Membraneous Glomerulonephritis and Non-Hodgkin’s Lymphoma in a Patient with Primary Sjögren’s Syndrome

Nozomi Iwanaga, Makoto Kamachi, Keita Fujikawa, Toshiyuki Aramaki, Yasumori Izumi, Kazuhiko Arima, Mami Tamaï, Kouichiro Aratake, Hideki Nakamura, Tomoki Origuchi, Hiroaki Ida, Atsushi Kawakami, Takashi Taguchi and Katsumi Eguchi

Abstract

The most common renal manifestation of Sjögren’s syndrome is tubulointerstitial nephritis, and glomerular disease is rare (3). A 62-year-old woman with primary Sjögren’s syndrome developed nephrotic syndrome. Kidney biopsy was consistent with membraneous glomerulonephritis. Steroid pulse therapy was not effective. Three months later she was diagnosed with non-Hodgkin’s lymphoma of the tongue, and she was given CHOP therapy and radiation. Both the lymphoma and membraneous glomerulonephritis were resolved.

Key words: Sjögren’s syndrome, membraneous glomerulonephritis, lymphoma

Introduction

Sjögren’s syndrome is an autoimmune disease characterized by lymphocytic infiltration of salivary and lacrimal glands, leading to the progressive destruction of these glands, and by the production of autoantibodies (1). Extraglandular manifestations are frequent and may include renal involvement (2). Tubulointerstitial nephritis with defects in tubular function is the most common renal manifestation of Sjögren’s syndrome, and glomerular disease is rare (3). Malignant lymphoma was first reported in patients with Sjögren’s syndrome in 1951 (4). Subsequently, adequate studies established strong associations between malignant non-Hodgkin’s lymphoma (NHL) and Sjögren’s syndrome. The risk of NHL in patients with Sjögren’s syndrome is estimated as being 44 times greater than that in the normal population (5). Here, we report a patient with primary Sjögren’s syndrome who developed membraneous glomerulonephritis and non-Hodgkin’s lymphoma of the tongue. The patient’s renal insufficiency and lymphoma resolved after treatment with CHOP and radiation.

For editorial comment, see p 155.
DOI: 10.2169/internalmedicine.46.0177

Case Report

The patient was a 62-year-old woman who was diagnosed with primary Sjögren’s syndrome 10 years previously. Since 1993, urinary beta2-microglobulin had been continuously high, but proteinuria had been negative. She had not been given steroid or immunosuppressive treatment. On May 20, 2000, she developed proteinuria, and on June 15, 2000, she was admitted to our hospital for examination. On admission, her blood pressure was 90/52 mmHg, pulse 66 bpm, and body temperature 36.5°C. She had pretibial edema. There was purpura and pigmentation on her lower extremities.

Urinalysis showed 4.4 g/day proteinuria, 5-10 red blood cells/μL, and 50-100 white blood cells/μL. The 24-hour urinary protein excretion was 4.4 g/day. The serum creatinine level was 1.0 mg/dL, and the estimated glomerular filtration rate (eGFR) was 60.2 mL/min/1.73 m². The serum albumin level was 3.4 g/dL, and the serum alpha-2-macroglobulin level was 190 mg/dL. The 24-hour urinary protein excretion was 4.4 g/day. The serum creatinine level was 1.0 mg/dL, and the estimated glomerular filtration rate (eGFR) was 60.2 mL/min/1.73 m². The serum albumin level was 3.4 g/dL, and the serum alpha-2-macroglobulin level was 190 mg/dL.

The patient was diagnosed with membraneous glomerulonephritis. Kidney biopsy was consistent with membraneous glomerulonephritis. Steroid pulse therapy was not effective. Three months later she was diagnosed with non-Hodgkin’s lymphoma of the tongue, and she was given CHOP therapy and radiation. Both the lymphoma and membraneous glomerulonephritis were resolved.

DOI: 10.2169/internalmedicine.46.1835

Received for publication 23, 2006; Accepted for publication 16, 2006
Correspondence to Dr. Nozomi Iwanaga, nozomi0620@yahoo.co.jp
cells per high-power field, and fatty casts. Total serum protein was 4.8 g/dl, serum albumin was 2.5 g/dl, and total cholesterol was 255 mg/dl. These findings met the criteria of nephrotic syndrome. Blood urea nitrogen was 18 mg/dl, creatinine was 1.0 mg/dl, and creatinine clearance was 54 ml/min. Other hematometry and chemistry were within normal limits. Serological tests were positive for anti-nuclear antibodies (ANA) 640× with a speckled pattern, positive for both anti-SS-A and anti-SS-B antibodies and negative for antibodies against DNA, ribonucleoproteins (RNP), Sm, and antineutrophil cytoplasmic antibodies. The levels of C3, C4, and total hemolytic complement (CH50) were within normal limits. The soluble IL-2 receptor was 900 U/ml. There was no evidence of hepatitis C virus, human T-cell lymphotropic virus type I, or Epstein-Barr virus infection. Cryoglobulin was not detected.

Percutaneous renal biopsy was performed on June 22. The specimen included 11 glomeruli, and 9 of these were sclerosed. Two glomeruli showed focal thickening of the basement membrane and mild mesangial proliferation (PAS staining, Fig. 1). No malignant cells were observed in the specimen. Immunofluorescent examination revealed granular deposits of IgG, C3, and C1q strongly in the capillary wall and focally in the mesangium (Fig. 2). On electron microscopy, subepithelial and mesangial electron-dense deposits were also detected (*). From the above pathological findings, the case was diagnosed as membranous glomerulonephritis of the secondary type.

Corticosteroid pulse therapy, methylprednisolone 250 mg/body for 3 days, was performed and repeated twice. Thereafter, oral prednisolone, 40 mg/day, was started, but 2-3 g/day proteinuria was continued. In August, we found an ulcer at the base of the patient’s tongue. Lingual biopsy was performed on August 28. Below the ulcerated surface, diffuse

Figure 1. Light microscopy. Glomeruli show focal thickening of the basement membrane and mild mesangial proliferation (PAS, 400×).

Figure 2. The immunofluorescent examination reveals granular deposits of IgG, C3, and C1q strongly in the capillary wall and focally in the mesangium (This figure shows deposits of IgG).

Figure 3. Electron-microscopy. Subepithelial electron-dense deposits are seen along the basement membrane (arrows) and mesangial electron-dense deposits were also detected (*).

Figure 4. Lingual biopsy specimen. The tumor cells are composed primarily of medium-sized to large centroblast-like cells. They have pale, oval nuclei with a few nucleoli (HE, 400×).
Glomerulonephritis resulting from malignant lymphoma is not as frequent, but there have been at least 37 reports of glomerulonephritis associated with malignant lymphoma. Histological characteristics of MALT lymphoma have been identified to include the presence of a diffuse infiltrate of centrocyte-like cells intermingled with immunoblasts of the same clone, plasma cell differentiation of the tumor cells, and reactive intratumoral lymphoid follicle. However, these features were not seen in the present case. Immunohistochemical results showed that the neoplastic cells expressed the B-cell antigen CD20. The diagnosis was diffuse large B-cell lymphoma. Staging determined that the lymphoma was localized to the tongue. Chemotherapy with the CHOP regimen (cyclophosphamide 750 mg/m² div, doxorubicin 50 mg/m² div, vincristine 1.4 mg/m² iv, prednisolone 100 mg po) was started in October. It was subsequently repeated for a total of 3 times, and thereafter predonisolone therapy, 25 mg, was continued for 4 weeks and was reduced by 2.5 mg every 4 weeks. In addition, radiation therapy was given in December. After this therapy, the lingual ulcer disappeared, and urinary protein decreased from 2.1 g/day to 0.3 g/day. There have been no signs of relapse over a period of 60 months.

Discussion

Lymphomas that appear after a prolonged course of Sjögren’s syndrome are usually localized extranodal low-grade B cell non-Hodgkin’s lymphoma (6) and are a good target for CHOP therapy. Nephrotic syndrome resulting from membranous glomerulonephritis is clinically well-recognized and generally shows a good response to steroid or immunosuppressive therapy. In contrast, nephrotic syndrome resulting from paraneoplastic glomerulonephritis is resistant to immunosuppressive therapies but in some cases responds to CHOP therapy for malignant lymphoma. We have reported a rare case of primary Sjögren’s syndrome complicated with membranous glomerulonephritis and non-Hodgkin’s lymphoma. In the present case, the renal biopsy showed subepithelial and mesangial deposits on electron microscopy, and subepithelial and mesangial deposits of IgG, C3, and Clq on immunofluorescent examination. These findings are often seen in secondary forms of membranous glomerulonephritis patients with Sjögren’s syndrome or malignancy-associated membranous glomerulonephritis (3, 7). Although we could not exclude the possibility of secondary membranous glomerulonephritis due to Sjögren’s syndrome, this case was more likely paraneoplastic glomerulonephritis related to malignant lymphoma for the following reasons: 1) Clinical prevalence and course; interstitial nephritis is the major renal complication of primary Sjögren’s syndrome, but membranous glomerulonephritis is rare. In contrast, membranous glomerulonephritis resulting from malignancies is a well-known clinical manifestation with an incidence of between 3% and 13%. Associated malignancies occur primarily in the lung and gastrointestinal tract (8). Glomerulonephritis with malignant lymphoma is not as frequent, but there have been at least 37 reports of glomerulonephritis associated with non-Hodgkin’s lymphoma (9-19), indicating a great variety of glomerular lesions, including membranous glomerulonephritis (33%) (9). In addition, 40-45% of patients with membranous glomerulonephritis related to malignancy develop nephrotic syndrome prior to the diagnosis of their tumor, suggesting their etiological relationship (20). In the present case, membranous glomerulonephritis and nephrotic syndrome were detected 3 months before the diagnosis of malignant lymphoma. 2) Serology: no anti-ds-DNA antibody, antineutrophil cytoplasmic antibodies or hypocomplementemia were detected. 3) Response to chemotherapy: nephrotic syndrome resulting from paraneoplastic syndrome has been reported to be steroid-resistant and to responsive to CHOP therapy. For example, a retrospective study (21) with non-Hodgkin’s lymphoma and chronic lymphocytic leukemia (CLL) in 700 patients showed 5 cases of membranous glomerulonephritis-associated lymphoma and CLL. Three of those cases achieved complete remission after chemotherapy (CHOP therapy) (21). Banks reported that aggressive therapy of the lymphoma alone results in complete remission of membranous glomerulonephritis. In some cases of membranous glomerulonephritis, the condition takes several months to resolve; therefore, the steroid therapy prior to CHOP therapy in the present case may have facilitated the clinical remission of nephritic syndrome. However, proteinuria, which did not respond well to high-dose steroid therapy for 4 months, rapidly disappeared with a reduction of lymphoma in response to CHOP therapy.
therapy. Remission of both lymphoma and membranous glomerulonephritis has been maintained for 5 years.

The pathogenesis of paraneoplastic glomerulonephritis is not fully understood, but has been assumed to be mediated by subepithelial immune complexes composed of tumor antigen and antibody, and other nonlymphocyte antigens including viral antigens (22). Sutherland and Mardiney have identified immune complex deposits containing virus-related antigen in the glomeruli of patients suffering from leukemia or lymphoma (23). It is likely that antibodies to lymphocyte antigen in the glomeruli of patients suffering from leukemia with low-grade lymphoma with various forms of glomerulonephritis. Mostly men with low-grade lymphoma with various forms of glomerulonephritis. Mostly men with low-grade lymphoma with various forms of glomerulonephritis.

In conclusion, we encountered a rare case of a patient with Sjögren’s syndrome complicated with membranous glomerulonephritis resulting from paraneoplastic syndrome related to malignant lymphoma. We recommend that patients with Sjögren’s syndrome be carefully evaluated for occult malignancy, in particular malignant lymphoma, when they develop membranous glomerulonephritis.

References


© 2007 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imindex.html