Paraneoplastic Focal Segmental Glomerulosclerosis in a Patient with Lung Adenocarcinoma

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Abstract

Focal segmental glomerulosclerosis (FSGS) is extremely rare among paraneoplastic nephrotic syndromes. We herein report a case of lung adenocarcinoma with nephrotic syndrome caused by paraneoplastic FSGS. A 68-year-old man visited our hospital for an evaluation of a right hilar mass on chest radiography and supraclavicular lymphadenopathy. Because an aspiration biopsy of the supraclavicular lymph node revealed adenocarcinoma, the patient was diagnosed with lung adenocarcinoma. He also had nephrotic syndrome, and the pathological findings of the renal biopsy demonstrated FSGS. Standard-dose carboplatin-containing chemotherapy led to a partial response for lung cancer and improved the patient's nephrotic syndrome without causing any adverse renal effects.

Key words: lung cancer, paraneoplastic syndrome, nephrotic syndrome, focal segmental glomerulosclerosis

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Introduction

The term paraneoplastic syndrome refers to clinical manifestations that are not directly related to tumor burden, invasion or metastasis and may be indirectly caused by the products secreted from tumor cells, such as hormones, growth factors, cytokines and tumor antigens (1). Paraneoplastic encephalitis, Lambert-Eaton syndrome and syndrome of inappropriate antidiuretic hormone secretion (SIADH) are well-known paraneoplastic syndromes observed in patients with lung cancer (1).

Among paraneoplastic syndromes, renal complications, namely paraneoplastic nephrotic syndrome, are relatively rare in patients with lung cancer (2). The glomerular lesions of paraneoplastic nephrotic syndrome usually present as membranous nephropathy, minimal-change disease or membranoproliferative glomerulonephritis, the most common of which is membranous nephropathy (3, 4). On the other hand, focal segmental glomerulosclerosis (FSGS) is extremely rare among paraneoplastic nephrotic syndromes. To the best of our knowledge, only one case of FSGS underly-

ing lung cancer has been reported (2). We herein describe the case of a patient with lung adenocarcinoma complicated by FSGS as a paraneoplastic syndrome who obtained a partial response following the administration of standard-dose carboplatin-containing chemotherapy.

Case Report

A 68-year-old man was referred to our hospital for an evaluation of a right hilar mass on chest radiography and supraclavicular lymphadenopathy. He had a 1-month history of back pain. He had no eruptions, arthralgia or peripheral edema. He had a 75 pack-year smoking history. His medical history included hypertension and cholecystectomy for cholecystitis. He was otherwise well and had never shown serum creatinine elevation, proteinuria or renal dysfunction. On a physical examination, the bilateral supraclavicular lymph nodes were palpable. No rales were auscultated. Chest radiography showed pulmonary overinflation and a right hilar mass (Fig. 1A). Chest CT revealed a 2-cm nodule in the right middle lobe. Positron-emission tomography-CT showed 18F-fluoro-deoxyglucose (FDG) accumulation in the

Figure 1. Chest radiography and positron emission tomography (PET)-CT. (A) Chest radiography showed a right hilar mass (arrow). PET-CT examination. (B) PET-CT showed FDG accumulation in the nodule as a primary lesion (arrowhead) and in the supraclavicular lymph nodes, mediastinal lymph nodes and thoracic vertebrae.

nodule, right mediastinal and supraclavicular lymph nodes and thoracic vertebrae, which was considered to be the cause of the patient's back pain (Fig. 1B). The laboratory test results were as follows: C-reactive protein, 0.24 mg/dL; white blood cell count, 6,060/ μ L; hemoglobin, 13.8 g/dL; platelets, 13.9×10^4 / μ L; sodium, 141 mmol/L; potassium, 3.3 mmol/L; total protein, 6.7 g/dL; serum albumin, 3.0 g/dL; blood urea nitrogen, 19.6 mg/dL; serum creatinine, 0.97 mg/dL; plasma glucose, 75 mg/dL; antinuclear antibody, $\times 640$; anti-DNA antibody (-); C3, 119 mg/dL; C4, 22 mg/dL; CH50, 26.3; IgA, 253 mg/dL; IgG, 2,229 mg/dL; IgM, 13 mg/dL; and total cholesterol, 214 mg/dL. A urinalysis revealed proteinuria and hematuria, and many hyaline casts were observed in the sediment. A 24-hour protein excretion reached 4.25 g/day, suggesting nephrotic syndrome. An aspiration biopsy of the left swollen supraclavicular lymph node revealed adenocarcinoma. The diagnosis was lung adenocarcinoma with a clinical stage of T1aN3M1b, stage IV. A renal biopsy was also performed. Light microscopy revealed FSGS (Fig. 2A). Immunofluorescence studies showed no deposition (data not shown). Epithelial foot process effacement was observed under electron microscopy (Fig. 2B). The patient was ultimately diagnosed with FSGS as the cause of his nephrotic syndrome.

First-line chemotherapy for lung cancer was initiated with standard-dose carboplatin (AUC: 5; 310 mg/body, GFR: 37 mL/min calculated according to the Cockcroft-Gault equation) and vinorelbine (25 mg/m²; 40 mg/body) on the first

day, followed by vinorelbine on day 8. We administered dexamethasone at a dose of 8 mg as an antiemetic drug on days 1 and 8. A partial response was observed, and the elevated serum creatinine level (1.67 mg/dL) decreased to 0.80 mg/dL after two cycles of chemotherapy, without any adverse renal events. The urinary protein level also decreased to 339 mg/day following the administration of chemotherapy (Fig. 3). The chemotherapy was stopped after two cycles due to febrile neutropenia. Ten months after the initiation of the first-line chemotherapy, the tumor progressed and the urinary protein level (qualitative test) increased. Second-line chemotherapy with vinorelbine monotherapy resulted in tumor regression, and the proteinuria again improved.

Based on the patient's clinical course, the FSGS was considered to be a paraneoplastic syndrome caused by lung adenocarcinoma.

Discussion

The diagnosis of paraneoplastic syndrome is determined based on the overall clinical course as well as featured symptoms in the presence of cancer. In the present case, nephrotic syndrome caused by FSGS was considered to be a paraneoplastic syndrome based on several findings, as follows: (1) a clear chronological relationship was observed between proteinuria and the occurrence of lung cancer; (2) the therapy targeting the cancer improved the proteinuria; (3) simultaneous progression of cancer and deterioration of prote-

Figure 2. Pathological examination. (A) Light microscopy showed focal segmental glomerulosclerosis (arrow). (B) Epithelial foot process effacement was observed. No electron-dense deposits were observed in the glomeruli. A: periodic acid-Schiff stain $\times 400$, B: electron microscopy $\times 2,000$.

Figure 3. The patient's clinical course. Decreases in the levels of urine protein and serum creatinine were observed following the administration of first-line chemotherapy. CBDCA: carboplatin, VNR: vinorelbine

inuria was observed; and (4) there were no other causes of proteinuria.

The diagnosis of FSGS requires the presence of areas of glomerular sclerosis and tuft collapse that are both focal and segmental (5). The clinical hallmarks include proteinuria, nephrotic syndrome and frequent progressive renal dysfunction (5). In adults, the diagnosis of nephrotic syndrome is typically defined as a urine protein level of more than 3.0 to 3.5 g/day (6). In the present case, focal and segmental glomerular sclerosis, epithelial cell foot process effacement and nephrotic syndrome were confirmed, and the patient was diagnosed with nephrotic syndrome caused by FSGS.

Paraneoplastic nephrotic syndrome is generally associated with hematologic malignancy (7). However, FSGS occurring in association with malignancy is rare (8). To our knowledge, only one case of FSGS in a patient with lung cancer has been reported in the English literature. Lin et al. (2) de-

scribed the case of a 61-year-old man with non-small cell lung cancer (2). In that case, paraneoplastic nephrotic syndrome caused by FSGS was improved by radiotherapy targeting the primary lung tumor.

It is well known that cisplatin-based chemotherapy causes more renal toxicity than regimens based on carboplatin. Ardizzoni, et al. reported that there are no statistically significant differences between the two protocols in the risk of death in patients with lung cancer and that, in a subgroup analysis, carboplatin exhibited inferiority to cisplatin (9). However, we selected treatment with carboplatin due to the reduced risk of renal toxicity. While several reports have shown that standard-dose carboplatin-containing chemotherapy is effective for treating paraneoplastic nephrotic syndrome (10, 11), no reports have demonstrated that standard-dose carboplatin-containing chemotherapy is effective for treating paraneoplastic nephrotic syndrome in patients with

lung cancer. In the present case, there were no adverse renal events during the administration of standard-dose carboplatin-containing chemotherapy, and the patient's nephrotic syndrome and renal dysfunction improved. Therefore, we suggest that the use of standard-dose carboplatin-based doublet chemotherapy is an option in cases of lung cancer complicated by nephrotic syndrome.

A fundamental question is to identify what factors cause FSGS in the presence of lung cancer. No products secreted from tumor cells that cause paraneoplastic FSGS have been reported.

FSGS has recently been regarded to be a podocyte disease (12). Podocytes reportedly undergo apoptosis in TGF- β 1 transgenic mice (13). On the other hand, apoptosis of podocytes and podocyte detachment from the glomerular basement membrane leads to FSGS in cases of chronic Masugi nephritis (14). Furthermore, it is well known that many lung cancer cells produce TGF- β (15, 16). Therefore, we propose the hypothesis that transforming growth factor (TGF)- β produced by lung cancer cells induced the podocyte apoptosis and caused the paraneoplastic nephrotic FSGS observed in this case. In addition, VEGF is thought to be a cause of paraneoplastic glomerulonephritis (17, 18). However, we did not examine the roles of TGF-beta or VEGF in this case.

In summary, FSGS can occur as a paraneoplastic nephrotic syndrome associated with lung adenocarcinoma. Standard-dose carboplatin-containing chemotherapy may also be effective for treating paraneoplastic FSGS secondary to lung adenocarcinoma without causing adverse renal events.

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

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