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【 CASE REPORT 】

Recurrent Neurological Episodes for 10 Years Preceding Skin Lesions in Neuro-Sweet Disease

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Abstract:
An absence of skin lesions at the neurological onset may obscure the diagnosis of neuro-Sweet disease (NSD). We herein report a 32-year-old man with NSD in whom neurological symptoms preceded the development of skin lesions by 10 years. The patient exhibited four distinct neurological episodes: meningoencephalitis, scattered brain lesions, ocular flutter, and isolated seizures. Acute relapses responded to corticosteroid therapy, and the patient was successfully maintained on corticosteroid and dapsone combination therapy. NSD should be considered in the differential diagnosis of patients with recurrent neurological manifestations, especially with both meningeal and brain parenchymal involvement, even if no skin lesions are observed.

Key words: Sweet's disease, neuro-Sweet disease, skin eruption, dapson, corticosteroid

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Introduction

Sweet's disease, or acute febrile neutrophilic dermatosis, is characterized by a fever, neutrophilia, and erythematous and tender skin lesions (1). Although aseptic neutrophilic inflammation can occur in other organs in Sweet's disease, cases of central nervous system (CNS) involvement - so-called "neuro-Sweet disease (NSD)" - are rare. The diagnosis of NSD may not be straightforward, particularly in the absence of skin lesions at the neurological onset (2, 3).

We herein report a patient with NSD who developed recurrent neurological episodes over a period of 10 years prior to the appearance of skin lesions.

Case Report

A 32-year-old Japanese man with no medical history presented to our hospital with a history of headache and a fever for the past 19 and 7 days, respectively. At admission, his body temperature was 37.6℃, and he was alert and cooperative. He exhibited neck stiffness with no other neurological signs observed. His peripheral white blood cell count was 15,200/mm^3, and the serum C-reactive protein level was 4.6 mg/dL.

A cerebrospinal fluid (CSF) examination revealed a nuclear blood cell count of 237/mm^3 (12% neutrophils and 88% lymphocytes) and glucose level of 60 mg/dL (simultaneous blood sugar level, 102 mg/dL). The CSF was negative for tuberculosis culture and cryptococcal antigen. The CSF adenosine deaminase level was 4.5 U/L. Brain computed tomography showed no abnormalities. The clinical history, physical examination findings, and elevated CSF lymphocyte levels were consistent with a diagnosis of aseptic meningitis; therefore, we opted for conservative therapy.

Seven days after admission, his level of consciousness deteriorated. A CSF examination showed worsening of pleocytosis (949/mm^3). Brain magnetic resonance imaging (MRI) showed no abnormalities. The anti-thyroid peroxidase antibody value was normal. Antibodies to the Sm, Ro, La, and RNP antigens and cytoplasmic/perinuclear antineutrophil cytoplasmic antibodies were all negative. Owing to the subacute clinical course, we suspected viral encephalomeningitis or tuberculosis meningitis and administered intravenous acyclovir and oral anti-tuberculosis agents without corticosteroid, but he showed no improvement and became semicomatose nine days after admission. Presuming the inflammation was not infectious in origin, corticosteroid therapy

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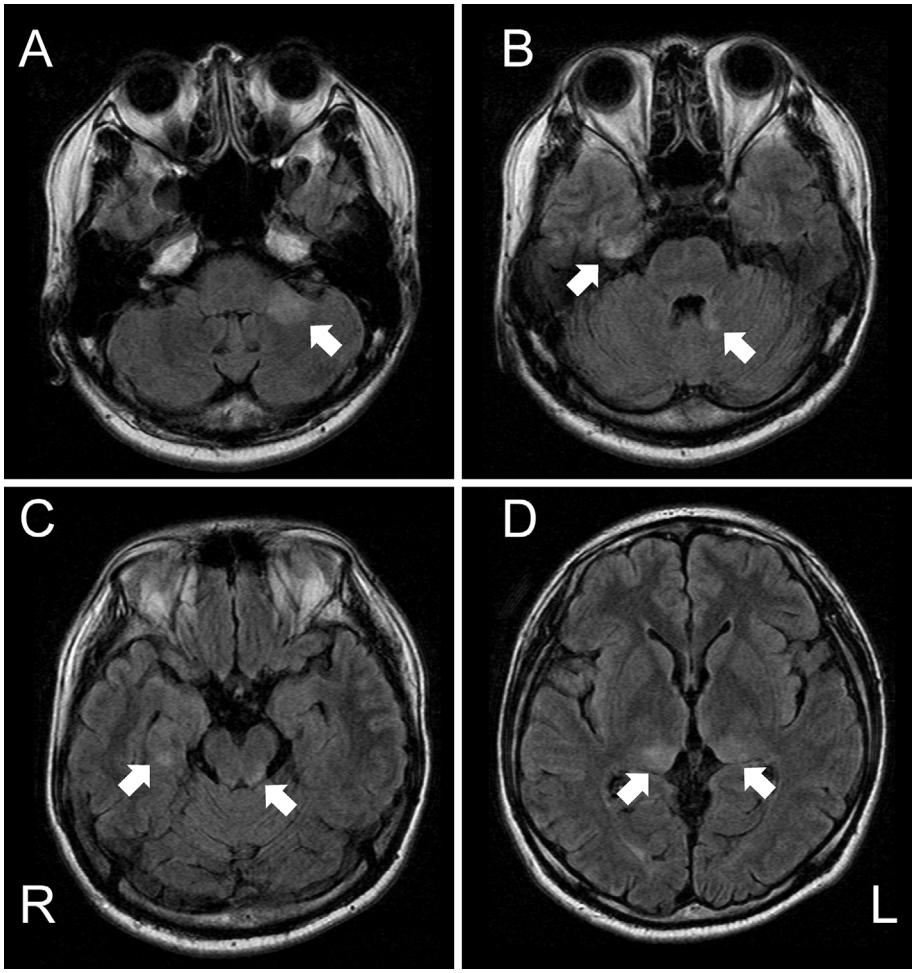

Figure 1. **Brain axial fluid-attenuated inversion recovery images at the second admission showing hyperintense signal areas (arrows) in the left cerebellum (A, B), right temporal lobe (B, C), left midbrain (C) and bilateral thalamus (D).**

was added for the management of meningoencephalitis. Intravenous methylprednisolone (mPSL) (1 g per day for 3 days) was administered, followed by oral prednisolone (PSL) 60 mg per day via a nasal feeding tube.

Clinical improvement started three days later, and he became alert eight days after the initiation of corticosteroids. His CSF examination 25 days after the onset showed improvement of pleocytosis (32/mm^3). He was discharged 26 days after admission with no residual signs or symptoms. Oral PSL was tapered and discontinued 57 days after corticosteroid initiation.

He experienced relapse 22 days after the cessation of corticosteroids, developed diplopia and gait disturbance, and was transferred to our hospital 2 days later. His body temperature was 38.2℃. He exhibited diplopia, gaze-evoked nystagmus on lateral gaze, and gait disturbance, with no headache or meningeal signs. Another CSF examination showed mild pleocytosis (14/mm^3). Brain MRI showed a high signal intensity in the bilateral thalamus, left cerebellum, left midbrain, and right medial temporal lobe (Fig. 1). mPSL pulse 1 g for 3 days followed by PSL 60 mg was initiated; his symptoms showed dramatic improvement. Human leucocyte antigen (HLA) typing showed positivity for B54 and Cw1 and negativity for B51. Although there were no skin lesions at this time, NSD was highly suspected considering the clinical course, findings, and good response to corticosteroids. PSL was gradually tapered, and maintenance therapy with oral PSL was continued.

Fifteen months after the onset of the disease and during maintenance therapy with PSL 7.5 mg, he again relapsed. He complained that "objects appear to move slowly." On an examination he was afebrile and had ocular flutter. There were no other neurological abnormalities. Another CSF examination showed mild pleocytosis (10/mm^3). Brain MRI was normal. He was re-treated with mPSL 1 g per day for 3 days followed by oral PSL, which was tapered gradually. His symptoms were completely alleviated.

He again experienced a relapse 52 months after the first neurological onset while receiving PSL 5 mg maintenance therapy. He developed generalized convulsions and was transferred to our hospital. No neurological deficit was observed. A CSF examination showed mild pleocytosis (58/mm^3), while brain MRI findings were normal. Carmabazepine was administered, and the dosage of PSL was increased from 5 mg to 30 mg. However, because of side effects of PSL (emotional lability), PSL was tapered

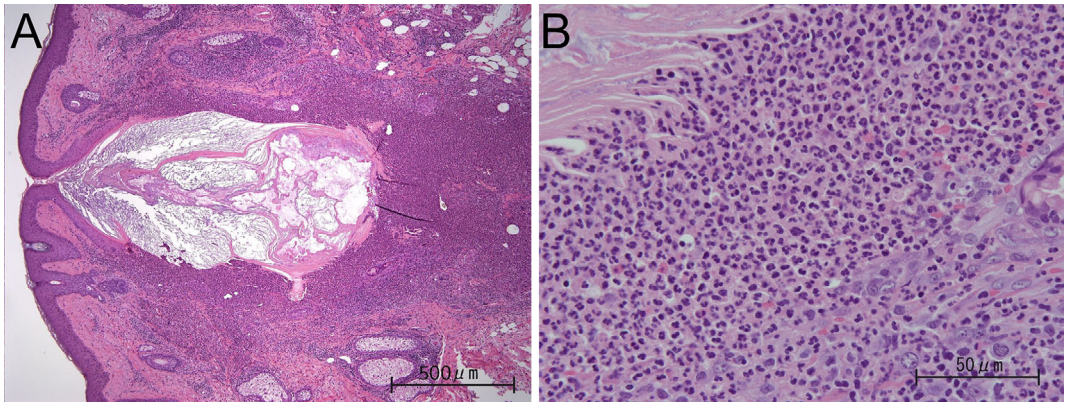

Figure 2. **Hematoxylin and Eosin staining section of facial skin biopsy specimen with a scale bar. Epidermoid cyst and dense dermal infiltration of neutrophils are observed, with no signs of vasculitis (A, ×4 magnification; B, ×40 magnification).**

earlier than after the previous relapse. Two months later, oral dapsone (50 mg followed by 100 mg per day) was administrated as preventive therapy while PSL was gradually tapered to 5 mg per day. No neurological relapse occurred over the subsequent 4.5 years, indicating that dapsone was effective in preventing neurologic relapse.

In the 118th month after the first neurological symptoms, he developed several painful eruptions on the face. A skin biopsy revealed epidermal cyst and dense neutorophilic infiltration in the dermis; no signs of vasculitis were noted (Fig. 2). Although skin infection was considered in the differential diagnosis, the inflammation pattern (absence of epidermal infiltration) was compatible with Sweet's disease. A diagnosis of NSD was established. The skin lesions resolved over several days. The patient did not have uveitis at any point throughout his clinical course.

Discussion

The present case was characterized by various neurological manifestations at each recurrence, and the neurological onset preceded the skin lesions by 10 years. Prior to skin lesion manifestation, HLA typing showed B54 and Cw1 combination, leading to a high suspicion index for NSD (2). In the present case, the patient was diagnosed with "probable" NSD on the basis of criteria for NSD (2). He specifically presented with corticosteroid-responsive relapsing encephalitis, painful red erythema with neutrophilic infiltration of the dermis and spared epidermis. However, vasculitis, uveitis and cutaneous vasculitis/thrombosis, which are generally seen in Behçet disease, were not observed in the patient. Our patient showed improvement with corticosteroid therapy and was successfully maintained on dapsone therapy, which is consistent with previous reports (4, 5).

According to a recent systemic review, a total of 69 cases of NSD were reported in the period of 1983-2017; these included both probable NSD cases (confirmed by skin biopsy) and possible NSD cases (absence of skin lesions). In addition, in 18.8% of these patients, the neurological findings preceded the onset of dermatologic involvement (3). In fact, the first patient diagnosed as "NSD" experienced recurrent meningitis for 2.5 years prior to the development of dermatologic manifestations (6). Furthermore, some patients with NSD initially presented with neurological symptoms for several years prior to the occurrence of skin lesions (5-7). Although the pathogenesis of NSD remains unclear and the organ that was the first inflammatory target in all cases of Sweet's disease is unidentified, our experience suggests that patients with Sweet's disease exhibit long-standing aseptic neutrophilic inflammation in CNS for almost 10 years without concomitant skin lesions. This renders the diagnosis and management of NSD challenging. The prolonged delay in the occurrence of skin lesions may be attributable to corticosteroid maintenance therapy for the prevention of neurological relapse. In patients with corticosteroid-responsive relapsing meningoencephalitis, meningitis, or encephalitis of unknown etiology, maintenance corticosteroid therapy can mask the occurrence of skin lesions if the underlying cause is NSD; this may delay the confirmation of the diagnosis of NSD. Another explanation is that resistance against neutrophilic inflammation in the target organ (including skin) may vary among patients.

Patients with NSD may exhibit various neurological manifestations, such as meningitis or encephalitis, and involvement of various regions on MRI; however, there are no specific neurological features or specific MRI abnormalities that are diagnostic of NSD (2, 3). In the present case, the patient did not undergo enhanced MRI. However, his clinical presentation indicated that he had both meningeal and brain parenchymal involvement. Our patient experienced four distinct episodes: meningoencephalitis with no MRI abnormalities; scattered intramedullary brain lesions; ocular flutter; and isolated seizure with CSF pleocytosis. These episodes were not consistent with other autoimmune encephalitis or demyelinating diseases. Unlike other CNS autoimmune encephalitis or demyelinating diseases, NSD can involve both the meninges and brain parenchyma. Therefore, recurrence of both meningeal and brain parenchymal involvement at

each neurological episode should be considered indicative of NSD or other collagen disease, if there is no skin eruption. We have excluded systematic lupus erythematosus or other collagen diseases through clinical and serological findings.

Currently, the diagnosis of NSD is based on skin biopsy results, implying that the diagnosis can be overlooked or delayed if neurological signs precede the skin lesions by several years. NSD should be considered in the differential diagnosis of patients with recurrent neurological manifestations, especially with both meningeal and brain parenchymal involvement, even in the absence of skin lesions. In such cases, an HLA assessment is useful for the diagnosis. Increased awareness of this form of NSD among neurologists may facilitate earlier recognition and appropriate treatment with corticosteroids, and occasionally, dapsone therapy.

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

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