Neuro-Sweet Disease

Benign Recurrent Encephalitis With Neutrophilic Dermatosis

Kinya Hisanaga, MD; Michiko Hosokawa, MD; Nobuyuki Sato, MD; Hiroshi Mochizuki, MD; Yasuto Itoyama, MD; Yuzo Iwasaki, MD

Objective: To describe benign recurrent encephalitis in a case of Sweet syndrome that also showed clinical features of Behçet disease.

Case Report: A 37-year-old Japanese man developed relapsing and remitting encephalitis and mucocutaneous symptoms mimicking Behçet disease. Magnetic resonance images showed at least 5 episodes of transient abnormal signal intensity in various cerebral regions over a period of 5 years. A skin biopsy specimen of the cutaneous edematous erythematous plaques revealed neutrophilic dermatitis compatible with Sweet syndrome. HLA typing showed B54, which is frequent in Sweet syndrome but rare in Behçet disease. Oral prednisolone therapy (10-60 mg/d) was remarkably effective for the encephalitis as well as for the mucocutaneous symptoms.

Conclusion: We propose that there is an entity that is like Sweet disease, but with recurrent encephalitis characterized by an association with HLA-B54 and a high responsiveness to corticosteroid therapy, which we have tentatively named neuro-Sweet disease, that is distinct from the classic central nervous system involvement of Behçet disease.

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Sweet Syndrome, or acute febrile neutrophilic dermatosis,1 is an unusual condition with clinical features of malaise, fever, leukocytosis, and distinctive skin lesions. The lesions, which heal without scarring, are symmetrical, tender, dull-red edematous plaques that usually occur on the face, neck, upper part of the trunk, and limbs.2 They consist of a dense dermal infiltrate composed of mature neutrophils with frequent nuclear fragmentation. The epidermis is spared, and signs of vasculitis are absent.3 Arthralgia, arthritis, conjunctivitis, and iridocyclitis are also common.4 Neutrophilia and elevated erythrocyte sedimentation rates are reported.2 Prednisolone therapy (10-30 mg/d) is known to be effective.2 Various malignant neoplasms and chronic inflammatory disorders, including rheumatoid arthritis, Sjögren syndrome, Behçet disease, and sarcoidosis, have been reported to coincide with Sweet syndrome.5-7 However, the involvement of the central nervous system (CNS) is rarely reported.5-9

We describe a Japanese man who developed biopsy-confirmed neutrophilic dermatosis compatible with Sweet syndrome and who suffered from chronic relapsing encephalitis for more than 5 years. Serial magnetic resonance images (MRIs) showed the development of transient abnormal signal intensity areas in the various cerebral regions. He also had oral aphthae, genital ulcers, and a pathergy phenomenon characteristic of Behçet disease.10 However, HLA typing showed B54, which is known to be frequent in Sweet syndrome11 but rare in Behçet disease.12 We know of another patient with HLA-B54 who had similar clinical features.

REPORT OF A CASE

In May 1992, a 32-year-old Japanese man was transferred to Miyagi National Hospital, Miyagi, Japan, because of altered consciousness following fever and malaise. On admission, he was disoriented as to time, place, and person. No other neurological abnormalities were noted except slight meningeal signs. Oral aphthae were present. His blood pressure reading was 116/66 mm Hg. The results of standard hematological and serum chemistry studies were within normal limits. The white blood cell count was 5.89 × 10⁹/L, with 0.76 polymorphonuclear leukocytes. The erythrocyte sedimentation rate was 28 mm/h, and the C-reactive protein level
was 1 mg/L (0.1 mg/dL). Antinuclear antibodies and rheumatoid factor were undetectable.

A lumbar puncture on admission disclosed normal pressure (110 mm H₂O) and moderate pleocytosis (70 cells per cubic millimeter, 0.60 lymphocytes, and 0.34 neutrophils without malignant cells). The protein content was 1.4 g/L, and the glucose level was 3.0 mmol/L (54 mg/dL). A culture of a cerebrospinal fluid (CSF) sample was negative for bacteria and fungi. Antibodies against herpes simplex virus, echoviruses, and coxsackieviruses were undetectable in the serum and CSF samples on 2 separate occasions.

An MRI revealed decreased signal intensity on T₁-weighted scans and increased signal intensity on T₂-weighted scans and proton images in the bilateral thalamus and globus pallidus and the right hypothalamus, putamen, and midbrain (Figure 1, A). A computed tomographic scan showed a decreased signal density in the same regions. No enhancement was observed after intravenous injections of contrast media. Dilatation of the lateral and fourth cerebral ventricles was evident. Electroencephalography showed an abundance of theta and delta activities, with right-sided predominance.

The patient almost completely recovered within 2 weeks with supportive treatments. At the time of discharge, symmetrical dilatation of cerebral ventricles, MRI signal abnormalities in the right caudate, and a low IQ of 61 on the Wechsler Adult Intelligence Scale–Revised were noted.

In July 1994, a symptomatic generalized seizure occurred. An electroencephalograph showed a few delta waves in the right frontotemporal lobe. Oral aphthae were again present. In November 1994, the patient was readmitted because of seizure recurrence. The patient was febrile and had oral aphthae, irregular erythematous eruptions on his face, and a genital ulceration, but no ophthalmologic abnormalities. Although an initial MRI on admission showed no additional abnormalities, a follow-up MRI 1 month later showed new lesions in the bilateral cerebral white matter (Figure 1, B). A tentative diagnosis of neuro-Behçet disease was made.

In February 1995, generalized seizures, diplopia, fever, and erythema recurred on the patient's face and trunk, but spontaneously diminished. Divergence palsies were transiently observed. A brain MRI showed new signal abnormalities in the left putamen (not shown). Prednisolone (10 mg/d) was prescribed for the prevention of recurrences, but the patient frequently failed to take it. A follow-up brain MRI in April showed a new abnormal signal intensity area in the right cerebral white matter (not shown), an apparently asymptomatic lesion. In October, the patient was admitted to Sendai Teishin Hospital, Sendai, Japan, because of fever and skin eruptions. Multiple tender, dull-red, edematous plaques 2 to 3 cm in diameter were noted on his face and extremities (Figure 2). He also had oral aphthae and a small genital ulcer. A biopsy specimen from the edematous erythema on his right arm revealed a dense infiltration of neutrophils in the dermis, without vasculitis. The epidermis was spared (Figure 3). These findings were compatible with Sweet syndrome. Prednisolone therapy (30 mg/d) dramatically improved the above-mentioned
symptoms within a week. All skin lesions healed without scarring.

In August 1997, the patient was readmitted to our hospital because of disorientation, fever, left elbow pain, oral aphthae, and a genital ulcer that had developed after the prednisolone therapy had been discontinued for a few months. A pathergy reaction was positive. Uveitis was absent. An MRI revealed a new abnormal signal intensity area in the bilateral thalamus (Figure 1, C). No enhancement was seen after contrast-medium injections on both MRI and computed tomographic scans. The white blood cell count was 10.56 \times 10^9/L, with 0.88 polymorphonuclear leukocytes. The C-reactive protein level was 38 mg/L (3.8 mg/dL). The erythrocyte sedimentation rate was 44 mm/h. Serum sample studies showed normal levels of granulocyte colony-stimulating factor, tumor necrosis factor \( \alpha \), angiotensin-converting enzyme, antinuclear antigen, anticardiolipin antibodies, anti–SS-A, anti–SS-B, antineutrophil cytoplasmic and perinuclear antineutrophil cytoplasmic antibodies, thyroglobulin, antithyroglobulin, anti–thyroid peroxidase, antithyrotropin receptor, cryoglobulin, CH50, C3, and C4. The serum level of interleukin (IL) 6 was elevated (24.4 pg/mL). Analysis of a CSF sample revealed increased pressure (290 mm H2O), cell count (58 cells per cubic millimeter, 0.64 lymphocytes, and 0.36 neutrophils, without malignant cells), and protein level (0.7 g/L), with no oligoclonal IgG and a normal myelin basic protein level. The glucose level was 3.3 mmol/L (60 mg/dL). HLA testing revealed A11, B39, B54, CW1, and CW7. The symptoms and abnormal MRI findings (Figure 1, D) resolved after treatment with intravenous methylprednisolone (1 g/d for 3 days), followed by oral prednisolone (60 mg/d). Since then, the patient has remained asymptomatic on a maintenance regimen of 5 mg of prednisolone per day.

**COMMENT**

To our knowledge, this is the first report of chronic relapsing encephalitis combined with the skin lesions of Sweet syndrome. Clinical features in the present case fulfill the criteria not only for Sweet syndrome but also for Behc¸et disease. Oral aphthae, genital ulcers, erythema nodosum–like eruptions, and a pathergy reaction, all of which are usually encountered in Behc¸et disease, were observed in the present case. However, these symptoms have also been previously documented in some cases of Sweet syndrome, although they have been less severe in Sweet syndrome than in Behc¸et disease.11 It is notable that the relapsing and remitting skin lesions as well as the recurrent encephalitis in the present case were benign. In addition to erythema nodosum–like eruptions on the legs, the patient had multiple edematous erythema. A biopsy specimen from the edematous erythematous plaques confirmed a diagnosis of Sweet syndrome. It is unlikely the patient’s disease coincided with other chronic inflammatory disorders, such as rheumatoid arthritis, Sjogren syndrome, and sarcoidosis, because of the clinical features and the results of serological studies, as described above.

Symmetrical dilatation of ventricles on the initial computed tomographic and MRI scans suggested preceding episodes of the CNS involvement, leading to a low IQ of 61. A series of subsequent brain MRI scans indicated that encephalitis occurred at least 5 times in 5 years. The patient recovered from each episode without any significant focal neurological deficits.

There have been only a few cases reported of Sweet syndrome with CNS involvement.7-9 A transient increase of neutrophils in CSF samples was reported in neonatal and adult patients with Sweet syndrome.10 Yoshiura et al11 reported a case of Sweet syndrome with disturbances of intelligence and eye movement. Lesions were demonstrated in the basal ganglia and brainstem on MRIs (in abstract form).

A unique feature of the present case is an association of HLA-B54. A high frequency of HLA-B54 is reported in patients with Sweet syndrome but not in patients with Behc¸et disease. It was reported that the frequency of HLA-B54 in a control Japanese population and in patients with Behc¸et disease was 13/90 and 1/30, respectively, while that of HLA-B-51 was 15/90 and 1/30, respectively.12 We also experienced another case with similar clinical features. A 34-year-old Japanese man with oral aphthae, genital ulcers, and uveitis developed moderate consciousness disturbance. Leukocytosis and an increased erythrocyte sedimentation rate were noted, and the CSF sample showed pleocytosis (29 cells per cubic millimeter) and an elevated protein level (0.8 g/L). The patient also had edematous skin eruptions, as in the present case. However, these symptoms have also been previously documented in some cases of Sweet syndrome.13-15 Yoshiura et al16 reported a case of Sweet syndrome with disturbances of intelligence and eye movement. Lesions were demonstrated in the basal ganglia and brainstem on MRIs.
compounded by CNS involvement. Prednisolone therapy was also highly effective in that case.

The etiology of Sweet syndrome is unknown, although the possible role of an abnormally increased chemotaxis of the neutrophils has been suggested. Cytokines, including granulocyte colony-stimulating factor and IL-6 and antineutrophil cytoplasmic antibody have been implicated in the pathogenesis of Sweet syndrome. Granulocyte colony-stimulating factor therapy for granuloma necrosis factor and tumor necrosis factor α are also known to be involved in the pathogenesis of Behçet disease. Further studies are needed to investigate the association of the cytokine system in Sweet syndrome as well as in Behçet disease, especially in reference to CNS involvement.

At present, it is not reasonable to rule out the diagnosis of Behçet disease in the case described herein. However, the recurrent encephalitis in Sweet syndrome, characterized by an association with HLA-B54 (and CW1) and high responsiveness to corticosteroid therapy, which we have termed neuro-Sweet disease, could be distinct from the classic CNS involvement in Behçet disease. From a therapeutic point of view, it is important to note the existence of such cases, since corticosteroid therapy may aggravate mucocutaneous symptoms and uveitis in classic Behçet disease but was highly beneficial in the cases described herein.

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Reprints: Kinya Hisanaga, MD, Department of Neurology, Miyagi National Hospital, 100 Kassenhara, Takase, Yamamoto, Watari, Miyagi 989-2202, Japan.

REFERENCES