 cells (25).

Based on these findings, we suspect that Th1 and Th17 cell levels increase in response to tuberculosis and that the mismatch between the Th1 and Th17 cell levels and the IL-10 levels results in inflammation. Such conditions may have caused BD-like symptoms in this patient with tuberculous lymphadenitis.

If the patient’s BD-like symptoms had been antecedent to his neck mass and he had been diagnosed with BD, his symptoms would have worsened. For this reason, it is important to search for curable causes of BD-like symptoms. The present case study is valuable in that it focuses on the etiology of BD. Further research on the mechanisms of BD is required.

The authors state that they have no Conflict of Interest (COI).

References

22. Hamzaoui K, Bouali E, Ghorbel I, et al. Expression of Th-17 and Th17 cells, defined by the production of IL-17A and IL-17F, play an important role in immunity against tuberculosis (24). Nathella et al. reported that tuberculous lymphadenitis is characterized by elevated levels of Th1 and Th17 cells (25).

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