Sjögren's Syndrome, Glomerulonephritis and Malignant Lymphoma

Susumu Sugai

Key words: nephrotic syndrome, B-cell lymphoma, paraneoplastic syndrome

(DOI: 10.2169/internalmedicine.46.0177)

An interesting case of Sjögren's syndrome was presented by Iwanaga et al in this issue (1). Their report documents a case of membranous glomerulonephritis and non-Hodgkin's B-cell lymphoma in a patient with Sjögren's syndrome. Lymphoma occurred shortly after the onset of nephrotic syndrome. The authors showed that treatment of lymphoma could induce remission of lymphoma and nephrotic syndrome for five years. The point of interest of their report is glomerulonephritis and malignant lymphoma associated with Sjögren's syndrome. They presented the conclusion that this case more likely had paraneoplastic glomerulonephritis related to malignant lymphoma rather than glomerulonephritis due to Sjögren's syndrome for the following three reasons: clinical prevalence and course, negative serology and response to chemotherapy.

See also p 191.

DOI: 10.2169/internal medicine.46.1835

Sjögren's syndrome is a chronic organ-specific autoimmune disease characterized by lymphocytic infiltration into the salivary and lacrimal glands, resulting in keratoconjunctivitis sicca and xerostomia (2, 3). Moreover, about half of the patients with Sjögren's syndrome develop systemic disorders. During disease progression from focal to systemic involvement, many organs develop lesions with lymphocytic infiltration which may involve the renal, pulmonary, hepatic, hematologic, dermatologic and other systems. Primary Sjögren's syndrome is defined as the sicca complex in the absence of connective tissue diseases, and secondary Sjögren's syndrome is defined as the sicca complex coexisting with another connective tissue disease.

It is well recognized that a number of autoimmune conditions predispose to the development of lymphomas. Most striking among these are organ specific autoimmune diseases, including Sjögren's syndrome and Hashimoto's thyroiditis. It has been reported that Caucasian patients with Sjögren's syndrome develop malignant lymphomas at a higher incidence (4). The progression from polyclonal lymphoproliferation to monoclonal lymphoproliferation, to mucosa-associated lymphoid tissue (MALT) lymphoma, and finally to high-grade malignant lymphoma is regarded as a multi-step process (5).

The kidney may be involved in primary Sjögren's syndrome. The most frequently recognized histopathological renal lesion is an interstitial lymphocytic infiltrate with tubular atrophy and fibrosis (6). Unlike other connective tissue diseases, such as systemic lupus erythematosus, glomerulonephritis is extremely rare in primary Sjögren's syndrome. Some cases have been reported with membranous, focal, proliferative and membranoproliferative glomerulonephritis. The pathogenesis appears to be based on the glomerular deposition of immune complexes which may overwhelm the clearance mechanisms of the glomerular mesangium and/or the reticuloendothelial system. Such a mechanism is implicated because of the demonstration of immunoglobulin and C3 within the glomeruli by immunofluorescent microscopy and by the numerous electron-dense deposits at electron microscopy. Some studies have shown that patients who have high rheumatoid factor titers and autoantibodies to Ro/SS-A are at greater risk of developing immune complex-mediated disease compared with other patients.

An association between membranous nephropathy and malignancy was first noted in the 1960s, most commonly with tumors of the lung and gastrointestinal tract. A wide range of other tumors has also been associated, although these are not sufficiently common to establish any causal relationship. The incidence of malignancy in patients with membranous nephropathy has been reported to range from 1.4% to 11% (7). The pathophysiology of glomerulonephritis in this type of patients associated with malignancy is not fully understood. Alteration of T lymphocytes in patients with neoplasms has been postulated to be the disorder responsible for minimal-change nephropathy. In other histological types, it has been postulated that the disease is mediated by subepithelial immune complexes composed of tumor antigen and antibody. The subepithelial immune complexes

in membranous nephropathy are believed to represent *in situ* immune complex formation rather than passive trapping of circulating preformed complexes. Data from Brueggemeyer and Ramirez (8) indicated that the relationship existed, confirming studies that have shown a relationship based on positive staining for cancer antigens in kidney biopsy specimens. In patients with lymphoproliferative disorders, nephrotic syndrome also has been reported to occur in the absence of amyloidosis or renal vein thrombosis. This association was most frequently found in patients with Hodgkin's disease. In contrast, non-Hodgkin's lymphoma was only occasionally associated with glomerular disease. Most non-Hodgkin's lymphoma are of B-cell lineage in this situation,

especially in adult patients, although the association of nephrotic syndrome with focal glomerulosclerosis and non-Hodgkin's lymphoma of the T-cell type has been reported. Glomerulonephritis can appear before, simultaneously or after the appearance of the lymphoma, whether it be Hodgkin's or non-Hodgkin's. It was reported that treatment of the neoplasia may cause remission of both lymphoma and glomerulonephritis when glomerular disease occurs at the same time as lymphoma.

The more accumulation of cases such as this in this issue (1) is necessary to reach a conclusion on the causal relationship between glomerulonephritis and lymphoma in patients with Sjögren's syndrome.

References

1. Iwanaga N, Kamachi M, Fujikawa K, et al. Membranous glomerulonephritis and non-Hodgkin's lymphoma in a patient with Sjögren's Syndrome. *Intern Med* **46**: 191-194, 2007
2. Talal N, Moutsopoulos HM, Kassan SS : Sjögren's Syndrome : Clinical and Immunological Aspects. Berlin, Germany, Springer-Verlag, 1987.
3. Moutsopoulos HM, Chused TM, Mann DL, et al. Sjögren's syndrome (Sicca syndrome) : current issues. *Ann Intern Med* **92**: 212-226, 1980.
4. Kassan SS, Thomas TL, Moutsopoulos HM, et al. Increased risk of lymphoma in sicca syndrome. *Ann Intern Med* **87**: 888-892, 1978.
5. Masaki Y, Sugai S. Lymphoproliferative disorders in Sjögren's Syndrome. *Autoimmun Rev* **3**: 175-182, 2004.
6. Tu WH, Shearn MA, Lee JC, Hopper J Jr. Interstitial nephritis in Sjögren's syndrome. *Ann Intern Med* **69**: 1163-1170, 1968.
7. Jefferson JA, Couser WG. Therapy of membranous nephropathy associated with malignancy and secondary causes. *Semin Nephrol* **23**: 400-405, 2003.
8. Brueggemeyer CD, Ramirez G. Membranous nephropathy: A concern for malignancy. *Am J Kidney Dis* **9**: 23-26, 1987.