Paraneoplastic Nephrotic Syndrome in Patients with Lung Cancer

Gen Ohara, Hiroaki Satoh, Koichi Kurishima, Morio Ohtsuka and Nobuyuki Hizawa

Abstract

Paraneoplastic nephrotic syndrome has been reported in various malignancies: malignant lymphoma, colon cancer, lung cancer, and prostate cancer. Of these, lung cancer is the most commonly associated with the syndrome. Here, we report 4 cases of nephrotic syndrome associated with lung cancer, in one of which urinary protein and edema were improved by steroid therapy. These results suggest that in patients with paraneoplastic nephrotic syndrome histologically diagnosed as having minimal change disease (MCD), it is important not only to treat the cancer itself but also to use steroids as early as possible. On the other hand, our results also showed that treatment is still difficult for locally advanced or metastatic tumors. Therefore, when we encounter patients with nephrotic syndrome, it is important to be aware of the association of nephrotic syndrome and lung cancer.

Key words: lung cancer, membranous nephropathy, paraneoplastic nephrotic syndrome

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Introduction

Paraneoplastic nephrotic syndrome is a rare manifestation reported to be associated with various malignancies, the most common of which is lung cancer (1-5). Here, we report 4 cases of nephrotic syndrome associated with lung cancer (Table 1).

Case Report

Case 1

A 59-year-old man was referred to our hospital for evaluation of a left hilar mass. Four months before being referred, he had noticed whole-body edema. Serum albumin was 1.9 g/dL and total cholesterol was 298 mg/dL. A 24-h urine sample contained 3.5 g of protein, and creatinine clearance (Ccr) was 125 mL/min. A renal biopsy revealed membranous nephropathy, which we evaluated as stage IV. Chest radiograph and computed tomography (CT) revealed a 50-mm left hilar mass invasion to the left pulmonary artery. Pathology samples could not be obtained by transbronchial biopsy of the lung. A left pneumonectomy was performed. The pathological diagnosis was large cell carcinoma. The postoperative course was uneventful. A few weeks after his surgery, his serum albumin level increased to 3.0 g/dL, and his proteinuria decreased to 1.0-2.0 g/day. Eight months after surgery, he was clinically free of nephrotic syndrome. However, there was a recurrence in the mediastinal lymph nodes, for which 60 Gy of radiation was given. Computed tomography showed a decrease in the size of the mediastinal lymph nodes, but he died of cancer 8 months after the radiotherapy. He did not have a relapse of nephrotic syndrome after the recurrence of lung cancer, nor did his Ccr deteriorate during his clinical course.

Case 2

A 75-year-old man was noted to have a lung nodule on a routine chest radiograph. A chest CT revealed a 15×13-mm left upper lobe (LUL) lung nodule. While no hilar or mediastinal lymph node swelling was observed, emphysematous changes were present in both lungs. Adenocarcinoma was diagnosed by percutaneous fine needle aspiration cytology of the pulmonary nodule. A brain CT, bone scan, and abdominal ultrasound scan were all negative for metastases.
Spirometry showed forced expiratory volume in 1 second of 0.56 L (32.9% predicted) and a flow volume loop consistent with severe chronic obstructive pulmonary disease. At the time of admission, his serum albumin was 4.4 g/dL, total cholesterol was 195 mg/dL, Ccr was 77 mL/min, and he had a 24-h urine volume of 400 mL containing 0.3 g of protein. After admission, the patient had gross edema in the lower extremities, and there was a decrease in his albumin to 1.6 g/dL and an increase in his proteinuria to 12 g/24-h and in his total cholesterol to 373 mg/dL. The Ccr was unchanged throughout his clinical course. Because of his poor respiratory condition, he was given 50 Gy of radiation to the LUL in 25 fractions. Treatment with prednisolone and furosemide led to a gradual improvement of the lower-extremity edema over 2 months. Computed tomography showed a decrease in the size of the LUL nodule. Urinary volume increased to 1,600 mL/24-h, and albumin increased to 3.2 g/dL, while proteinuria decreased to 300 mg/24-h, and total cholesterol to 226 mg/dL. Six months after radiotherapy, metastases were found in the skin and left ilium, but he did not have a relapse of nephrotic syndrome. We followed him for 3 months thereafter, but he did not return afterwards for a check-up at our hospital.

**Case 3**

A 73-year-old man was admitted to the hospital with dyspnea, a right hiliar mass, and pleural effusions. Four months before admission, he had been pathologically diagnosed at another hospital as having diffuse membranous nephropathy (stage I) in which inflammatory monocyte permeation was moderate (around 20% of permeation in the renal cortex). Gross edema of the extremities was present. The initial laboratory studies showed a serum albumin level of 1.6 g/dL, total cholesterol of 410 mg/dL. The 24-h urine collection revealed proteinuria of 8.5 g/day, and Ccr was 114 mL/min. Physical examination revealed pitting edema in the lower extremities. A chest radiograph and CT scan showed a 32×30-mm mass in the right lower lobe with mediastinal and bilateral hilar lymph node enlargements and right pleural effusions. Biopsies revealed adenocarcinoma of the lung. Malignant effusions were diagnosed by pleural fluid cytology. The patient was given 1 cycle of carboplatin (AUC = 5, Calvert formula) on day 1 and paclitaxel (180 mg/m²) on day 1. However, the disease progressed; complications included gastrointestinal bleeding, multiple cerebral infarction, sepsis, pneumonia, and respiratory failure. Urinary protein levels did not decrease, and his renal function worsened to a Ccr of 22 mL/min, and he died 2 months after the chemotherapy.

Laboratory data including the renal function of the 4 cases are summarized in Table 2.

**Discussion**

Lee et al first reported malignancies in patients with nephrotic syndrome, noting a much higher incidence of cancer in patients with nephrotic syndrome than in a similar population group without renal disorders (1). Nephrotic syndrome is one of the manifestations of malignancy-associated paraneoplastic syndrome. Paraneoplastic nephrotic syndrome is generally associated with malignant lymphoma and other nonepithelial neoplasms. As for the underlying disease, epithelial neoplasms are less common, but lung cancer is one of the most frequent (1-9). The glomerular lesion of paraneoplastic nephrotic syndrome usually presents as a membranous nephropathy (1, 4, 5, 7, 8, 10, 11). Different glomerular diseases are associated with different neoplasms: whereas the nephrotic syndrome is generally due to membranous nephropathy (MN) in patients with solid tumors, cases of MCD, membranoproliferative glomerulonephritis

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**Table 1. Characteristics and Outcomes of Patients**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age / Gender</th>
<th>Clinical onset of renal lesion</th>
<th>Discovery of cancer</th>
<th>Histological type of lung cancer / TNM / stage</th>
<th>Histological type of renal disease</th>
<th>Tx</th>
<th>Clinical improvement of renal symptoms after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59M</td>
<td>Feb. 2002</td>
<td>Jul. 2002</td>
<td>LA/T4N2M0iaIIIa</td>
<td>MN</td>
<td>OP</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>75M</td>
<td>Nov. 1988</td>
<td>Aug. 1988</td>
<td>AD/T1N0M0sx,IA</td>
<td>N/A</td>
<td>RTx</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>73M</td>
<td>Nov. 2000</td>
<td>May 2001</td>
<td>SM/T4N3M1sxIV</td>
<td>MN</td>
<td>CTx</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>60M</td>
<td>Oct. 2006</td>
<td>Dec. 2006</td>
<td>AD/T4N3M0isxIIIb</td>
<td>N/A</td>
<td>CTx</td>
<td>No</td>
</tr>
</tbody>
</table>

Tx, therapy; M, male; LA, large cell carcinoma; AD, adenocarcinoma; SM, small cell cancer; MN, membranous nephropathy; N/A, not applicable; OP, operation; RTx, radiotherapy; CTx, chemotherapy.
(MPGN), IgA nephropathy (IgA-N), focal and segmental glomerulosclerosis (FSGS), mesangiocapillary glomerulonephritis, crescentic glomerulonephritis, amyloidosis, and thrombotic microangiopathies have been reported (7). Minimal change disease is strongly associated with Hodgkin’s lymphoma (7, 12), and there are a few reports of it in solid tumors, particularly in lung cancer (6). Membranoproliferative glomerulonephritis has also been reported in lung cancer (8, 12, 13). Membranous nephropathy is the most commonly seen glomerular lesion of cases of paraneoplastic nephrotic syndrome (1, 4, 5, 10, 11). In lung cancer patients, the most common histologic types associated with paraneoplastic glomerular disease are MN and MCD. Sixty percent (6/10) and 10% (1/10) of patients with SCLC had MN and MCD, respectively. And 45% (14/31) and 26% (8/31) of patients with non-small cell lung cancer had MN and MCD, respectively (6). Birkeland and Storm suggested an association between nephrotic syndrome with malignancies and persistent virus infections, which cause glomerulonephritis first and then malignancies (8). The pathogenesis of this paraneoplastic syndrome has been attributed to the host-antibody response of the shedding of tumor antigen as an early manifestation of cancer. It has been suggested that the circulating tumor antigen-antibody complexes may inhibit or suppress tumor-specific cell-mediated immunity, interfering with the antineoplastic effects of tumor-specific cytotoxic lymphocytes (4, 14-19). The general autoimmune antibodies associated with nephrotic syndrome were negative in all 4 of the cases presented here.

In case 1, the nephrotic syndrome improved after treatment and did not relapse after lung cancer recurrence. We may postulate two possible reasons for this. First, in many cases of recurrence, the initial effective treatment becomes non-effective. For the same reason, MN does not occur at the time of the recurrence because the property of the cancer and the tumor antigen-antibody complexes themselves changed. Second, at the time of the recurrence, the exposure time to the tumor antigen-antibody complexes was so short that MN did not occur.

As suggested by previous reports, MCD is more steroid effective than other histologic types. In case 2, the onset was sudden, and the patient had more than 10 g/day albuminuria, but steroid therapy and irradiation resulted in good control of his nephrotic syndrome without recurrence. Nephrotic syndrome did not recur despite the subsequent detection of a metastatic lesion. Because of this, we supposed that the histologic type of this patient was MCD. Thus in cases of cancer-associated nephrotic syndrome with a histologic diagnosis of MCD, it is important not only to treat the cancer itself but also to use steroids.

In case 3, the patient’s renal function had already deteriorated to a Ccr of 45 mL/min at the time of his hospitalization, and it worsened to a Ccr of 20 mL/min after 3 courses of the chemotherapy. In cases of cancer-associated MN, renal function tends to worsen more than in cases of idiopathic MN (9). And the presence of glomerular leukocytic infiltrates strongly increases the likelihood of malignancy in MN patients (9). On the basis of a hypothesis by Lefaucheur et al (9), we considered this to be a case of cancer-associated, not idiopathic, MN.

In case 4, the patient’s lung cancer had already advanced and his status was so bad at the time of his hospitalization that we could not search for the cause of the nephrotic syndrome. Therefore, it was also difficult to conjecture about its cause. Although the patient received chemotherapy, the renal function had further worsened. It was difficult to guess the cause of the worsened renal function.

In the patients of this retrospective survey, the interval between proteinuria and the malignancy was variable. However, as in other reported cases (2), nephrotic syndrome predated the lung cancer by several months in 3 of our 4 cases. Presentation with nephrotic syndrome occurs before the diagnosis of cancer in approximately 40% of patients, at the time of diagnosis in 40% of patients, and after diagnosis in 20% of patients (2).

The treatment of paraneoplastic nephrotic syndrome is complicated. Although surgical therapy has been shown to be effective in paraneoplastic nephrotic syndrome (20, 21), no standard therapy has been established for the syndrome when it is associated with advanced cancer with an unresectable lesion. Shikata et al reported 2 cases of nephrotic syndrome associated with locally advanced lung cancer, in which urinary protein excretion and edema were markedly improved by radiation therapy (3). Lin et al also reported a non-small cell lung cancer patient successfully treated with radiotherapy (22). Yangui et al recently reported a SCLC patient treated with chemoradiotherapy. Complete remission of the tumor and resolution of the nephrotic syndrome was achieved, but tumor progression occurred together with rapidly fatal renal failure (23). Miyajima et al also reported a locally advanced lung adenocarcinoma successfully treated with chemoradiotherapy (24). These results suggest that radiotherapy and chemoradiotherapy may be one of the choices of treatment for some locally advanced lung cancer patients with paraneoplastic nephrotic syndrome. As observed here in case 3, several reports have mentioned the in-

### Table 2. Laboratory Data Including Renal Function of 4 Cases Before/After Treatment

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alb (g/dL)</td>
<td>Ccr (mL/min)</td>
<td>Pro (g/day)</td>
<td>Alb (g/dL)</td>
</tr>
<tr>
<td>before</td>
<td>1.9</td>
<td>125</td>
<td>3.5</td>
</tr>
<tr>
<td>after</td>
<td>3.0</td>
<td>90</td>
<td>1.0-2.0</td>
</tr>
</tbody>
</table>

Alb, serum albumin; Ccr, creatinine clearance; Pro, proteinuria

patients who have renal or neurological impairment, care frequently associated with paraneoplastic syndromes. Cisplatin is its lesser nephrotoxicity and neurotoxicity. These have classically been used. The advantage of carboplatin over cisplatin is still difficult for locally advanced or metastatic tumors. When we encounter patients with nephrotic syndrome and lung cancer. Our results suggested that surgery as well as irradiation resulting in the reduction of tumor mass can be the first-choice treatment of nephrotic syndrome due to cancer-associated MN. On the other hand, in patients histologically diagnosed as having MCD, it is important not only to treat the cancer itself but also to use steroids as early as possible. However, treatment is still difficult for locally advanced or metastatic tumors. Therefore, when we encounter patients with nephrotic syndrome, it is important to be aware of the association of nephrotic syndrome and lung cancer.

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References


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