An autopsy case of Sjögren's syndrome with acute encephalomyelopathy

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Abstract

A 40-year-old woman developed acute myelopathy and brainstem dysfunction. Magnetic resonance imaging (MRI) revealed high-intensity lesions on T2-weighted axial images (T2WI) in the medulla oblongata and cervical spinal cord. We established a diagnosis of Sjögren's syndrome (SjS) according to the European Community criteria. The patient was treated with methylprednisolone (500 mg/day intravenously) for three days, followed by oral prednisolone. Although her neurological symptoms improved, her general condition deteriorated after the onset of acute colonic pseudo-obstruction and she died of multiple organ failure associated with hemophagocytosis. Autopsy showed atrophy of the secretory glands and an accumulation of lymphocytes around the ducts, confirming the diagnosis of Sjögren's syndrome. Neuropathological examination revealed multifocal lesions in the cervical spinal cord and medulla, along with scattered perivascular lymphocytic infiltration. In addition, there was demyelination, spongy change and axonal swelling in the white matter, but no remarkable vasculitic changes were seen in the central nervous system.
1. Introduction

Sjögren’s syndrome (SjS) is an autoimmune disease that may be primary or secondary to other connective tissue diseases. The syndrome is characterized by mononuclear cell infiltration and the destruction of salivary and lacrimal glands, leading to xerostomia and xerophthalmia[1]. Beginning in 1980, Alexander and others published a series of reports [2][3][4][5] indicating that neurological manifestations, mostly involving the peripheral nervous system (PNS), are observed in approximately 20-25% of SjS patients. However, the exact prevalence remains controversial. Delalande et al. reported that the frequency of central nervous system (CNS) involvement by SjS is similar to that of the PNS [2]. Recently, we experienced a patient with SjS that presented with brainstem and cervical spinal cord lesions at autopsy. Here, we report this case with a description of the CNS pathology.

2. Case report

A 40-year-old woman developed weakness in all four limbs. Her symptoms worsened gradually for a few weeks, and she was admitted to our hospital. The patient had a history of diabetes mellitus (HbA1c 7.6%). On neurological examination, she was alert and her visual function was normal, but she had nasal voice and horizontal gaze nystagmus. She was unable to walk because of spastic tetraparesis with bilateral
Babinski sign and Chaddock reflex. Muscle weakness without muscle atrophy was also revealed. (bilateral upper extremities were 4/5 of normal, and bilateral lower extremities were 3/5 of normal). Superficial sensory disturbance below the neck, paresthesia of four limbs and bladder dysfunction (ischuria) were also observed. Cerebellar ataxia, optic neuritis and involuntary movement were not observed. On admission, her body temperature was 36.8 °C, blood pressure was 112/68 mmHg, and respiratory rate was 16/min. The thoracic and abdominal examinations were normal. She had dry eyes and a dry mouth. In regards to her laboratory data, complete blood count, serum electrolytes, creatinine, glucose, coagulation tests, liver functional tests, lactic dehydrogenase, and creatine kinase were normal. IgG (2,359 mg/dl) was moderately elevated, and anti-nuclear antibody (ANA) was positive (86.71 Index). An assay for antibodies to Sjögren's syndrome A (SSA) was 117 indexed, while the assays for antibodies to Sjögren's syndrome B (SSB), anti-double-stranded deoxyribonucleic acid antibody, anti-Smith antibody, anti-nuclear ribonucleoprotein antibody, myeloperoxidase, anti-neutrophil cytoplasmic autoantibodies, proteinase-3 anti-neutrophil cytoplasmic autoantibodies and rheumatoid factor were negative. Serum angiotensin-converting enzyme (ACE) was 5.3 U/l. Anti-HIV antibody was also negative. The cell count in the cerebrospinal fluid (CSF) was moderately increased and all of the cells were
mononuclear cells (cell count 27 /µl), while CSF protein (47mg/dl) was normal. The glucose level (134mg/dl) was not decreased. (Serum glucose level was 232mg/dl.) In addition, the cytology of the CSF was negative. Although MRI of the brain and cervical cord showed high-intensity lesions in the medulla and upper cervical spinal cord on T2WI and fluid-attenuated inversion recovery (FLAIR) images, the lesions were not enhanced by gadolinium. (Fig. 1)

Both Schirmer’s test and the Rose Bengal test during the hospital stay were positive. Therefore, she was diagnosed with primary SjS according to the European Community criteria [1][6], and her neurological symptoms were attributed to CNS lesions caused by SjS. Therefore, 500 mg/day of methylprednisolone was given intravenously for three days as steroid pulse therapy, followed by oral prednisolone at 60 mg/day for four weeks (which was tapered at rate of 10 mg every two weeks). After steroid therapy was initiated, her symptoms improved considerably. On the 10th hospital day, her nystagmus resolved. Her spastic tetraparesis improved gradually. On the 43rd day, she became able to walk by herself with a walker. However, on day 44, she developed acute pseudo-obstruction of the colon, which induced septic shock. Although blood transfusion, antibiotic treatment and hemocatharsis were performed, she died on day 56 of multiple organ failure with hemophagocytosis.
3. Autopsy findings

Malignant tumors were not observed in the general autopsy findings. The entire small intestine was distended by gas and a watery brown feculent fluid, confirming acute intestinal pseudo-obstruction. Superimposed bacterial infections, which possibly included *Clostridium septicum* were indicated. Reactive hemophagocytosis in the bone marrow was also seen. The salivary glands showed destruction and mononuclear cell infiltration, which confirmed the diagnosis of SjS.

The brain weighed 1000 g. On the macroscopic inspection, there were no specific findings (Fig. 2). Microscopically, multifocal changes were observed in the white matter of the pons, medulla and cervical spinal cord (Fig. 3A). Each lesion was composed of a region of spongy change with infiltration of lipid laden macrophages (Fig. 3D,E,G), myelin pallor (Fig. 3B,C), and axonal swelling (Fig. 3F,G). The margin of myelin pallor was obscure. In addition, we observed perivascular lymphocytic infiltration in some lesions (Fig. 3H), though vasculitis, thrombotic microangiopathy, and an invasion of neutrophil or eosinophil leukocytes were not observed. A tissue slice stained by anti-human IgG antibody revealed no deposit of IgG within the inflammatory changes (Fig. 3I). In contrast, CD68 immunoactive macrophages appeared in the lesions (Fig.
Pathological changes were most prominent in the anterior funiculus, the posterior funiculus, and near the central canal of the cervical spinal cord. In the medulla, there was involvement of the tractus solitarius, medial longitudinal fasciculus, medial lemniscus and internal arcuate fibers. Similar changes were also observed in the base of the pons, but the midbrain, cerebellum, and cerebrum were intact.

In the PNS (intracostal nerves, cauda equina and lumbar plexus), demyelination, axonal degeneration and inflammatory cell invasion were not observed.

4. Discussion

Many neurological symptoms can occur in patients with primary SjS. According to previous reports, the CNS lesions in primary SjS are diverse, with both the brain and spinal cord showing focal or diffuse involvement. Delalande et al. reported that the frequency of CNS involvement is similar to that of PNS involvement. The spinal cord was affected in 34.1% of their SjS patients, and spinal lesions resulted in the initial symptoms in 21% of their patients. In addition, 15% of their patients had acute myelopathy [2].

Our patient was considered to have primary SjS both clinically and pathologically, according to the criteria of the European Community [6]. We diagnosed the neurological
symptoms as due to SjS.

In this case, the clinical findings resembled those in Neuromyelitis optica (NMO) / Opticospinal multiple sclerosis (OSMS), multiple sclerosis (MS), systemic lupus erythematosis (SLE), paraneoplastic syndrome, astrocytoma, ependymoma, lymphoma, and parainfectious and postinfectious myelitis, among other conditions[7]. Primary demyelinating pathology such as MS reveals sharp, focal and complete loss of myelin[8]. On the other hand, poorly-demarcated myelin pallor was observed in our case. The pathological changes suggest the possibility of secondary demyelination differentiating from MS. The clinical findings in our case did not fulfill the criteria for SLE [9], and our patient did not have cancer or a brain tumor. AIDS myelopathy was ruled out by the laboratory data. She was able to feed herself, and her total cholesterol, cholinesterase and Vitamin B1 were within normal ranges. Since the lack of macrocytic anemia indicated normal Vitamin B12 and folic acid levels, subacute combined degeneration of the spinal cord was ruled out.

In NMO/OSMS patients, autoantibodies involving SSA and ANA are detected occasionally [10][11][12]. Wang et al. [13] reported a very high prevalence (50%) of Primary Sjogren syndrome in 12 patients, who fulfilled MS criteria of both Poser et al. [14] and McDonald et al.[15]. Additionally, clinical and laboratory studies, as well as
MRI findings were characteristic of OSMS rather than conventional MS. While we were unable to assay for NMO-IgG, no optic neuritis was observed and our patient did not fulfill the criteria of NMO [16] [17]. In regards to the CNS of NMO patients, pathological changes range from perivascular inflammatory demyelination to necrotic destruction of both grey and white matter [18]. Large numbers of eosinophils, polymorphonuclear cells and macrophage are often found in the inflammatory infiltrate [18]. Additionally, IgG deposits are present around vessel walls [18]. Lennon et al suggested that NMO-IgG are the primary cause of NMO through targeting of aquaporin-4[19]. Since there was lymphocytic infiltration instead of eosinophils and no IgG deposits in the inflammatory lesions, it is unlikely that our case was NMO/OSMS.

There have been some reports examining PNS pathology in SjS patients, with vasculitis and perivascular cell invasion being the most common findings[20][21]. However, little information is available concerning pathological changes in the CNS. In particular, there have been few descriptions of myelitis. Several reports [22], [23], [24] have described the CNS pathology of SjS with subsiding angitis and necrosis. On the other hand, Ichikawa et al.[25] reported that necrotic lesions with some perivascular cuffing was the primary change, though granulomatous arteritis at a single focus was observed. Caselli et al. reported five cases of steroid-responsive encephalopathy and proposed the term,
nonvasculitic autoimmune inflammatory meningoencephalitis (NAIM) [26]. One of the reported cases was due to SjS [27]. The pathologic feature was perivascular lymphocytic cuffs without evidence of vasculitis. Joseph et al. also reported that active SjS might cause an NAIM-like syndrome [28]. These reports suggest the possibility that CNS lesions in primary SjS are not necessarily related to vasculitis.

Only a few autopsy cases have described pathological changes in the CNS in SjS patients. Although the steroid therapy may have had a significant influence, the main pathological finding in our case was not vasculitis, but axonal degeneration with spongy change and axonal swelling.

References


Figure 1

A) T2-weighted sagittal MRI of the cervical spine showing hyperintense lesions affecting the brain stem and spinal cord. B) and C) T2-weighted axial image obtained at the level of the lesion showing hyperintensities.

E) Gd-enhanced sagittal MRI of the cervical spine showing no enhanced lesions.

F) FLAIR sagittal MRI of the brain, G) and H) FLAIR axial MRI of brain. Showing no cerebrum lesion.

Figure 2

A) and B) Macroscopic examination.

Figure 3

A) Axial section obtained at the spinomedullary junction. There is severe degeneration of the dorsal funiculus, near the central canal, and the ventral funiculus. ([]:dorsal) (Kluver-Barrera stain)

B) Enlargement of A), poorly-demarcated myelin pallor near ventral funiculus. (K-B stain, 40x)

C) Enlargement of A), spongy change and myelin pallor in lesions in the dorsal funiculus of the spinomedullary junction. (K-B stain, 200x)

D) Lipid laden macrophage infiltration and spongy change near the dorsal funiculus at
the spinomedullary junction. (Hematoxin&Eosin stain, 100x)

E) Enlargement of D), lipid laden macrophage(arrow) and spongy change( inconsolably) can be observed. (H-E stain, 200x)

F) Enlargement of E), axonal swelling (arrow) can be observed. (H-E stain, 400x)

G) Near F), lipid laden macrophage infiltration and axonal swelling (arrow) can be observed in lesions of the dorsal funiculus at the spinomedullary junction. (Bodian stain, 400x)

H) Perivascular lymphocytic infiltration in lesions near the central canal at the spinomedullary junction. (arrow) (H&E stain, 200x)

I) No deposit of IgG with spongy change and loss of myelin sheath. (anti-human IgG stain, 100x)

J) Macrophage invasion in the lesion near Figure 2F (anti-CD68 stain, 100x)
Figure 1
Figure 2

A)

B)