Type II Diabetes Mellitus and Primary Sjögren's Syndrome Complicated by Pleural Effusion

Yoshio HORITA, Masanobu MIYAZAKI, Jun-ichi KADOTA, Takashi WATANABE*, Miwako YAMASHITA**, Kiyooki NISHIURA***, Takashi TAGUCHI****, Takeshi MATSUO*****, Yoshiyuki OZONO and Shigeru KOHNO

Abstract

A 73-year-old man was admitted to our hospital because of pleural effusion and nephrotic syndrome. Sjögren's syndrome (Sjs) was diagnosed based on a positive test for antibodies to Ro and La, and the result of labial salivary gland biopsy. The pleural effusion showed a high number of lymphocytes and high titers of antibodies to Ro and La. By immunohistochemistry, it was determined that infiltrating CD3⁺ cells predominated over infiltrating CD20⁺ cells in the pleura. Nephrotic syndrome was also present, which, as confirmed by renal biopsy was due to advanced diabetic nephropathy. Here, we report a case of Type II diabetes mellitus and primary Sjs complicated by pleural effusion, discuss the available treatment for pleural effusion. (Internal Medicine 39: 979-984, 2000)

Key words: pleurisy, anti Ro/La antibodies, labial salivary gland, diabetic nephropathy

Introduction

Sjögren's syndrome (Sjs) is a systemic autoimmune disorder characterized by lymphocyte proliferation and infiltration in exocrine glands, with clinical manifestations of dry eyes (keratoconjunctivitis sicca), dry mouth (xerostomia), and renal injury. It may exist as a primary (primary Sjs) or secondary condition (secondary Sjs) in association with other autoimmune disorders such as rheumatoid arthritis or systemic lupus erythematosus (SLE). There are some reports of Sjs associated with pleural effusion (1-4). In such cases, the pleural effusion shows a high number of lymphocytes and high titers of antibodies to Ro (SS-A) and La (SS-B), implicating the autoimmune mechanisms of Sjs itself in the development of pleural effusion (1, 2).

Although diabetes mellitus (DM) is a rare complication in Sjs, a few cases have been reported (5, 6). Alspaugh and Whaley (6) examined 171 patients with Sjs and found 7 (4.1%) with DM. Binder et al (5) indicated that the association of Sjs with DM might be more frequent than previously thought. Here, we report a 73-year-old man with Sjs and Type II DM, who presented with pleural effusion, which was most likely related to Sjs and diabetic nephropathy.

Case Report

A 73-year-old Japanese man with a 4-month history of dyspnea and pretibial edema was admitted to the Municipal Hospital because of bilateral pleural effusion and severe proteinuria. There was no chest pain, cough, or expectoration. He had a 10-year history of Type II DM and hypertension. Both conditions were controlled by diet, and no oral hypoglycemic agent or insulin was used. The funduscopy showed bilateral preproliferative diabetic retinopathy, and he had sensory deficits. This family history was unremarkable. Physical examination showed no fever (body temperature 36.6°C) and a blood pressure of 134/80 mmHg. There was no alopecia, lymphadenopathy, oral ulceration, organomegaly, or synovitis.

Laboratory tests showed a white blood cell count of 4,100/mm³, hemoglobin at 11.2 g/dl, hematocrit at 32.7%, and platelet count of 21.2×10⁴/mm³. Blood urea nitrogen was 21.5 mg/dl, serum creatinine 2.0 mg/dl, sodium 138 mEq/l, potassium 3.8 mEq/l, chloride 101 mEq/l, total protein 7.3 g/dl, albumin 2.2 g/dl, amylase 87 IU/l, lipase 32 IU/l, C-reactive protein 2.0 mg/dl, blood sugar 108 mg/dl, and glycohemoglobin A_{1c} (HbA_{1c}) 6.2%; liver function was normal. Urinalysis showed severe proteinuria (4.7 g/24 hour, nephrotic range) but no leukocytes or erythrocytes. Blood gas analysis while breathing room air showed a pH of 7.48, PCO₂ 45 mmHg, PO₂ 89 mmHg, and HCO₃ 30 mmol/l. Serologic profile performed at admission showed a high antinuclear antibody titer (1:320, speckled type) and a high titer of rheumatoid factor (1:160). Serum

From the Second Department of Internal Medicine, Nagasaki University School of Medicine, Nagasaki, *the Departments of Internal Medicine, **Ophthalmology and ***Surgery, Matsuura Municipal Hospital, Nagasaki, ****the Second Department of Pathology, Nagasaki University School of Medicine, Nagasaki and *****Pathology Section, Kyushu Biseibutsu Laboratory, Nagasaki

Received for publication September 24, 1999; Accepted for publication May 11, 2000

Reprint requests should be addressed to Professor Shigeru Kohno, the Second Department of Internal Medicine, Nagasaki University School of Medicine, 1-7-1 Sakamoto, Nagasaki 852-8501

complement levels were normal. Antibodies to Ro were 25.9 (normal <20.0) and to La were 59.1 (normal <25.0), but antibodies to single- and double-stranded DNA, RNP, Sm, and Scl-70 were negative. Thyroid stimulating hormone was 3.2 μ IU/ml (normal 0.4 to 3.7), free triiodothyronine was 2.5 pg/ml (normal 2.2 to 4.1), and free thyroxine was 1.2 ng/dl (normal 0.8 to 1.7). C-ANCA and MPO-ANCA, cryoglobulin, anti-glutamic acid decarboxylase (GAD) antibody, anti-insulin antibody, and human T cell lymphotropic virus type I (HTLV-I) antibodies were negative. A skin test with purified protein derivative of tuberculin was negative. Schirmer's test revealed that both strips recorded only 1 mm at 5 minutes. Rose Bengal conjunctival staining was positive. The minor salivary glands of the lower lip were chosen for biopsy. A biopsy of the labial salivary gland showed dense lymphocytic infiltration of around the ducts and atrophic acini [grade 3 by Chisholm and Masson (7)] (Fig. 2). Findings fulfilled the diagnostic criteria for primary SjS of the Research Committee on SjS of the Ministry of the Health and Welfare of the Japanese Government (8) as well as the criteria for definite SjS proposed by the European Community Study Group on Diagnostic Criteria for SjS (9). Radiographs of the hands showed no destructive changes in the joints. Chest X-ray (Fig. 1) and chest computed tomography revealed bilateral pleural effusion but no abnormal lesion in the lung fields or cardiomegaly. Ultrasonic cardiography showed no ischemic changes and no pericardial effusion.

Pleurocentesis performed on the left side showed turbid exudate. Biochemical analysis of the effusion showed a total protein level of 3.7 g/dl, lactate dehydrogenase of 284 IU/l, and glucose of 88 mg/dl. Bacterial culture and polymerase chain reaction analysis for *Mycobacterium tuberculosis* DNA were negative. Antibodies to Ro and La were detected by ELISA at 22.3 and 76.4, respectively. Analysis of the pleural effusion revealed a total cell count of 2,400/mm², and a greater number

of lymphocytes than of neutrophils. No malignant cells were detected in the pleural effusion. Pleural biopsy was performed 30 days after hospitalization. The specimen showed fibrotic changes and infiltration of mononuclear cells (Fig. 3). Renal biopsy was performed 45 days after hospitalization for further evaluation of the nephrotic proteinuria. The specimen contained 14 glomeruli, which were examined by light microscopy. Many glomeruli were characterized by nodular and diffuse glomerulosclerosis (Fig. 4A). There was marked subintimal hyaline thickening of the afferent and efferent arterioles (Fig. 4B). In the interstitium, focal but massive infiltration of mononuclear cells associated with focal tubular atrophy was observed. The

Figure 2. Photomicrograph of the labial salivary gland shows lymphocytic infiltration around salivary gland ducts (*) and atrophic acini (arrowheads) (HE stain, $\times 400$).

Figure 1. Chest X-ray film showing bilateral pleural effusion.

Figure 3. Pleural biopsy specimen shows fibrous changes and infiltration of lymphocytes (HE stain, $\times 100$).

A

B

Figure 4. Histopathologic examination of a renal biopsy specimen. A: A glomerulus with diffuse mesangial widening due to increased mesangial matrix material, characteristic of nodular glomerulosclerosis in a patient with long-standing Type II DM (Periodic acid-Schiff stain, $\times 400$). B: Photomicrograph of an afferent and efferent arteriole illustrating the typical appearance of subintimal hyaline deposition (arrowhead) (HE stain, $\times 400$).

arteries showed mild to moderate arteriosclerotic changes. Immunofluorescence studies showed diffuse linear depositions of immunoglobulin G (IgG) along glomerular capillary walls and tubular basement membranes. Electron microscopy showed the mesangial area to be occupied by mesangial matrix material with atrophic mesangial cells. The glomerular basement membrane of the peripheral capillary loop was markedly thickened. Focal effacement of the foot processes of visceral epithelial cells was noted (Fig. 5). These findings were compatible with advanced diabetic nephropathy rather than secondary lesions caused by Sj.

For immunohistochemical analysis of the pleural and renal biopsies, paraffin-embedded sections were prepared and stained by a previously reported method (10). The mouse monoclonal antibodies used were anti-CD3 (UCTH-1) and anti-CD20 (L-26) (Chemicon International Inc., USA). CD3 is a specific marker for T cells and CD20 is a specific marker for B cells. Serial sections stained with hematoxylin were used to count the total number of mononuclear cells. Immunohistochemical staining of the lymphocyte subsets in the pleural and renal biopsy specimens is shown in Fig. 6. A predominance of CD3⁺ T cells over CD20⁺ B cells was observed in the mononuclear cell infiltrates of the pleural biopsy and interstitium of the renal biopsy specimen.

Administration of diuretics and intravenous serum albumin was begun, but this failed to resolve the pleural effusion. Since the pleural effusion was thought to be related to Sj based on the antibodies to Ro and La and the mononuclear cell infiltration of the pleura, prednisolone (30 mg/day) was administered for 3 weeks. However, this treatment failed to clear the pleural effusion. Thus, the left pleural effusion was drained under a low-level suction pressure. This was followed by administration of tetracycline (500 mg) into the pleural space. This treatment completely cleared the left pleural space. Right-side effusion was only mild and it did not change throughout the hospitalization.

Discussion

Respiratory manifestations associated with Sj have been reported by several groups (4). Pleural effusion occurs only infrequently in cases of primary Sj. To our knowledge, only 2 cases of primary Sj demonstrating pleural effusion have been reported (1, 2). The 2 reported cases showed features of pleural effusion similar to those of the present case. In all 3 cases, a high number of lymphocytes was present in pleural effusion together with autoantibodies such as La. Moreover, infiltration of mononuclear cells was observed in the 2 earlier cases upon examination of pleural biopsy (1, 2), which is compatible with the features of primary Sj in the extraglandular stage (11). Mononuclear cells in the pleural biopsy specimen were shown by immunohistochemistry analysis to be mostly CD3⁺ T cells (2). These findings strongly suggested that autoimmune mechanisms are involved in the pathogenesis of pleural effusion (1, 2). However, the response to steroid therapy in the present case differed from the responses in the two earlier cases (1, 2); pleural effusion disappeared after steroid treatment in the two prior cases, but not in our case. If autoimmune mechanisms are involved in pleural effusion, steroid therapy should be effective. Administration of 30 mg prednisolone for 3 weeks is generally sufficient for the treatment of Sj, and some degree of pleural effusion clearance should be expected. Refractoriness to steroid in our case suggested the involvement of other diseases in the development of pleural effusion. Pleural effusions secondary to collagen disease such as SLE are rarely steroid-resistant pleural effusions; treatment has included talc poudrage, tetracycline pleurodesis, and pleurectomy (12–14). Tetracycline, in

A

B

Figure 5. Transmission electron micrograph illustrating the typical appearance of nodular glomerulosclerosis. **A:** The mesangium is largely replaced by mesangial matrix material in which atrophic mesangial cells (*) are present. Note effacement of the foot processes of visceral epithelial cells (arrowheads) in several areas and a marked reduction in the diameter of the capillary lumen. **B:** There is marked thickening of the glomerular basement membrane of the peripheral capillary. Double staining with uranyl acetate and lead citrate, $\times 3,750$ (A), $\times 4,150$ (B).

Figure 6. Immunohistochemistry examination serial sections A predominance of CD3⁺ T cells (A, C) over CD20⁺ B cells (B, D) was observed among the infiltrating mononuclear cells in both the pleural and renal interstitium. [(A, B) pleural biopsy specimen, (C, D) renal biopsy specimen, (E) glomerulus.] $\times 200$ (A–E).

particular, had been widely used in the management of recurrent pleural effusions of different etiologies. It should no longer be assumed that pleural effusions such as in SLE are always responsive to steroids. Pleurodesis should be considered early in the management of recurrent large pleural effusions (13). A relationship between Sjs and respiratory manifestations has been reported in HTLV-1-positive patients (15, 16). Since antibody to HTLV-1 was negative in the present case, involvement of HTLV-1 infection was unlikely. Our possible reasons for pleural effusion include hypoalbuminemia due to nephrotic syndrome. This patient had suffered from Type II DM for 10 years. Although control of the DM had been fairly good by diet alone, the presence of advanced diabetic nephropathy was confirmed by renal biopsy. It is important to rule out renal involvement due to Sjs. Twenty-five to fifty percent of patients with primary Sjs have associated renal lesions (17, 18). However, in general, interstitial nephritis is a more common find-

ing than glomerulonephritis (17, 18). It is unclear whether tubulointerstitial damage in our patient was associated with a secondary change due to the advanced diabetic nephropathy or associated with the Sjs. Defects in renal acidification occur regularly in patients with Sjs, and distal renal tubular acidosis and a defect in urinary concentrating ability are almost invariably associated with hypokalemic, hyperglobulinemia, which is a serologic marker for severe chronic tubulointerstitial injury with Sjs (17, 18). However, our patient did not have renal tubular acidosis, hypokalemia, or urinary concentrating abnormality. The cellular response of the interstitium in diabetic nephropathy, which often includes large numbers of lymphocytes, was indistinguishable from that observed in other forms of chronic renal disease (19). Some investigations have revealed that the interstitial cellular infiltrates in tubulo-interstitial disease, glomerulonephritis, systemic disease, and DM were predominantly T cells, whereas the B cell population accounted

for less than 20% of the infiltrates (19–21). In the present case, interstitial infiltration of mononuclear cells comprised mostly T cells. Because steroid therapy is usually beneficial for renal injury in patients with Sjs without chronic renal failure (22), the present renal biopsy results strongly suggest that the main pathologic findings in this case were due to DM. Nephrotic proteinuria can then be explained by advanced diabetic nephropathy and pleural effusion, and the leg edema can be considered a complication of the diabetic nephropathy. In cases of advanced diabetic nephropathy, management of pleural effusion and edema is often difficult despite the administration of diuretics and albumin. Our clinical findings suggest that the pleural effusion in this patient was most likely due to immunologic abnormalities of Sjs and nephrotic syndrome induced by diabetic nephropathy. As such, steroid therapy would not be effective for the pleural effusion.

Few studies have described the association between Sjs and DM. Alspaugh and Whaley (6) examined 171 patients with Sjs and found 7 (4.1%) with DM. Based on the fact that 55% of patients with Type I DM showed sicca symptoms with a positive test for anti-Ro antibody, Binder et al (5) concluded that Sjs may be associated with Type I DM (5). Moreover, Pal (23) studied 43 Type I DM and 57 Type II DM patients and showed a positive Schirmer's test in 6 (13.9%) Type I DM and 22 (38.6%) Type II DM patients. The relation between these two disorders was also supported in experimental studies conducted by Goillot et al (24), who demonstrated development of lymphocytic infiltration in the salivary glands in non-obese diabetic mice, suggesting the possible existence of common immunologic abnormalities between Sjs and DM. The association between the two diseases was not clear in the present case.

Acknowledgements: The authors thanks Dr. K. Taira, M.D., Department of Internal Medicine, Taira Clinic, Nagasaki, and Mr. Y. Fukayama, Pathology Section, Kyushu Biseibutsu Laboratory, Nagasaki, for their valuable advice.

References

- Ogihara T, Nakatani A, Ito H, et al. Sjögren's syndrome with pleural effusion. *Intern Med* **34**: 811–814, 1995.
- Kawamata K, Haraoka H, Hirohata S, Hashimoto T, Jenkins RN, Lipsky PE. Pleurisy in primary Sjögren's syndrome: T cell receptor beta-chain variable region gene bias and local autoantibody production in the pleural effusion. *Clin Exp Rheumatol* **15**: 193–196, 1997.
- Suzuki H, Hickling P, Lyons CBA. A case of primary Sjögren's syndrome, complicated by cryoglobulinaemic glomerulonephritis, pericardial and pleural effusions. *Br J Rheumatol* **35**: 72–75, 1996.
- Constantopoulos SH, Papadimitriou CS, Moutsopoulos HM. Respiratory manifestations in primary Sjögren's syndrome. A clinical, functional, and histological study. *Chest* **88**: 226–229, 1985.
- Binder A, Maddison PJ, Skinner P, Kurtz A, Isenberg DA. Sjögren's syndrome: Association with type-1 diabetes mellitus. *Br J Rheumatol* **28**: 518–520, 1989 (see comments).
- Alspaugh MA, Whaley K. Sjögren's syndrome. in: *Textbook of Rheumatology*, Kelly WN, Harris ED, Ruddy S, Sledge CB, Eds. W. B. Saunders Co., Philadelphia, 1981: 971–979.
- Chisholm DM, Masson DK. Labial salivary gland biopsy in Sjögren's disease. *J Clin Pathol* **21**: 656–660, 1968.
- Homma M, Tojo T, Akizuki M, Yamagata H. Criteria for Sjögren's syndrome in Japan. *Scand J Rheumatol Suppl* **61**: 26–27, 1986.
- Vitali C, Bombardieri S, Moutsopoulos HM, et al. Preliminary criteria for the classification of Sjögren's syndrome: Results of a prospective concerted action supported by the European Community. *Arthritis Rheum* **36**: 340–347, 1993.
- Miyazaki M, Nikolic-Paterson DJ, Endoh M, et al. A sensitive method of non-radioactive in situ hybridization for mRNA localization within human renal biopsy specimens: Use of digoxigenin labeled oligonucleotides. *Intern Med* **33**: 87–91, 1994.
- Bottazzo GF, Todd I, Mirakian R, Belfiore A, Pujol-Borrell R. Organ-specific autoimmunity: A 1986 overview. *Immunol Rev* **94**: 137–169, 1986.
- Kaine JL. Refractory massive pleural effusion in systemic lupus erythematosus treated with talc poudrage. *Ann Rheum Dis* **44**: 61–64, 1985.
- Gilleece MH, Evans CC, Bucknall RC. Steroid resistant pleural effusion in systemic lupus erythematosus treated with tetracycline pleurodesis. *Ann Rheum Dis* **47**: 1031–1032, 1988.
- Elborn JS, Conn P, Roberts SD. Refractory massive pleural effusion in systemic lupus erythematosus treated by pleurectomy. *Ann Rheum Dis* **46**: 77–80, 1987.
- Mukae H, Kohno S, Morikawa N, Kadota J, Matsukura S, Hara K. Increase in T-cells bearing CD25 in bronchoalveolar lavage fluid from HAM/TSP patients and HTLV-I carriers. *Microbiol Immunol* **38**: 55–62, 1994.
- Higashiyama Y, Katamine S, Kohno S, et al. Expression of human T lymphotropic virus type 1 (HTLV-1) tax/rex gene in fresh bronchoalveolar lavage cells of HTLV-1-infected individuals. *Clin Exp Immunol* **96**: 193–201, 1994.
- Talal N, Zisman E, Schur PH. Renal tubular acidosis, glomerulonephritis, and immunologic factors in Sjögren's syndrome. *Arthritis Rheum* **11**: 774–786, 1968.
- Siamopoulos KC, Mavridis AK, Elisaf M, Drosos AA, Moutsopoulos HM. Kidney involvement in primary Sjögren's syndrome. *Scand J Rheumatol Suppl* **61**: 156–160, 1986.
- Boucher A, Droz D, Adafer E, Noel LH. Characterization of mononuclear cell subsets in renal cellular interstitial infiltrates. *Kidney Int* **29**: 1043–1049, 1986.
- Bending JJ, Lobo-Yeo A, Vergani D, Viberti GC. Proteinuria and activated T-lymphocytes in diabetic nephropathy. *Diabetes* **37**: 507–511, 1988.
- Furuta T, Saito T, Ootaka T, et al. The role of macrophages in diabetic glomerulosclerosis. *Am J Kid Dis* **21**: 480–485, 1993.
- Frankel AH, Singer DR, Winearls CG, Evans DJ, Rees AJ, Pusey CD. Type II essential mixed cryoglobulinemia: Presentation, treatment and outcome in 13 patients. *Q J Med* **298**: 101–124, 1992.
- Pal B. Sjögren's syndrome and diabetes mellitus. *Br J Rheumatol* **29**: 157–158, 1990 (letter: comment).
- Goillot E, Mutin M, Touraine J-L. Sialadenitis in non-obese diabetic mice: transfer into syngeneic healthy neonates by splenic T lymphocytes. *Clin Immunol Immunopathol* **59**: 462–473, 1991.