Case Report

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급성 결핵성수막염의 양상을 보이는 속립성 결핵에 동반된 신경 베체증후군

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Neuro-Behçet's Syndrome with Miliary Tuberculosis Presenting with Features Mimicking Acute Tuberculous Meningitis

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A 14-year-old girl diagnosed with Behçet's disease 15 months previously presented at the emergency department with severe headache, fever, and vomiting. Chest radiographic and computed tomography findings were consistent with miliary tuberculosis, and pleocytosis and increased protein levels were found on examination of cerebrospinal fluid (CSF). Tuberculous meningitis associated with miliary pulmonary tuberculosis was suspected, and a four-drug regimen for tuberculosis plus intravenous dexamethasone was initiated. However, negative results of real-time polymerase chain reaction and CSF cultures led us to reconsider our initial diagnosis. On brain magnetic resonance imaging, the results supported neuro-Behçet's syndrome rather than tuberculous meningitis. However, it is unclear how miliary tuberculosis complicated neuro-Behçet's syndrome because the patient had no history of tuberculosis or contact with patients with tuberculosis, and had not used any immunosuppressive agents such as anti-tumor necrosis factor-alpha drugs. This is a very rare case of neuro-Behçet's syndrome associated with miliary tuberculosis. More commonly, cases of neuro-Behçet's syndrome presenting with features mimicking acute tuberculous meningitis have been reported. Neuro-Behçet's syndrome should be considered in patients with a history of Behçet's disease presenting with signs of meningeal irritation.

Key Words: Behcet syndrome, Tuberculosis, Miliary

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Introduction

Behçet's disease is a relapsing vasculitis of unknown etiology, characterized by oral ulcers, genital ulcers, skin lesions, intraocular inflammation, and other organ involvement[1]. Central nervous system (CNS) involvement in Behçet's disease has a significant impact on patient prognosis and quality of life, and this condition is known as neuro-Behçet's syndrome. In most cases, neuro-Behçet's syndrome is characterized by aseptic meningitis, cerebellar signs, intracranial hypertension, and pyramidal alterations. Generally, CNS involvement is observed in about 3%–10% of patients with Behçet's disease; however, CNS involvement was found at autopsy in 34% of Japanese patients with the disease, so it is estimated that such involvement occurs more frequently than expected in these patients[2]. According

to recent reports, CNS involvement is found in 5% of Korean patients with Behçet's disease[3]. Miliary tuberculosis is a potentially lethal disease if not diagnosed and treated early. This condition is often observed in immunosuppressed individuals but is not commonly associated with or reported in patients with Behçet's disease. Here, we report a case of neuro-Behçet's syndrome in a 14-year-old girl with a history of Behçet's disease who presented with meningeal signs and pulmonary miliary tuberculosis.

Case Report

A 14-year-old girl presented to the emergency department with severe headache, fever, and vomiting, which had started at dawn on the same day. On the day before hospitalization, she had been examined for severe headache as an outpatient in the Pediatrics Department. Physical examination and brain computed tomography (CT) did not reveal the cause of the headache, but chest radiographic findings were consistent with miliary tuberculosis. Therefore, she was scheduled to be admitted on the next day for further work-up. She had been diagnosed with Behçet's disease 15 months previously and had had no headache, fever, or vomiting, and chest X-rays were normal during that time. The initial clinical course showed oral and genital ulcers; she was treated with oral steroids, but the lesions did not improve. She was transferred to the Division of Rheumatology for evaluation. An antinuclear antibody test gave weakly positive results (1:40), human leukocyte antigen (HLA)-B51 was detected, and skin biopsy showed mild vasculitis with neutrophilic infiltration. Finally, she was diagnosed with Behçet's disease and colchicine therapy was started that has been sustained so far. She was initially prescribed colchicine 1.2 mg/day plus methylprednisolone 8 mg/day for one month by the Dermatology Department, followed by colchicine 1.2 mg/day plus methylprednisolone 4 mg/day for the following 3 months. Thereafter, she was prescribed only colchicine 1.2 mg/day. The genital ulcers disappeared, but the oral ulcers spread deep into the throat, and she had developed a severe sore throat and tinnitus 3 months before hospitalization.

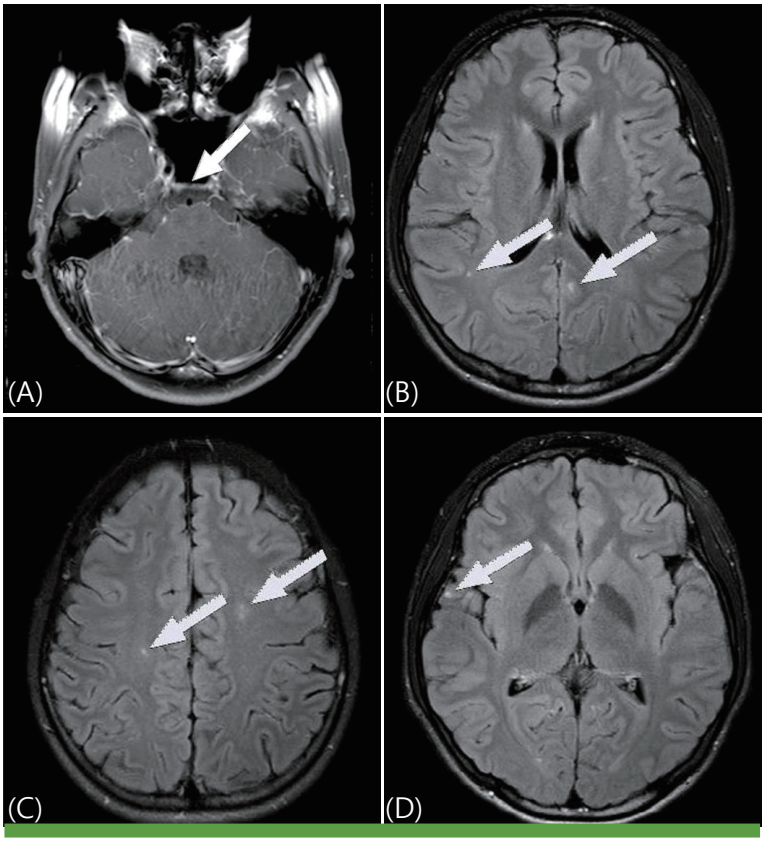

Fig. 1. T1-weighted magnetic resonance image of the brain showing diffuse pial enhancement in the brainstem (A). T2-weighted magnetic resonance images of the brain showing enhancement in the left precuneus and right opercular gyrus (B), and multifocal lesions predominantly within the centrum semiovale (C) and right parietotemporal white matter (D).

She visited the ENT Department 2 months before hospitalization because of gradually worsening tinnitus, but the auditory test results were negative. She experienced intermittent headaches during that time. Moreover, she developed a remittent fever (up to 38.7℃) and began coughing intermittently 2 weeks before hospitalization, but had no weight loss. On neurological examination at the emergency department on the day of hospitalization, she had neck stiffness and positive signs of meningeal irritation. Meningitis was strongly suspected and a lumbar puncture was performed. Blood tests showed the following results: hemoglobin, 12.5 g/dL; white blood cell count, 4,820/mm^3 with 76.6% segmented neutrophils; platelets, 339,000/μL; C-reactive protein, 6.28 mg/dL (upper limit of normal 0.5 mg/dL); glucose, 110 mg/dL; sodium, 134 mEq/L; potassium, 4.5 mEq/L; chloride, 98 mEq/L; creatinine, 0.66 mg/dL; blood urea nitrogen, 9 mg/dL; alanine aminotransferase, 19 μ/L, aspartate aminotransferase, 24 μ/L; and serum albumin, 2.1 g/dL. Examination of the CSF showed the following results: CSF/serum glucose ratio, 0.38; total protein level, 128.5 mg/dL; white blood cell count, 83/mm^3; lymphocyte level, 100%; opening pressure, 245 mm H_2O; and glucose level, 40 mg/dL. An elevated total protein level and high lymphocyte count were suggestive of tuberculous meningitis. Laboratory test results were nonspecific, whereas the interferon-gamma release assay test and Mantoux test results were positive. The serum/CSF adenosine deaminase level was 65.3/8.6 IU/L. Results of culture, Gram staining, acid-fast bacillus staining of sputum, and real-time polymerase chain reaction (PCR) analysis of sputum and CSF were all negative. Moreover, the results of real-time PCR of nasal aspirate samples were negative. High-resolution chest CT showed a diffuse micronodular pattern of miliary pulmonary tuberculosis. On the basis of these results, tuberculous meningitis with miliary pulmonary tuberculosis was diagnosed initially. After admission, treatment with isoniazid, ethambutol, pyrazinamide, rifampicin, and dexamethasone was initiated for tuberculous meningitis. Because headache and fever persisted until day 5 of hospitalization, contrast-enhanced brain magnetic resonance imaging (MRI) was performed on day 6, and showed diffuse pial enhancement in the brainstem, left precuneus, and right opercular gyrus, and multifocal enhancing lesions predominantly within the bilateral centrum semiovale and right parietotemporal white matter in the T2 weighted images (Fig. 1). Because these findings were consistent with neuro-Behçet's syndrome, we came to favor a diagnosis of neuro-Behçet's syndrome rather than tuberculous meningitis. From day 6 onwards, she had no fever and her intermittent headaches improved. A follow-up CSF examination performed on day 16 showed the following results: CSF/serum glucose ratio, 0.54; white blood cell count, 16/mm^3; lymphocyte level, 99%; total protein level, 54.7 mg/dL; lactate dehydrogenase level, 26 IU/L; glucose level, 52 mg/dL; and red blood cell count, 40/mm^3. Real-time PCR results for CSF samples were negative. Therefore, there was a dramatic improvement overall in the CSF examination results. Follow-up chest radiographic and high-resolution chest CT findings showed improvement in the micronodular pattern of miliary tuberculosis (Fig. 2). The drug regimen (rifampicin, isoniazid, pyrazinamide, and ethambutol) for tuberculosis was continued until the day of discharge, and steroid therapy was changed from intravenous dexamethasone to oral prednisolone on day 13 of hospitalization. The patient was discharged on day 19 and was free of headaches. Take home medications were as follows: a four-drug regimen (isoniazid, rifampin, ethambutol, and pyrazinamide) for 8 weeks, a two-drug regimen (isoniazid, ethambutol) for next 28 weeks for miliary tuberculosis, and prednisolone 50 mg for 4 weeks and tapering for next 2 months for neuro-Behçet's syndrome. She have not experienced any

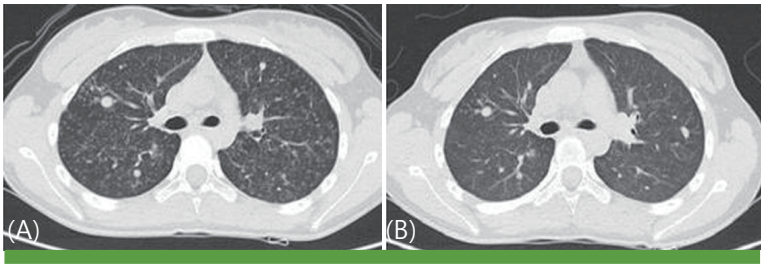

Fig. 2. (A) Initial high-resolution chest CT. Mixed pattern of diffuse miliary pulmonary tuberculosis and active pulmonary tuberculosis. Extensive bronchogenic spread in both lungs with combined tuberculous lymphadenitis at both hila and the mediastinum. (B) Follow-up high-resolution chest CT. Compared with previous chest CT, there is improvement of the mixed pattern of diffuse miliary pulmonary tuberculosis and active pulmonary tuberculosis. Abbreviation: CT, computed tomography

specific symptoms after discharge and we couldn't have found any signs of neuro-Behcet's syndrome and miliary pulmonary tuberculosis for over 2 years in the outpatient clinic of the Pediatrics Department.

Discussion

The criteria for a diagnosis of Behçet's disease, proposed in 1990 by the International Study Group for Behçet's disease, include oral ulcerations observed by the physician or reported reliably by the patient that recur at least three times in a 12-month period, along with at least two of the following symptoms: recurrent genital ulceration or scarring, skin lesions, anterior uveitis, posterior uveitis, or retinal vasculitis observed by the ophthalmologist and a positive pathergy test[4]. These criteria were fulfilled by our patient, who reliably reported genital and oral ulcerations that recurred more than three times in a year along with vitiligo lesions, although she did not have uveitis and her pathergy test result was negative. She had HLA-B51 genotype, which is reported to be strongly associated with Behçet's disease. CNS involvement in Behçet's disease, known as neuro-Behçet's syndrome, occurs in 3.3%–25% of patients with Behçet's disease, with varying prevalence in different populations. According to recent reports, CNS involvement has been observed in 5% of patients with Behçet's disease in South Korea[3] and in 16.6% of patients with the disease in France[5]. Neurologic involvement in Behçet's syndrome can follow a parenchymal or a non-parenchymal pattern. In parenchymal involvement, inflammation is primarily within the parenchyma of the nervous system, whereas in non-parenchymal involvement, the main pathology is secondary to vascular complications within the nervous system[6]. MRI is currently the most sensitive imaging technique for studying neuro-Behçet's syndrome. In patients with parenchymal involvement, lesions most commonly extend from the brainstem to the basal ganglia unilaterally or bilaterally, appear hyperintense on T2-weighted images, and frequently demonstrate central contrast enhancement[7]. CSF analysis might assist in the diagnosis of parenchymal neuro-Behçet's syndrome, showing increased protein and cell contents in patients with the condition. Aseptic meningitis commonly occurs in patients with neuro-Behçet's disease and parenchymal involvement, which might cause fever, headache, and neck stiffness[7]. In parenchymal disease, CSF pleocytosis with headache, fever, and signs of meningeal irritation might easily lead to a misdiagnosis of bacterial meningitis or tuberculous meningitis. In the past, some patients who were reported to have aseptic meningitis might have been misdiagnosed because of the lack of sensitive imaging data[8]. We initially diagnosed our patient with tuberculous meningitis as having miliary pulmonary tuberculosis because the CSF findings and clinical features were consistent with tuberculous meningitis and chest radiographic and high-resolution chest CT findings showed miliary tuberculosis. A recent study reported that in patients with "probable or possible" tuberculous meningitis, real-time PCR of CSF samples showed a sensitivity of 98% (95% confidence interval 94–99) and specificity of 98% (95% confidence interval 96–99)[9]. We reconsidered our initial diagnosis because we obtained negative real-time PCR results as well as negative culture results for CSF samples. On the basis of brain MRI results, we came to favor a diagnosis of neuro-Behçet's syndrome rather than tuberculous meningitis. There is a report from Turkey of a patient with neuro-Behçet's syndrome presenting with features mimicking acute tuberculous meningitis. Even in that case, brain MRI played an important role in establishing an exact diagnosis[8]. Of course, our patient could be diagnosed with "probable tuberculous meningitis" according to the criteria for a clinical diagnosis of tuberculous meningitis suggested by Heemskerk et al[10]. Thus, we could not exclude the possibility of coexistence of neuro-Behçet's syndrome and tuberculous meningitis.

The present case is unique in that the patient had miliary tuberculosis with neuro-Behçet's syndrome. She had no history of tuberculosis or contact with patients who had the disease. In this case, the cause of miliary tuberculosis was unclear. Recently, it was reported that a woman with oculocutaneous Behçet's disease developed primary tuberculosis while being treated with infliximab, a tumor necrosis factor-alpha blocker. This can be explained as an opportunistic infection due to immunosuppression by infliximab[11]. Another study reported a case of tuberculosis with such a disseminated course in a patient who received conventional immunosuppressive treatment with prednisolone, cyclosporine A, and azathioprine[12]. However, our patient was treated for Behçet's disease with colchicine alone without any immunosuppressive agents, except for short-term steroid therapy more than a year earlier. Colchicine, a plant alkaloid, has never been reported to cause immunosuppression, and the cause of miliary tuberculosis in our patient could not be determined. Even in the absence of a history of or contact with tuberculosis and immunosuppressive therapy, there exist a number of factors that might increase the risk of development of tuberculosis in patients with Behçet's disease. One possibility is that the disease itself may produce a defect in cell-mediated immunity, which may increase the individual's susceptibility to tuberculosis. However, to date, no study has specifically examined cell-mediated immune responses to pulmonary tuberculosis in patients with Behçet's disease, so

this condition remains unclear. Another interesting possibility is that there might be a common genetic predisposition to both pulmonary tuberculosis and neuro-Behçet's syndrome. In a previous study, tissue typing revealed that three patients with Behçet's disease and pulmonary tuberculosis were HLA-B5-positive; interestingly, this HLA type has been reported to be strongly associated with the risk of tuberculosis, particularly in African-American individuals[13]. Moreover, HLA-B5 has been reported to occur with increased frequency in patients with Behçet's disease[14]; and our patient was positive for HLA-B51. There appears to be an HLA-associated or immunogenic predisposition to specific tissue involvement in patients with Behçet's disease; however, few studies have investigated HLA typing in patients with pulmonary involvement, and those that have done so have found no clear association. We hope that our study will add to the data on the unusual association between neuro-Behçet's syndrome and miliary tuberculosis in patients with Behçet's disease.

요약

신경베체증후군은 베체병 환자에게 있어서 중추신경계 침범이 이루어진 경우로서 환자의 삶의 질과 예후에 심각한 영향을 끼칠 수 있는 질병이다. 베체병에서 중추신경계 침범은 한국에서는 5%정도인 것으로 알려져 있다. 속립성 결핵은 조기에 진단 치료되지 않으면 심각한 결과를 초래할 수 있는 질환으로서 면역 억제 환자에게서는 흔하게 나타나지만 베체병 환자에게서는 흔하게 나타나는 질환은 아닌 것으로 알려져있다. 저자들은 베체병을 진단받아 콜키친 치료를 받아온 환자에게 신경베체증후군의 증상이 속립성 결핵에 동반되어 나타난 사례를 경험하였기에 이에 보고하는 바이다. 베체병으로 콜키친 치료를 받아오던 14세 여아가 심각한 두통, 발열, 구토를 주소로 응급실에 내원하였고, 흉부 방사선 검사와 컴퓨터 단층 촬영 소견은 속립성 결핵에 부합하였으며, 뇌척수액 검사 소견은 결핵성 수막염에 부합하여 결핵 4제 요법과 함께 덱사메타손 정맥 주사 요법을 시행하였다. 그러나 뇌척수액에 대한 실시간 중합효소 연쇄 반응검사 및 배양검사 결과가 음성으로 나와 초기 진단에 대해 재고하게 되었고, 뇌 자기공명 영상 검사 결과 신경베체증후군에 부합하는 소견이 발견되어 우리는 결핵성 수막염 보다는 속립성 폐결핵이 동반된 신경베체증후군을 더욱 지지하게 되었다. 그러나, 환자는 결핵의 과거력이 없고, 결핵환자와 접촉한 이력이 없으며, TNF-α 와 같은 면역억제제를 사용한 이력이 없었으므로 어떠한 경로로 속립성결핵이 신경베체증후군에 합병되었는지는 불확실하다. 또한 실제로 결핵성 수막염과 신경베체증후군이 동시에 존재하였을 가능성도 완전히 배제할 수는 없었다. 급성 결핵성 수막염과 유사한 증상을 보이는 신경베체증후군의 사례는 이전에도 종종 보고된 바 있으나 본 사례는 속립성 결핵을 동반한 신경베체증후군의 사례로서 매우 드문 케이스라 할 것이다. 향후에도 수막 자극증상을 보이는 베체병 환자에게 있어서는 신경 베체증후군을 반드시 고려해보아야 할 것으로 사료된다.

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