Sjögren's Syndrome with Primary Biliary Cirrhosis, Complicated by Transverse Myelitis and Malignant Lymphoma

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Abstract

A 53-year-old woman with Sjögren's syndrome (SS) and primary biliary cirrhosis (PBC) complicated by transverse myelitis (TM) and malignant lymphoma (ML) is reported. TM has been described only in seven cases of primary SS, including three with PBC and four without PBC. The features of SS associated with PBC and complicated by TM were less typical compared with those seen in SS without PBC complicated by TM. This case is the first report of a case with SS, PBC, TM and ML. SS in association with PBC is, in general, overlooked, but such cases must be investigated with great caution for extraglandular complications. (Internal Medicine 39: 260–265, 2000)

Key words: primary Sjögren's syndrome, necrotizing vasculitis, antineural antibody, antiphospholipid syndrome

Introduction

Primary Sjögren's syndrome (SS) is considered to be the most common disease among the chronic systemic rheumatic diseases. The clinical manifestations are classified into glandular and extraglandular, or exocrine and nonexocrine (1). Clinical manifestations, such as dryness of the skin and mucosa, internal organ involvement, proliferative lymphocytic disorders, thyroiditis and inflammatory vascular diseases appear either concomitantly or more often, independently. Transverse myelitis is a rarely encountered complication in SS. We present here the first case of SS with primary biliary cirrhosis (PBC) complicated by transverse myelitis and malignant lymphoma.

For editorial comment, see p 193.

Case Report

A 53-year-old woman was admitted to our Department of Internal Medicine II, Fukushima Medical University Hospital in April 1995 for the investigation of liver dysfunction, and excessive thirst and dry eyes which were first noticed in 1994. She had been diagnosed as having chronic keratoconjunctivitis in 1994.

The main laboratory data at presentation were as follows

Serum CRP: 0.1 mg/dl (normal: <0.3); WBC: 3,600/mm³ (normal: 2,800–8,800); Hb: 11.4 g/dl (normal: 11.6–14.0); Blood platelets: 13.3×10⁴/mm³ (normal: 14.7–34.1×10⁴); Serum AST: 56 IU/l (normal: 10–30), ALT: 32 IU/l (normal: 6–29), LDH: 506 IU/l (normal: 250–410), ALP: 250 IU/l (normal: 125–335), TB: 1.5 mg/dl (normal: 0.4–1.2), DB: 0.4 mg/dl (normal: 0.2–0.4), TTT: 31.3 KU (normal: 1–5) and ZTT: 27.7 KU (normal: 1–12); anti-hepatitis C virus (HCV) antibody: positive; HCV RNA (probe method): 19 mEq/l; antimitochondrial antibodies: ×80 (normal: <×80); anti-pyruvate dehydrogenase complex M2 antibody: positive; anti-branched chain α-keto acid dehydrogenase complex M2 antibody: positive; antinuclear antibody: <80 (cytoplasmic pattern) (normal: <×80); The titers of anti-SS-A and SS-B antibodies were 7.2 U/ml (normal: <7, borderline: 7–20, positive: ≥20) and 0 U/ml (normal <10, borderline: 10–25, positive: ≥25), respectively, by enzyme immunoassay; Rheumatoid factor: 61 U (<5). Both anticardiolipin antibody and anti-CL β2 GP-1 antibody were negative. The lupus anticoagulant was not measured, but APTT was 35.8 seconds (normal: 31–45).

Decreased salivation was diagnosed in the Department of Otorhinolaryngology of our hospital, but quantitative determination of the volume of saliva was not performed. Histological analysis of a minor salivary gland in an oral mucosal biopsy revealed sparse lymphocytic infiltration and fibrosis around the minor salivary glands. Schirmer's test of both eyes revealed 0 mm wetting in 5 minutes. The tear fluid breakup time (2) was 3 seconds for both eyes (normal: >30 seconds). The rose

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bengal test (van Bijsterveld score) was 9 for corneal erosion.

She complained of a sudden onset of numbness, pain in the lower extremities and dizziness while walking in March 1996. In the meantime, she felt impaired sensation of temperature while bathing, but she did not have a fever consistently. She was referred to the Department of Orthopedics of our hospital and was admitted to that department in April 1996.

The neurological findings were as follows

Impaired sensation of touch, pain and temperature was noted below the Th3~5 level and numbness below the level of Th7. The manual muscle test was 4/5 in the right lower extremity. The knee and ankle jerks were exaggerated. No pathologic reflex was noted. Urine retension and constipation were noted.

The findings on cerebrospinal fluid examination were as follows

Pandy reaction: positive; Nonne-Apelt reaction: negative; glucose: 51 mg/dl; total protein: 37 mg/dl (normal: <40); cell count: 27/3 fields (mononuclear cells: 89%, polymorphonuclear cells: 11%); IgG: 173 mg/dl (normal: <3).

Multiple sclerosis was considered as a differential diagnosis, but she lacked disturbance of visual activity and was too old to be diagnosed as having multiple sclerosis. The serum vitamin B12 level was 790 pg/ml (249–938) and the antibody for HTLV-1 was negative in both the serum and cerebrospinal fluid.

The findings of magnetic resonance imaging of the spine are shown in Fig. 1. The area of Th4~6 was slightly swollen and isointense in T1-weighted images (T1WI), hyperintense

Figure 1. Findings of magnetic resonance imaging of the spinal cord. Sagittal images are shown in A–C. The area of Th3~6 is slightly swollen (arrows), and isointense in T1-weighted images (T1WI), hyperintense in T2WI and enhanced by gadolinium in T2WI as shown in A, B and C, respectively. A transverse T2WI enhanced by gadolinium is shown in D.

Figure 2. Findings of CT and gallium scintigraphy. CT scan revealed swelling of paraaortic and parapancreatic lymph nodes as shown in A (arrows). Gallium scintigraphy revealed accumulation of gallium in cervical, axillary, inguinal, infrahepatic to parapancreatic and paraaortic regions as shown in B.

Figure 3. Histopathological examination of cervical lymph node. HE staining, CD3 staining (Dako, Japan) and CD20 staining (Dako, Japan) were shown in (A), (B) and (C), respectively. The diffuse growth and loss of normal structures such as sinuses and lymphoid follicles were noted. Surface staining for CD20 of lymphocytes clustered in the lymph node were observed, but not for CD3, revealing diffuse non-Hodgkin's, large B-cell type lymphoma (A: $\times 40$, B: $\times 100$ and C: $\times 100$).

in T2WI and enhanced by gadolinium in T2WI. These findings are indicative of an inflammatory rather than a tumorous lesion.

She was administered 1,000 mg/day of methylprednisolone for 3 days under the presumptive diagnosis of inflammatory myelopathy. After a couple of months, the neurological findings such as the decrease in sensation and muscle weakness of the right lower extremity improved, but the sense of numbness below the level of Th7 remained. She was discharged in the month of June 1996.

She was hospitalized again in September 1998, at the Department of Internal Medicine II of our university for the investigation of swollen lymph nodes. A CT scan of the abdomen revealed swelling of the paraaortic and parapancreatic lymph nodes as shown in Fig. 2A. Gallium scintigraphy revealed accumulation of gallium in the cervical, axillary, inguinal and infrahepatic to parapancreatic and paraaortic regions as shown in Fig. 2B. Cervical lymph node and liver biopsy revealed diffuse non-Hodgkin's, large B-cell type lymphoma (NHL) as shown in Fig. 3 and PBC stage II as shown in Fig. 4.

Discussion

The present patient had dry eyes with corneal erosion and dry mouth without definite histologic evidence of sialoadeni-

Figure 4. Histopathological examination of liver. Moderate infiltration of mononuclear cells and destroyed small bile ducts in the enlarged portal area were noted. The intensity of ductal proliferation was slight and bridging necrosis was not found. These findings were compatible with PBC stage II (HE staining, $\times 180$).

tis. The titers of anti-SS-A antibody and anti-SS-B antibody were borderline and normal, respectively. According to the European criteria for the diagnosis of SS (3), the sicca syn-

Table 1. The Findings fulfill the Criteria for Sjögren's Syndrome in Primary Sjögren's Syndrome with Transverse Myelitis

		Ocular symptoms*	Oral symptoms*	Ocular signs*	Histopathologic features*	Salivary gland involvement*	Autoantibodies*
SS with TM and PBC**							
1	35-year-old woman (ref. 9)	dry eye	dry mouth	Schirmer's test: (+) slit lamp examination: (+)	characteristic	not described	SS-A: (-); SS-B: (-)
2	44 year-old woman (ref. 10)	(-)	(-)	ocular gland test: (-)	grade 2 cell infiltrate	salivary gland test: (-)	SS-A: (+)
3	53-year-old woman (present case)	dry eye	dry mouth	Schirmer test: (+) tear break up time: 3 sec. rose bengal test: (+)	not characteristic	Saxon test: (-) Gum test: (-)	SS-A: borderline; SS-B: (-) RF: (+)
SS with TM, but without PBC**							
4	50-year-old woman (ref. 11)	dry eye	dry mouth	Schirmer's test: (+)	not described	salivary gland swelling(+)	SS-A: (+); SS-B: (-)
5	54-year-old woman (ref. 12)	dry eye	dry mouth	Schirmer's test: (+) tear break up time: 5 sec. rose bengal test: (+)	characteristic	salivary gland test: (+)	SS-B: (+)
6	51-year-old woman (ref. 13)	dry eye	dry mouth	Schirmer's test: (+) rose bengal test: (+)	characteristic	not described	SS-A: (+); SS-B: (-) anticardiolipin antibody: (-)
7	46-year-old woman (ref. 14)	dry eye	dry mouth	Schirmer's test: (+) rose bengal test: (+) fluorescein test: (+)	characteristic	scintigraphy: hypofunction of salivary glands	SS-A: (+); SS-B: (+) anticardiolipin antibody: (-) lupus anticoagulant: (-)

*Criteria are from reference 3. **Patients with SS and TM were divided into two groups; those with PBC and those without PBC. SS: Sjögren's syndrome, PBC: primary biliary cirrhosis, TM: transverse myelitis, SS-A, SS-B: anti-SS-A, SS-B antibody.

drome in this patient cannot be diagnosed as definite SS, but can be diagnosed as probable SS. This patient also had liver dysfunction with HCV and antimitochondrial antibodies. Histopathological examination clearly revealed the liver dysfunction as being due to PBC and not due to HCV.

We thus examined the relationship between transverse myelitis and malignant lymphoma, and the above-mentioned SS with PBC. In regard to the relationship between hepatitis viruses and transverse myelitis, hepatitis type B virus (HBV) has been implicated in transverse myelitis, and the molecular mimicry of HBV and myelin basic protein was proposed as being the cause of transverse myelitis in HBV carriers and following HBV vaccination (4–6). There are also reports of hepatitis type A virus in association with transverse myelitis (7, 8). However, to our knowledge, there have been no reports of HCV in association with transverse myelitis.

SS is classified into primary and secondary types. Although the central nervous system involvement in connective tissue vascular diseases such as systemic lupus erythematosus and polyarteritis nodosa is well known, transverse myelitis has been described in only seven cases with primary SS (9–14) as shown in Table 1.

Cases 1–3 have primary SS as well as PBC. Among these three cases, Case 1 was negative for anti-SS-A and SS-B antibodies, Case 2 did not have positive results on ocular and salivary gland tests and Case 3, the present case, has a borderline elevation in the titer of anti-SS-A antibody, is negative for anti-SS-B antibody, and the histopathological findings in the minor salivary glands were not typical for SS.

On the other hand, cases 4–7 having primary SS more satisfactorily fulfil the European criteria for the diagnosis of SS (3) than those patients with PBC. As a matter of fact, the mean number of findings which fulfil the criteria in patients with primary SS with PBC and transverse myelitis and in patients with primary SS without PBC and with transverse myelitis was 3 and 5.5, respectively.

We wish to propose that, when associated with PBC and complicated by transverse myelitis, SS exhibits less features of the syndrome, although this would be difficult to conclude from this study because of the limited number of cases with SS exhibiting the complication of transverse myelitis. Comparing the number of primary SS patients with PBC with those without PBC, transverse myelitis seems to be more frequent in patients of SS with PBC.

The transverse myelitis could be caused in patients with SS by 4 mechanisms: [1] necrotizing vasculitis (11), [2] ganglionitis with T-cell infiltration (15, 16), [3] antineural antibody-mediated neural cytotoxicity (17) and [4] vascular thrombosis. Here, ganglionitis was seen in the dorsal root and by hyperintensity on T2WI, but it was not enhanced by gadolinium in T2WI (16). In another report, a patient with transverse myelitis did not have antineural antibody and patients with antibody were manifested by neurologic findings such as polyneuropathy, organic brain syndrome, migraine and sensory neuronopathy (17). The present patient did not have anticardiolipin antibody or anti-CL β 2 GP-1 antibody, and

APTT was within the normal limit. From these findings, we suppose that this patient with SS was complicated by transverse myelitis due to necrotizing vasculitis.

Later, the present patient developed NHL. Patients with SS have a 43.8 times higher probability of developing malignant lymphoma than expected from the rates of cancer prevailing among women of comparable age in the general population (18). Patients with primary SS have a greater risk of developing NHL compared with those with secondary SS (19). Although monoclonality of lymphocytes does not unequivocally indicate malignancy, it is considered to be a precursor of the development of NHL in SS. Polyclonal lymphoproliferation characterizing SS might in some instances transform into monoclonal proliferation, and then go on to become malignant (20). In developing malignant lymphoma, monoclonal proliferation in the background of polyclonal proliferation of lymphocytes occurs, resulting in deterioration of the features of SS. We suppose that this transformation from polyclonal into monoclonal proliferation might be one of the reasons why she exhibits less features of SS.

It should be mentioned that PBC can also be complicated by malignant lymphoma. A few reports describe the development of malignant lymphoma in the liver (21, 22), but it is a very rare condition; moreover, malignant lymphoma of extrahepatic sites such as in our case is extremely rare (23). Among those patients of PBC complicated by malignant lymphoma, the association between PBC and malignant lymphoma is discussed in relation to SS complicating PBC (24).

This is the first report of a case with PBC, SS, transverse myelitis and malignant lymphoma. SS in PBC is, in general, overlooked, but such cases must be investigated with great caution for extraglandular and glandular complications.

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