Clinical Case Report

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Nephrotic syndrome associated with metastatic thymoma treated with chemotherapy

Shin Hye Yoo, MD[a], Hyean-Ji Kim, MD[a], Jeong-Han Kim, MD[a], Gyeong-Won Lee, MD[c], Jeong Hee Lee, MD, PhD[d], Se Hyun Kim, MD[b,*], Ji-Won Kim, MD[b], Jin Won Kim, MD[b], Jeong-Ok Lee, MD[b], Yu Jung Kim, MD, PhD[b], Keun-Wook Lee, MD, PhD[b], Jee Hyun Kim, MD, PhD[b], Soo-Mee Bang, MD, PhD[b], Jong Seok Lee, MD, PhD[b]

Abstract

Rationale: Nephropathy with concurrent invasive thymoma is a type of paraneoplastic syndrome.

Patient concerns and Diagnoses: We report a 32-year-old female with nephrotic syndrome that was first diagnosed along with invasive thymoma and treated by means of cisplatin-based chemotherapy for the thymoma. The patient initially presented with dyspnea and generalized edema. Chest radiography and computed tomography scans revealed right pleural effusion and a mass in the right middle lung field, which were confirmed by a percutaneous lung biopsy as metastatic invasive thymoma. Severe hypoalbuminemia, heavy proteinuria, hyponatremia, and hypercholesterolemia were features of the nephrotic syndrome. A kidney needle biopsy suggested focal segmental glomerulosclerosis.

Interventions and Outcomes: All of the symptoms of nephrotic syndrome were resolved simultaneously during the first 2 cycles of chemotherapy. The patient was on regular follow-up with no specific treatment for nephrotic syndrome and underwent successful resection of the left pleura and anterior thymoma. The patient has shown no evidence of recurrence for 2 years.

Lessons: We conclude that chemotherapy for invasive thymoma is an effective treatment for nephrotic syndrome accompanying the thymoma.

Abbreviations: ADOC = adriamycin cisplatin vincristine and cyclophosphamide, C3 = complement 3, CT = computed tomography, Ig = immunoglobulin, Na = sodium.

Keywords: case reports, nephrotic syndrome, paraneoplastic syndromes, thymoma

1. Introduction

Thymomas are uncommon neoplasms that develop from thymic epithelial cells with an annual incidence of 0.13 per 100,000 individuals in 2003 in the United States of America.[1] The median 5-year survival rate varies from 45% to 74%, which influenced by histologic staging based on the guidelines of the World Health Organization.[2] Reports suggest that paraneoplastic syndromes associated with thymoma are diverse, including myasthenia gravis, Hashimoto thyroiditis, and pure red cell aplasia.[3]

Nephrotic syndrome is characterized by 24-hour proteinuria above 3.5 g, hypoalbuminemia, elevated cholesterol level, and edema,[4] and includes primary nephrotic syndrome without clear cause and secondary nephrotic syndrome with various etiologies such as viral infection, autoimmune disease, and diabetes mellitus.[4] Secondary nephrotic syndrome related to malignant neoplasms has also been reported.[5,6] In such cases, patients with decreased renal function may be unable to tolerate treatment-related toxicities, leading to difficulties in neoplasm management.

Here, we report a case of a metastatic thymoma accompanied by nephrotic syndrome that was resolved after 2 cycles of chemotherapy against the malignancy.

2. Case report

A 32-year-old, nonsmoking female came to Seoul National University Bundang Hospital with dyspnea and generalized edema. Prior medical history and family history of hypertension and diabetes were not documented. At admission, her vital signs were blood pressure—137/84 mm Hg, pulse rate—89 beats/min, respiration rate—18 breaths/min, body temperature—36.6 °C, height—162.8 cm, and body weight—73.35 kg. The patient had gained 10 kg in body weight over the preceding 1 month. Mental status was alert. Scleral icterus and anemic conjunctiva were not observed. Lymph nodes were not palpated. Auscultatory chest examination revealed fine inspiratory crackles in the bilateral

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Ethics: The ethical approval from the Ethics Committee was not necessary to report this case because this case was reviewed retrospectively. Informed consent was obtained from the patient.

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[a] Department of Internal Medicine, Seoul National University Hospital, Seoul, [b] Division of Hemato-medical Oncology, Department of Internal Medicine, Seoul National University Bundang Hospital, Gyeong-gi, [c] Division of Hematology-Oncology, Department of Internal Medicine, Gyeongsang Institute of Health Science, Gyeongsang National University Hospital, Gyeongsang National University School of Medicine, Jinju, [d] Department of Pathology, Gyeonsang National University College of Medicine, Jinju, Korea.

[*] Correspondence: Se Hyun Kim, Department of Internal Medicine, Seoul National University Bundang Hospital, 82 Gumi-ro 173, Bundang-gu, Seongnam, Korea (e-mail: sehyunkim@snubh.org)

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lower lung field with decreased lung sound. The patient had pitting edema on both lower extremities.

Laboratory results included white blood cell count—7490/mm^3, hemoglobin—14.2 g/dL, platelet count in peripheral complete blood—253,000/mm^3, blood urea nitrogen—13 mg/dL, creatinine—0.9 mg/dL, total protein—3.1 g/dL, albumin—1.1 g/dL, total bilirubin—0.2 mg/dL, aspartate transaminase—18 IU/L, alanine transaminase—6 IU/L, alkaline phosphatase—81 IU/L, total cholesterol—480 mg/dL, sodium (Na)—132 mEq/L, potassium—2.7 mEq/L, and chloride—93 mEq/L. A dipstick test showed 3+ albuminuria and 3+ hematuria. Twenty-four-hour urine included 37,731 mg protein, 34,081 mg microalbumin, and 1.0 mg creatinine. Serologic markers were negative for hepatitis B and C. Rheumatoid factor, anticytoplasmic antibody, antineutrophil antibody, and anti–double-stranded DNA antibody tests were negative. Monoclonality (M-spike) was not found in serum and urine electrophoresis results. Other laboratory results included immunoglobulin (Ig) G/A/M—144/112/134 mg/dL (reference range: 700–1700/90–400/45–230 mg/dL) and complement 3 (C3)/complement 4—74.6/20.9 mg/dL (reference range: 70–150/10–35 mg/dL). A chest X-ray revealed a mass in the right middle lung. Computed tomography (CT) scans of the chest revealed right pulmonary and pleural metastases with a malignant mass in the anterior mediastinum (Fig. 1A and B). CT-guided pleural biopsy was performed.

Review at Gyeongsang National University Hospital of a fine-needle biopsy specimen taken from the kidney suggested that most glomeruli were normal in size and cellularity. Light-microscopic findings of global glomerulosclerosis and interstitial lymphocytic infiltrations were not compatible with minimal change disease (Fig. 2A). Electron-microscopic examination showed diffuse effacement of epithelial foot processes compatible with focal segmental glomerulosclerosis (Fig. 2B). Immunofluorescent staining of IgG, IgA, IgM, C3, C1q, and fibrin was negative, which is compatible with focal segmental glomerulosclerosis.

Lymphocytes and epithelial cells from the thymus were confirmed in a right pleural biopsy specimen (Fig. 3). A final diagnosis of metastatic thymoma was made. Pleuropneumonectomy was planned contingent upon a good response to neoadjuvant chemotherapy. Testing for c-kit mutation was performed to exclude thymic carcinoma and to consider a targeted agent; exons 9, 11, 13, and 17 were unidentified.

The patient was admitted to the hospital for the first cycle of ADOC (Adriamycin (Ildong Pharmaceutical, Seoul, Korea) 40 mg/m^2, Cisplatin (Ildong Pharmaceutical, Seoul, Korea) 50 mg/m^2, Vincristine (Hospira Korea, Seoul, Korea) 0.6 mg/m^2, and Cyclophosphamide (Baxter Korea, Seoul, Korea) 700 mg/m^2 every 3 weeks, full dose). At that time, the patient's body weight was 69.8 kg, compared with 63 kg in her healthy state. Pitting edema on both legs was severely palpated. The patient's serum Na level had decreased to 127 mEq/L. For differential diagnosis, the results of a rapid adrenocorticotropic hormone stimulation test were within the normal range, and the results of a thyroid function test were thyroid-stimulating hormone—4.5 μIU/mL (reference range: 0.3–4.0 μIU/mL), free T4—0.85 ng/dL (reference range: 0.89–1.79 ng/dL), and T3—51 ng/dL (reference range: 79–200 ng/dL). Hence, the illness was considered non-thyroidal.

Following chemotherapy, the patient's urine output decreased to <1 L/d, but recovered after 2 days with a dose of aldosterone receptor antagonist added to loop diuretics. Because the recovery appeared to be reliant on the steroid included in the chemotherapy regimen, diuretics were stopped. With no water restriction, hyponatremia improved and body weight returned to normal (Fig. 4A). The overall trends of proteinuria, hypercholesterolemia, and hyponatremia improved throughout the 2 cycles of chemotherapy (Fig. 4B), suggesting that the nephrotic syndrome was paraneoplastic and was associated with the malignant thymoma.

The patient was monitored without further treatment for nephrotic syndrome. After partial remission was achieved following the completion of 6 cycles of ADOC regimen, the

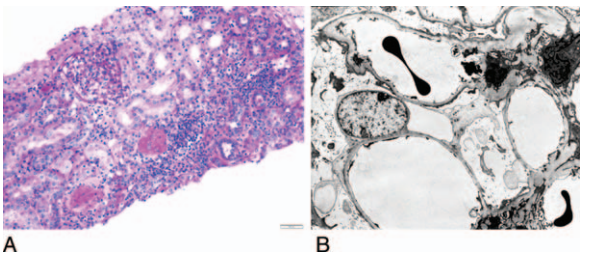

Figure 2. A kidney needle biopsy suggested focal segmental glomerulosclerosis. (A) Upon light-microscopic examination, most glomeruli were normal in size and cellularity, but there were global glomerulosclerosis and interstitial lymphocytic infiltrations, which are not compatible with minimal change disease (hematoxylin and eosin stain, 200×). (B) Electron microscopic examination showed diffuse effacement of epithelial foot processes, which is compatible with focal segmental glomerulosclerosis.

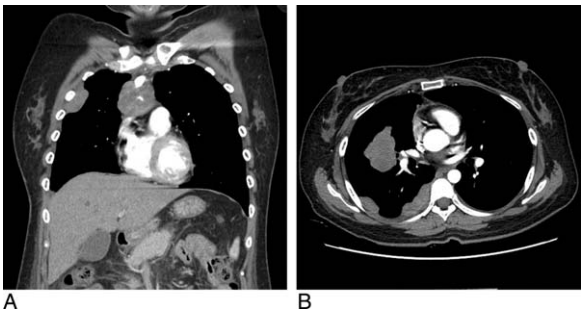

Figure 1. Enhanced chest computed tomography scan of the patient at admission (baseline). (A) Coronal plane view. (B) Transverse plane view.

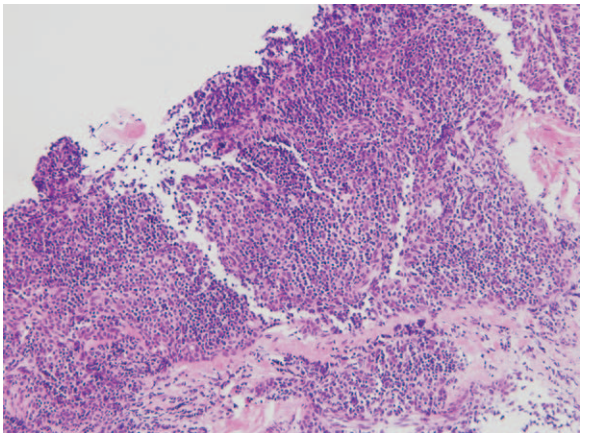

Figure 3. Pathology of the right pleural biopsy (hematoxylin and eosin stain seen under light microscopy, 200×).

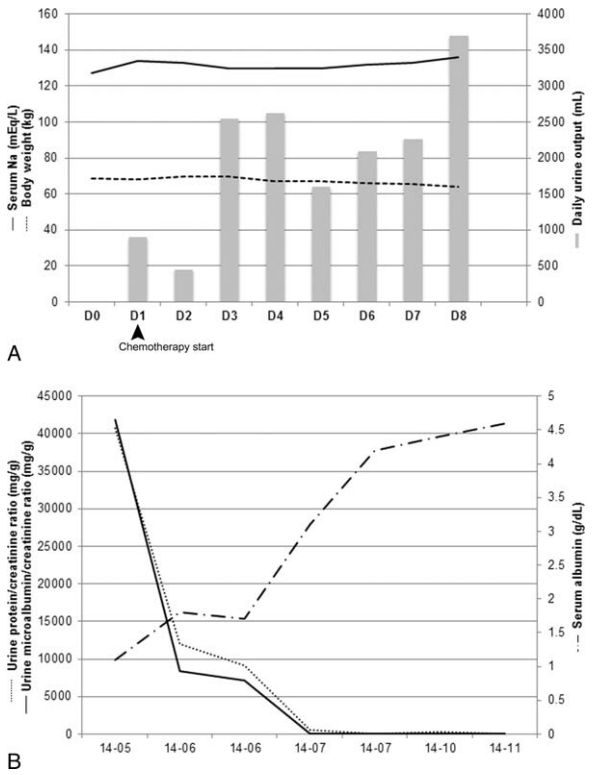

Figure 4. Results of serial follow-up of the patient. (A) Trend of serum sodium level, daily urine output, and body weight. (B) Trend of proteinuria (spot urine protein/creatinine ratio and spot urine microalbumin/creatinine ratio) and serum albumin levels.

left diaphragm, left pleura, and anterior thymomectomy were removed, and the disease was confirmed as malignant thymoma (surgical staging: Masaoka stage IVa, World Health Organization type B3). No evidence of recurrence of thymoma or nephrotic syndrome has been observed to date.

3. Discussion

Paraneoplastic nephropathy is a rare disease category with different clinical presentations, pathophysiologic mechanisms, management, and prognoses, depending on the type of associating malignancies.[7] Paraneoplastic glomerulonephritis associated with solid tumors commonly occurs when the materials induced by the cancer form immune complexes that damage the endothelial cells of the glomerulus.[8] Membranous nephropathy is the most common pathologic type of paraneoplastic glomerulonephritis associated with solid tumors, which is followed by minimal change disease.

Cytokines, such as interleukin (IL)-12 and interferon, that are related to T-helper 1 cells, may play a role in the development of membranous nephropathy associated with solid tumors.[9] However, minimal change disease is the most common pathologic type of paraneoplastic glomerulonephritis associated with hematologic malignancies and thymic neoplasms. Vascular endothelial growth factor and cytokines such as IL-2, IL-4, and IL-13 induced by T-helper 2 cells and macrophages[10] affect the pathogenesis of minimal change disease, resulting in increased permeability of the glomerular basement membrane.[3,11,12] T-cell dysregulation is the key point of the pathogenesis because thymoma is a disorder of the thymus that functions in T-lymphocyte maturation.[13]

Paraneoplastic glomerulonephritis affects only 2% of patients with thymic malignancies.[6] Cases of nephrotic syndrome associated with malignant thymoma have been reported in Korea and in Western countries.[11,14] In early reports, nephrotic syndrome developed several years after thymectomy or other treatments in a majority of cases.[11,15] However, additional reports have indicated that treatment for nephrotic syndrome preceded the diagnosis of thymoma.[14] In a systematic review of reported cases of minimal change disease and solid malignant tumors, including thymoma,[16] nephrotic syndrome and malignant thymoma were simultaneously diagnosed in only 20% of the cases, whereas nephrotic syndrome was diagnosed after the diagnosis of thymoma in 65% of the cases. Besides minimal change disease, which is the most common pathologic type of nephrotic syndrome associated with thymoma, focal segmental sclerosis, membranous nephropathy, and membranoproliferative glomerulonephritis are also associated with malignant thymoma.[4,6,13,15,17,18] Only a few cases of focal segmental glomerulosclerosis associated with thymoma, such as the case presented here, were reported previously.[13,17,19,20] Most of the previously reported cases showed malignant thymic pathology, except for 1 case that presented with grade-A benign thymoma.

Among the reported cases of minimal change disease accompanied by thymoma,[16] 43% responded completely to corticosteroid and/or immunosuppressive agents, and 22% responded partially to treatments. Overall patient survival appears to be better in paraneoplastic minimal change disease accompanied by malignant thymoma than in that accompanied by solid tumors (53% and 30%, respectively).[16] There is little prognostic data from cases of focal segmental glomerulosclerosis, because such cases are scarce. Responses to treatments and survival outcomes vary among cases. One patient who received steroid treatment achieved a complete response,[13] whereas another patient did not respond to steroid therapy and required maintenance hemodialysis.[17] Renal function in the latter patient improved after thymectomy, and she stopped hemodialysis eventually. Another patient had a good response to steroid treatment, but died of severe neutropenia followed by neutropenic sepsis and multiorgan failure.[19]

There are considerations for treating thymoma with nephrotic syndrome. First, we should be particularly cautious of infection after chemotherapy or steroid treatment for thymoma, because nephrotic syndrome usually increases the risk of infection. We should also consider prophylactic administration of granulocyte-colony stimulating factor if possible, although there was no sign of infection in the case reported here. Next, we should consider limiting the use of cisplatin-based chemotherapeutic agents because of patients' decreased renal function. In the case presented here, we applied cisplatin because the patient's renal function was in the normal range; however, some physicians have substituted carboplatin[21] or paclitaxel-based regimens for cisplatin. Finally, for secondary nephrotic syndrome, the management plan should be tailored by considering that secondary nephrotic syndrome has a chance to get better after management of the primary tumor with chemotherapy or surgical resection. Octreotide treatment has been utilized in certain cases of thymoma, as have targeted agents such as c-kit inhibitors or epidermal growth factor–receptor inhibitors.[22] In such situations, dose adjustment or careful selection of the medication is necessary.

Thymic tumors respond to neoadjuvant chemotherapy in approximately 90% of cases.[2,22] In particular, patients who underwent resection after shrinking of the tumor with preoperative agents showed good prognosis; however, approximately 15% of those patients did not remain in a disease-free state.[22] It is important to trace the symptoms and signs of paraneoplastic syndrome, because they may hint at recurrence during the follow-up period.[15]

In summary, a case of nephrotic syndrome, which presented initially as a paraneoplastic syndrome with metastatic thymoma, resolved after chemotherapy for the thymoma.

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