A Case of Cervical Cancer-related Membranous Nephropathy Treated with Radiation Therapy

Chiharu Ito, Tetsu Akimoto, Eiko Nakazawa, Satoko Komori, Taro Sugase, Junko Chinda, Hideaki Takahashi, Takashi Ioka, Shigeaki Muto and Eiji Kusano

Abstract

Paraneoplastic nephropathy is a rare complication of malignant disease. We present a case of cervical cancer with biopsy-proven membranous nephropathy and associated nephrotic syndrome. Irradiation to the specific neoplasm site and to the metastatic paraaortic lymph node tissues lead to regression of the nephrotic syndrome without causing severe adverse events. Radiation therapy can be the first choice in the treatment of paraneoplastic nephrotic syndrome if the primary neoplasm is unresectable. Invasiveness of intervention and patient prognosis should be carefully deliberated in the management of the two diseases.

Key words: membranous nephropathy, uterine cervical cancer, radiation therapy, squamous cell carcinoma-related antigen

(Intern Med 50: 47-51, 2011)
(DOI: 10.2169/internalmedicine.50.4341)

Introduction

Galloway reported the first case of paraneoplastic nephrotic syndrome (1). The pathological feature is usually membranous nephropathy (MN) or minimal change type, which occurs in association with a solid neoplasm of the lung, stomach, mammary gland, prostate, or colon. Reportedly, complete surgical resection of cancer resulted in remission of the nephrotic syndrome (2, 3). However, treatment of paraneoplastic syndrome is sometimes complicated because it is associated with advanced cancer with unresectable lesions. Here, we report a patient with cervical cancer and paraneoplastic nephrotic syndrome for whom radiation therapy remarkably improved urinary protein excretion and edema.

Case Report

A 75-year-old woman noticed bilateral lower leg edema in mid-November 2006. As nephrotic syndrome was suspected at an affiliate hospital, she was referred to our hospital. She never complained of persistent diarrhea stool. Her past history included old cerebral infarction. Tizanidine hydrochloride and amantadine hydrochloride had been administered for the after effect of old cerebral infarction. No other medication was prescribed at the first medical examination. On admission to our ward in late November, physical examination showed blood pressure of 134/76 mmHg, clear breath sounds, and 2+ lower extremity pitting edema. Her laboratory findings were serum creatinine level 0.8 mg/dL, serum total protein 5.0 g/dL, serum albumin 1.3 g/dL, serum total cholesterol 395 mg/dL, serum aspartate aminotransferase 25 mU/mL, and serum alanine aminotransferase 15 mU/mL. Serological test results for hepatitis B surface antigen, anti-hepatitis C antibody, and anti-double stranded deoxyribonucleic acid antibody were negative. Immunologic test results for antistreptolysin O titer, C3, C4, and C-reactive protein were within normal range. An abdominal ultrasound analysis did not reveal liver cirrhosis and hydrenephrosis. A high titer of squamous cell carcinoma (SCC)-related antigen (SCCA) (16.6 ng/mL) was found and the existence of SCC in her body was assumed. A diagnosis of nephrotic syndrome was established and renal biopsy was performed in early December.

Her renal specimen, which included 16 glomeruli, showed no interstitial cellular infiltration. No findings of glomerular sclerosis, crescentic formation, adhesion to Bowman’s cap-
Figure 1. Microscopic findings of the renal tissue at needle biopsy. a: Periodic acid-Schiff stain of glomeruli. Scale bar corresponds to 50 μm. b: High magnification of the same glomeruli in A. Scale bar corresponds to 50 μm. No spike formation was found on the basement membrane. c: Immunofluorescence staining for IgG antibody. d: Immunofluorescence staining for C3c antibody.

Figure 2. Electronmicroscopy findings of the renal tissue at needle biopsy (×10000). Subepithelial bead-like high-density deposits were observed.

A survey for malignancy was conducted and histological findings of her cervical biopsy specimen showed invasive SCC. She never complained of atypical vaginal bleeding, vaginal fluor, and genital pain. Pelvic examination revealed stage Ib1 cervical cancer. Computed tomography (CT) showed a cervical tumor (Fig. 3a) and paraaortic and iliac vein bifurcation swollen lymph nodes (Fig. 3b). She was diagnosed as having stage I MN associated with cervical cancer. Abdominal CT did not detect renal vein thrombosis.

Administration of 40 mg/day of furosemide and 25 mg/day of spironolactone improved her edema though 5-6.5 g/day (8-10 g/urine-creatinine) urinary protein excretion remained (Fig. 4). Low remission rate of nephrotic syndrome with immunosuppressant in tumor-associated MN was reported (6) and complete remission would be expected in nearly half of the cases whose tumor was in remission in tumor-associated MN (6). Then, we decided to introduce her to the gynecology unit of our hospital to initiate the treatment of the original lesion of her SCC. In consideration of her complications including after effect of old cerebral infarction and nephrotic syndrome, invasive operation was avoided. External irradiation to the whole pelvis (49.4 Gy) with an additional bilateral parametrial sidewall boost (59.6 Gy) was delivered from the end of December 2006 to the
beginning of February 2007. During this period, intracavitary brachytherapy was combined with a remotely controlled afterloading system to point A (68.2 Gy). Immediately after the radiation therapy, her urine protein excretion increased transiently, then reverted to her original level (Fig. 4); nevertheless, the size of her primary SCC lesion was reduced (Fig. 3c). She was discharged from our hospital and subsequently re-entered to take a second session of irradiation from early March to early May 2007. Four-port irradiation (45 Gy to her twelfth thoracic to fourth lumbar vertebrae and 58.8 Gy) was delivered to her swollen paraaortic lymph nodes. No serious radiation complications occurred in her rectum or bladder. Tumor lysis syndrome was absent and her renal function did not become exacerbated throughout the treatment period. Later CT scanning showed that the lymph node swelling was improved (Fig. 3d). The titer of
serum SCCA fell to 5.0 ng/mL immediately after the first session of radiation therapy and subsequently decreased to 1.7 ng/mL after the second session (Fig. 4). Her protein excretion gradually decreased and her hypoalbuminemia improved. She was observed as an outpatient and her nephrotic syndrome was kept in partial remission.

Unfortunately, her serum SCCA level increased gradually after the irradiation sessions (Fig. 4); reevaluation of abdominal CT showed recurrence of swollen paraaortic lymph nodes. Additional radiation therapy was not performed because of her poor physical condition.

In late September 2007, she was lethargic and had a poor appetite. She visited the emergency care unit with stiff extremities and transient left leg spasm. Her laboratory data showed hyponatremia (112 mmol/L) with excessive urine sodium excretion (71 mmol/L). Her cervical spine MRI and bone scintigraphy showed bone metastases to C6, C7, and Th1. The cause of her hyponatremia was suspected to be dehydration because of insufficient intake of sodium chloride and the consecutive use of diuretics. Her hyponatremia improved after the hypertonic saline loading. Involvement of syndrome of inappropriate of anti-diuretic hormone secretion was ruled out. Irradiation to her vertebrae was not conducted. She subsequently died as a result of upper gastrointestinal bleeding. An autopsy was not permitted.

Discussion

Membranous nephropathy has been associated with various malignant neoplasms including those of the bronchial and digestive systems (4). However, MN has rarely occurred with gynecological neoplasms. Within our survey, only two cases of MN associated with cervical cancer in adults have been reported (5, 6). Furthermore, the documentation of reported MN cases with uterine cancer could not be found within our literature retrieval system.

The clue to identify the cervical cancer was the high titer of serum SCCA in the present case. The patient did not complain of major manifestations such as atypical vaginal bleeding associated with cervical cancer. In general, the measurement of serum SCCA for the screening of SCC is not conducted because of the low positive rate of serum SCCA in the early stage of cancer (7). Regarding that the prevalence of cancer among patients over 60 years old with nephrotic syndrome was 22% (8) and that 24% of cancer accompanied MN patients had SCC (6), the SCC screening with SCCA measurement would be reasonable to consider. In addition, monitoring of serum SCCA in cervical cancer patients is useful for clinical decision making and predicting prognosis (9-11), or detection of recurrence of carcinoma (7, 12).

A morphological pattern of glomerular injury called MN has been seen in various diseases. The paraneoplastic MN is histologically identical to that of idiopathic MN (13). Recently, Lefaucheur et al reported that the number of inflammatory cells infiltrating the glomeruli was significantly higher in patients with cancer-associated MN than in idiopathic MN (6). In the present case, glomerular inflammatory cell infiltration was not particularly noted. The significance of inflammatory glomeruli infiltration in paraneoplastic MN has not been clearly defined; therefore, accumulation of pathological evidence would be helpful.

Ohtani et al reported the strong glomerular immunofluorescence intensity of IgG1 and IgG2 in the MN cases with malignant neoplasm (14). In their study, glomerular IgG3 deposit in 10 MN cases with malignant neoplasm was weak compared with those of IgG1, IgG2, and IgG4. The significance of sole IgG3 deposition in the glomeruli of the present case was obscure.

The links between malignancy and MN are not understood. The establishment of a causal relation requires the criteria (13). The first is a close temporal connection between the clinical appearance of renal disease and neoplasms. Burstein et al reported that approximately 40-45% of patients with solid neoplasms and MN clinically manifest the nephrotic syndrome prior to the diagnosis of their neoplasms (15). Simultaneous presentation appears in roughly 40% of patients. The remaining 15-20% manifest the renal disease following the diagnosis of their neoplasm. In the present case, the covert cervical cancer was discovered incidentally after the manifestation of nephrotic syndrome. A temporary association may be suggested between her MN and cervical SCC. Delayed diagnosis of malignancy in the nephrotic syndrome patients can influence their life prognoses. Since immunosuppression by corticosteroid and calcineurin inhibitor therapy might engender severe problems in malignancy patients, a survey of the malignant neoplasms is extremely important for elderly nephrotic syndrome patients.

Secondly, remission or complete removal of a neoplasm is usually associated with remission of the renal disease in paraneoplastic MN cases. Remission of MN-related nephrotic syndrome by cancer resection (2, 3, 16, 17), chemotherapy (18), or radiation therapy (19) has been reported. In the present case, the extent of urinary protein excretion and edema did not change after the first session of radiation therapy to the pelvis. However, the nephrotic condition improved drastically after the second session of radiation therapy which included irradiation of the lymph nodes. Case reports of improved paraneoplastic syndromes following treatment of metastatic tissues are rare in the relevant literature. The precise pathological association remains unknown.

Third, in the paraneoplastic syndrome cases, the recurrence of malignancy accompanies the original paraneoplastic symptom. In the present case, recurrence of the nephrotic syndrome was absent, although high titers of SCCA in the serum were sustained when the metastases of lymph nodes and vertebrae were discovered. Within our survey, reported cases which fit this criterion were rarely documented and the disability of neoplasm itself to cause MN was suggested.

Fourth, renal biopsy demonstrates malignancy-related antigen and associated antibody in glomerular deposits seen in
paraneoplastic membranous nephropathy (20, 21). We performed immunohistological detection of SCCA1 and SCCA2 in the patient’s kidney biopsy tissues with anti-SCCA1 and anti-SCCA2 antibodies (Santa Cruz Biotechnology, Santa Cruz, CA, U.S.A.). No staining of SCCA1 and SCCA2 was detected beneath the glomerular peripheral wall (data not shown). These findings implied that SCCA itself unlikely acts as a pro-protein factor which can directly damage of the glomerular peripheral wall. Thus, the present case did not fulfill the criteria of paraneoplastic nephropathy proposed by Wagrowska-Danilewicz and Danilewicz (13).

Treatment priority considerations in nephrotic syndrome cases with malignant neoplasms are dependent on the patient’s general condition and are sometimes complicated. The nephrotic syndrome in MN is usually resistant to corticosteroid treatment. Therefore, treatment of the primary neoplasms should be the first choice. Shikata et al reported success with irradiation for unresectable lung SCC (19). There is little evidence for how to treat patients with MN cases and cervical SCC. However, radiation therapy for unresectable cervical cancer should be considered to maintain activities of daily living.

In conclusion, a patient with cervical SCC had nephrotic syndrome with MN. The nephrotic syndrome responded to radiation therapy to the original region followed by radiation to metastatic paraaortic lymph node tissues. The treatment of the underlying cervical SCC led to resolution of the nephrotic syndrome. Although the causality is not clear, it seemed that there was an association between MN and cervical cancer in the present case. The survey for malignancy should be undertaken prior to the decision of the treatment.

The authors state that they have no Conflict of Interest (COI).

References