INTERNAL MEDICINE

□ CASE REPORT □

Membranous Nephropathy Complicating Nasopharyngeal Carcinoma

Tadashi Uramatsu[1], Akira Furusu[1], Tomoya Nishino[2], Yoko Obata[3], Yasuhide Kanamoto[4], Satoru Komuro[5], Masahiro Ito[6], Takashi Taguchi[7] and Shigeru Kohno[1]

Abstract

The patient was a 38-year-old woman diagnosed with nephrotic syndrome. Steroid pulse therapy and mizoribine was started in late October 2002 and continued for about 10 months, but no apparent therapeutic effect was obtained. During this period, the patient was diagnosed with nasopharyngeal carcinoma. As nephrotic syndrome did not improve, renal biopsy was performed and membranous nephropathy (MN) was diagnosed. After resection of nasopharyngeal carcinoma was performed, the urinary protein level decreased rapidly. Since MN caused by nasopharyngeal carcinoma is very rare, this represents an interesting case of malignancy-associated MN.

Key words: secondary membranous nephropathy, nasopharyngeal carcinoma, nephrotic syndrome

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Introduction

Membranous nephropathy (MN) is the most common cause of nephrotic syndrome in adults. Pathologically, subepithelial electron-dense deposits of immune complexes are present on the outer aspect of the glomerular basement membrane. Many cases of MN are idiopathic, but 20-30% of them develop as secondary MN with causes including systemic lupus erythematosus, hepatitis B and C virus infections, drugs, and malignancies. The complication of malignancy by MN is well known and the incidence has been reported to be 1.4-11% (1). The main causative malignancies are lung, colorectal, stomach and renal cancers, Hodgkin disease, and chronic lymphocytic leukemia. Here, we report a rare case of MN manifesting as intractable nephrotic syndrome in which nasopharyngeal carcinoma was found during the course and the nephrotic syndrome remitted completely following resection of the tumor.

Case Report

A 38-year-old woman noticed edema of the lower legs in early October 2002. The patient visited a physician and was diagnosed with nephrotic syndrome based on findings of urinary protein (4+), urinary occult blood (+), 4.6 g/dL total protein, and 1.6 g/dL albumin. Minimal-change nephrotic syndrome was suspected based on the acute onset and thus 0.5 gram of intravenous methylprednisolone combined with oral prednisolone (20-40 mg) was initiated for three consecutive days in late October. Mizoribine (150 mg) was added during the course and treatment was continued for about 10 months, but no apparent therapeutic effect was obtained. During this period, the patient visited the otolaryngology department of our hospital for a chief complaint of rhinostenosis and was diagnosed with nasopharyngeal carcinoma (clinical stage T2N0M0, stage II). Radiotherapy for the carcinoma was initiated in July 2003 (70 Gy/35 fr.), but was ineffective and the tumor size was unchanged. Since

[1]Second Department of Internal Medicine, Nagasaki University School of Medicine, Nagasaki, [2]Division of Blood Purification, Nagasaki University Hospital, Nagasaki, [3]Career Development Center for Medical Doctor, Nagasaki University Hospital, Nagasaki, [4]Shinzato Nephro Clinic, Nagasaki, [5]Department of Otolaryngology, National Hospital Organization Nagasaki Medical Center, Omura, [6]Department of Pathology, National Hospital Organization Nagasaki Medical Center, Omura and [7]Department of Pathology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki
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Correspondence to Dr. Akira Furusu, furusua-ngs@umin.ac.jp

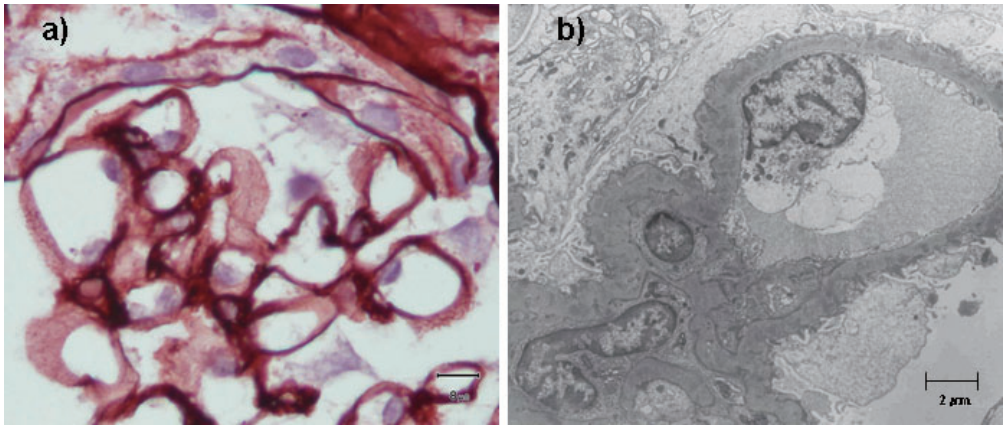

Figure 1. **a) Light microscopy of a sample from renal biopsy (PAM staining). The basement membrane was slightly thickened. b) Electron microscopy of a renal biopsy sample. Deposits were present in the subepithelial regions of the glomerular basement membrane (GBM). Fresh dense and old low-density deposits were observed. No deposits were observed in the mesangium.**

nephrotic syndrome was also not improved, the possibility of an association of nephrotic syndrome with the malignant tumor was considered, and the patient was admitted to our department for a renal biopsy in October 2003.

On admission, her blood pressure was 110/70 mmHg. She presented with no anemia or jaundice in the palpebra or bulbar conjunctiva, but edema was present in her lower legs. Total protein and albumin were decreased to 4.6 g/dL and 1.4 g/dL, respectively, and total cholesterol was elevated to 291 mg/dL. Urinalysis indicated a urinary protein level of 3+ and 3.5 g/day in qualitative and quantitative tests, respectively. Urinary occult blood was 2+ in a qualitative test, and 0-1 red blood cells were present per visual field in the sediment. Fatty casts were noted and urinary N-acetyl-β-D-glucosamidase (NAG) was elevated among renal tubular disorder markers. In seroimmunological tests, CRP was elevated and IgG was decreased. Tests for infection, collagen disease and diabetes, which may cause secondary nephrotic syndrome, were negative.

A chest X-ray revealed no pulmonary congestion or cardiac enlargement and abdominal echography showed no marked change in the kidneys. A CT scan of the head revealed a localized tumor in the epipharyngeal posterior wall without apparent infiltration into the surrounding region.

Renal biopsy was performed with echo-guidance to examine nephrotic syndrome on the day following admission. Light microscopy showed mild thickening of the basement membrane, as noted on PAM staining. A spike was not apparent, but vacuolar changes were present at many sites. Granular depositions of IgG and C3 along the basement membrane were detected using fluorescent antibodies. Electron microscopy revealed electron-dense deposits under the epithelium of the glomerular basement membrane, including both fresh and old deposits with high and low densities, respectively (Fig. 1). No deposits were present under the endothelium or in the mesangium. MN (Stage II-IV) was diagnosed based on these findings. Since nasopharyngeal carcinoma was present and there was no other apparent cause of MN, we suspected secondary development of MN following nasopharyngeal carcinoma. The tumor was resected about 1 month after the renal biopsy and diagnosed pathologically as squamous cell carcinoma. Nephrotic syndrome had initially been treated with oral prednisolone and mizoribine, but no therapeutic effect had been obtained over 14 months. However, after resection of the carcinoma, the urinary protein level was markedly decreased and the serum protein level was elevated; the nephrotic syndrome remitted completely 2 months postoperatively. Mizoribine and prednisolone were discontinued 3 and 4 months after surgery, respectively. Urinary protein has been negative for about 5 years thereafter, maintaining complete remission (Fig. 2).

Three tumor antigens associated with squamous cell carcinoma (involucrin and cytokeratin 18 and 19) were investigated in the renal tissue by immunohistochemical staining, but no positive reactions were detected in the glomeruli.

Discussion

The complication of malignancies and nephrotic syndrome has been described in the literature, by Lee et al who reported a concomitant malignancy in 10.9% of 101 adult patients with nephrotic syndrome over a 10-year period, with an incidence that was 10 times higher than that in the general population (2). Eagen found that MN was the most frequent causative disease for nephrotic syndrome complicating malignancies, accounting for 68% of cases (3), and Brueggemeyer and Ramirez reported an incidence of malignancies in patients with MN that was more than 5 times higher than that in the general population (4).

About 30% of cases of MN occur secondarily to an underlying condition, with the cause being drugs, malignancies, collagen diseases, and infections in 29%, 23%, 21% and 14% of cases, respectively (5). The incidence of concomitant malignancies in MN patients has been reported to be 1.4-11%, but is 22% in patients aged 60 years old or older (1). Lung, colorectal, stomach and renal cancers,

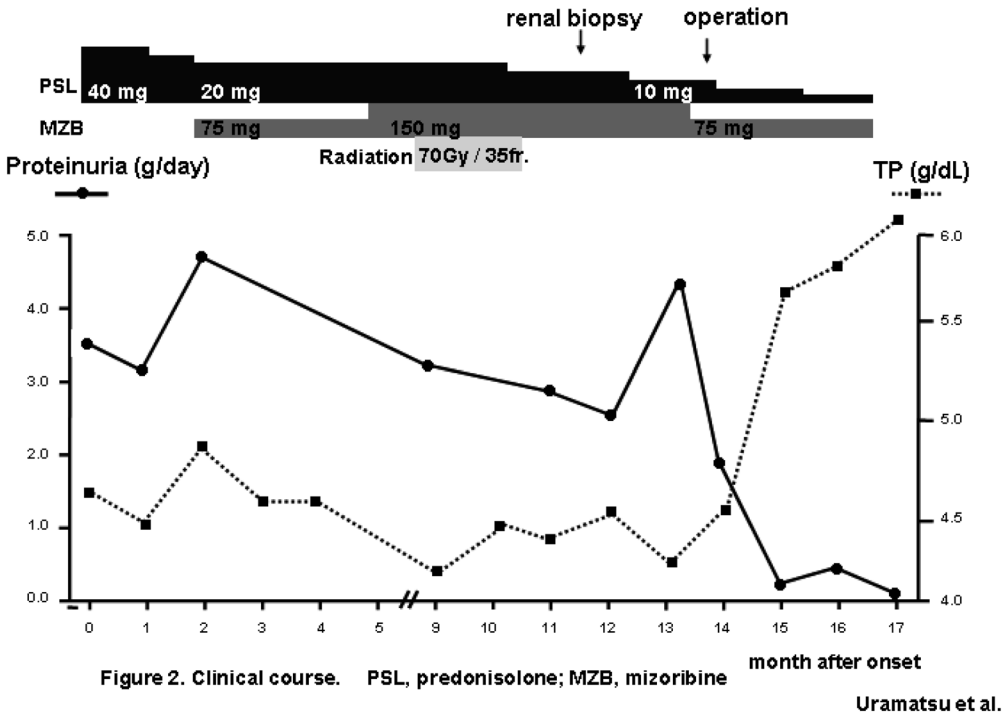

Figure 2. Clinical course.

Hodgkin disease, and chronic lymphocytic leukemia are the main causative malignancies of secondary MN. In contrast, only one case of MN due to pharyngeal cancer has been described [by Lee et al in 1966 (2)] and the present patient may represent the second such case. Eagan found that 2 of 67 patients with cancer-associated nephrotic syndrome had squamous cell carcinoma-associated MN (3), and lung and esophageal squamous cell carcinomas can also lead to nephrotic syndrome (6, 7). Radiotherapy for lung squamous cell carcinoma has been used to reduce the size of the primary lesion and the urinary protein level (6), but in the present patient radiotherapy had no effect.

Nephrotic syndrome complicating malignancies has been found to precede diagnosis of the tumor in 40-45% of cases, with simultaneous onset in 40% and development of renal lesions after the cancer diagnosis in 15-20%. In most cases, both diseases became apparent within 12 months of each other (8). The nasopharyngeal carcinoma in the present patient was diagnosed 8 months after the onset of nephrotic syndrome. Regarding screening for malignancies in MN, Jefferson and Couser recommended that an interview including familial medical history, consultation, fecal occult blood test, colonoscopy, chest X-ray, mammography, and measurement of CEA and PSA should be performed for patients aged 50 years old or older (1). However, the malignancy may be undetectble in these examinations, as in our patient. When the primary lesion is undetectable in these examinations, as in the present patient, nasopharyngeal cancer should be considered in the differential diagnosis of primary lesion in secondary MN.

The developmental mechanism of malignancy-associated MN is assumed to involve tumor-related antigens and antibodies against the antigens forming immune complexes that are deposited in the glomeruli, thereby inducing the disease. The presence of tumor-related antigens assocaited with tracheal tumor, melanoma, and colorectal cancer in deposits under the glomerular epithelium has been demostrated, but tumor-related immune complexes have not been found (1). A squamous cell carcinoma-related antigen was not detected in the present patient, but we cannot rule out the possibility that an unidentified antigen was involved in the development of MN.

Concerning the differential diagnosis between the idiopathic and secondary forms of MN, Ohtani et al reported a high staining intensity for IgG1 and IgG2 using a fluorescent antibody in malignancy-associated MN, and recommended careful investigation of malignancies when this feature is noted in patients aged 40 years old or older (9). In addition, several histological characteristics have been identified by electron microscopy that may be useful in distinguishing between idiopathic and secondary forms of MN (1). In Class V lupus nephritis and MN associated with hepatitis B virus infection deposits are present in the mesangium and subendothelium, whereas in MN associated with malignancies deposits of a relatively small size are observed only in the mesangium. In the present patient, there were no deposits in the mesangium, and small and large deposits were present under the epithelium. Although these findings differed from the typical pathology of secondary MN, nephrotic syndrome remitted after tumor resection, no other cause of nephrotic syndrome was present, and nephrotic syndrome had developed 8 months before the diagnosis of nasopharyngeal carcinoma, suggesting that this case is consistent with malignant tumor-associated MN.

The treatment of choice of nasopharyngeal carcinoma is radiotherapy, but this did not reduce the tumor size or urinary protein level in the present case (10). However, the refractory nephrotic syndrome rapidly and completely remitted after tumor resection. This suggests that the course of urinary protein excretion may serve as an index of the effect of cancer therapy in cases of malignancy-associated MN. Furthermore, it is possible that a future increase in the urinary protein level may reflect recurrence of nasopharyngeal carcinoma, and we intend to follow-up the patient carefully in this regard.

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