Long-term Survival of a Patient with Extensive Small Cell Carcinoma of Unknown Primary Etiology Complicated by Nephrotic Syndrome

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Abstract

We experienced a case of nephrotic syndrome (membranous nephropathy) complicated by extensive small cell carcinoma of unknown primary etiology that was diagnosed based on the findings of bilateral cervical and mediastinal lymphadenopathy. A complete cancer response and proteinuria remission following radical chemoradiation therapy were documented. The status of a complete response and nephrosis remission persisted for more than three years. This is the first report to demonstrate the long-term survival of a patient with extensive small cell carcinoma of unknown primary etiology complicated by paraneoplastic nephrotic syndrome.

Key words: small cell carcinoma, paraneoplastic nephrotic syndrome, chemoradiation therapy

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Introduction

Paraneoplastic nephrotic syndrome was first reported in 1966 (1). The most common causative tumor is malignant lymphoma, while lung cancer is the most frequent causative epithelial cancer (2). In cases of nephrotic syndrome in adult patients, the presence of a possible underlying malignancy should be investigated. A previous study reported that approximately 10% of adult-onset membranous glomerulonephritis cases are associated with malignant tumors, with notably poor prognoses (3). We herein present the case of a patient with extensive small cell carcinoma of unknown primary etiology and complete nephrotic syndrome remission who demonstrated long-term survival after receiving radical chemoradiation therapy.

Case Report

A 57-year-old woman who complained of bilateral cervical lymphadenopathy and progressive bilateral edema in the lower extremities was admitted to our hospital in September 2008. A diagnosis of small cell carcinoma was made by a previous physician; the pathological examination results are shown in Fig. 1. The patient's medical history included hypertension and hypothyroidism, for which she was receiving thyroid hormone replacement therapy. She had a 1 pack/day smoking history for more than 25 years. On a physical examination, bilateral cervical lymphadenopathy, bilateral diminished respiratory sounds and marked edema in the lower extremities were found. The laboratory results showed hypoaalbuminemia (serum albumin level: 1.8 g/dL) and massive proteinuria (urine protein level: 5.0 g/day) complicated by an abnormal renal function (creatinine clearance rate: 48.1 mL/min). Tests for serum tumor markers demonstrated...
progastrin-releasing peptide and neuron-specific enolase levels of 20.2 pg/mL (normal limit <80.0 pg/mL) and 79.6 ng/mL (normal limit <10.0 ng/mL), respectively. The levels of antinuclear antibodies, complement, antineutrophil cytoplasmic antibodies and hepatitis antigens/antibodies were within the reference ranges. Contrast-enhanced chest computed tomography disclosed a tumor with cervical and mediastinal lymph node enlargement and massive bilateral pleural effusion (Fig. 2A). However, we were unable to identify the primary lesion, even after performing whole-trunk computed tomography with contrast-enhanced systemic bone scintigraphy, brain magnetic resonance imaging and gastrointestinal endoscopy. A bone marrow examination ruled out the possibility of bone marrow metastasis. Subsequently, a renal biopsy was performed, which disclosed glomerular granular capillary immunoglobulin G (IgG) deposition (predominantly IgG-2 deposition and negative IgG-4 deposition) on immunofluorescent staining (Fig. 3). Furthermore, the pathology obtained using light microscopy did not show either crescentic glomerulonephritis or mesangial cell proliferation. A diagnosis of paraneoplastic nephrotic syndrome (membranous nephropathy) associated with extensive small cell carcinoma of unknown primary etiology was made. Systemic chemotherapy with cycles of carboplatin (area under the curve [AUC] =480 mg/body on day 1) plus irinotecan (60 mg/m² =100 mg/body on days 1, 8 and 15) every four weeks were initiated during hospital admission. A favorable response achieved after two chemotherapy cycles (Fig. 2B) permitted the addition of radiation therapy to the two subsequent chemotherapy cycles of carboplatin (AUC =300 mg/body on day 1) plus etoposide (80 mg/m² =130 mg/body on days 1, 2 and 3) every four weeks. Specifically, radical irradiation of the cervical and mediastinal lymph nodes (45 Gy, given in 30 fractions) was coadministered via accelerated hyperfractionation. In the two months after therapy completion, the proteinuria level improved to within the reference range. Prophylactic cranial irradiation (25 Gy, given in 10
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Figure 1. The tumor exhibits diffuse proliferation of small-sized T-cells with very scant cytoplasm and round hyperchromatic nuclei (Hematoxylin and Eosin staining).

Figure 2. Computed tomographic image showing a tumor with cervical and mediastinal lymph node enlargement and bilateral massive pleural effusion at the time of admission (A). A complete response was documented two months after the administration of first-line chemotherapy (B).
fractions) was added following the administration of first-line chemoradiation therapy in July 2010. No recurrence of the malignancy or nephrosis was observed during the follow-up examination conducted in March 2013. The patient’s detailed clinical course is shown in Fig. 4.

Discussion

Nephrosis associated with malignancy can result from amyloidosis, renal vein thrombosis or malignant cell infiltration. In patients with membranous glomerulonephritis, the most commonly observed glomerular lesion among solid tumors, the subepithelial deposition of circulatory immune complexes with tumor antigens has been documented. This immune complex deposition can damage the basement membrane, leading to protein leakage. IgG1 and IgG2 with complement are predominantly found in patients with secondary (paraneoplastic) nephrosis, whereas IgG4 is primarily found in patients with idiopathic nephrotic syndrome, which implies that different mechanisms lead to the development of proteinuria in patients with idiopathic membranous glomerulonephritis (4). In half of patients, proteinuria improvement can be achieved following treatment of malignancy (5). Furthermore, complete nephrosis regression can be expected in 25% of cases in which the tumor is successfully treated. However, most membranous glomerular diseases associated with solid tumors have poor prognoses because they are surgically incurable at presentation (6).

The coexistence of paraneoplastic nephrotic syndrome and small cell carcinoma has been previously reported (7). A study reported that 60% of patients with small cell lung cancer and nephrotic syndrome had membranous glomerulonephritis (8). The prognosis of small cell carcinoma patients with paraneoplastic nephrotic syndrome is extremely poor (7, 9, 10).

A previous study reported that the primary sites of extrapulmonary small cell carcinoma include the gastrointestinal system (29 patients), ear, nose and throat (14 patients), genitourinary system (12 patients), internal genitalia (10 patients), upper respiratory system (five patients), unknown primary lymph nodes (five patients), unknown primary other (two patients), the thymus (three patients) and peritoneum (one patient) (11). Although we made a final diagnosis of small cell carcinoma of unknown primary etiology in this case, the investigation to identify the primary lesion was inadequate, which is considered to be a limitation of our study. In particular, we should have performed bronchoscopy and positron emission tomography and consulted a urologist for a genitourinary examination.

The combination of etoposide and cisplatin, which is similar to the regimens administered for small cell lung carcinoma, is one of the most frequently used regimens for extrapulmonary small cell carcinoma, with a response rate of 69% (12). However, we chose carboplatin plus irinotecan in order to prevent volume overloading in the cisplatin regimen while accounting for the patient’s complicated renal failure. The effects and less toxic aspects of the irinotecan plus carboplatin treatment have been previously demonstrated (13). In the present case, we initiated radiation therapy along with the third and fourth chemotherapy cycles. The rationale for this decision was based on the findings of a study that indicated that the addition of radiation therapy to the treatment regimen in the most favorable subset of patients with extensive small cell lung cancer results in improved survival compared with that obtained with chemotherapy alone (14). In general, the prognosis of small cell carcinoma patients is extremely poor, especially when the disease is complicated by paraneoplastic nephrotic syndrome, as stated earlier. A previous phase III trial of small cell lung cancer with extensive disease showed a median survival of approximately 12.8 months (15). Furthermore, the median survival of patients with extrapulmonary small cell carcinoma with extensive disease has been reported to be 0.7 years (16). However, based on the present case, we affirm the possible effectiveness of multimodal therapy for treating rapidly
growing, advanced-stage carcinomas associated with nephrotic syndrome. This is the first report to demonstrate the long-term survival of a patient with extensive small cell carcinoma of unknown primary etiology complicated by paraneoplastic nephrotic syndrome following treatment with multidisciplinary anticancer therapy.

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

References