

## A Case of Paraneoplastic Nephrotic Syndrome in a Patient with Ovarian Carcinoma

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Nephrotic syndrome is a rare manifestation of malignancy associated with paraneoplastic syndrome.

Paraneoplastic nephrotic syndrome has been reported in various malignancies: malignant lymphoma, colon cancer, lung cancer and prostate cancer. However, an ovarian carcinoma associated with nephrotic syndrome has rarely been reported. Only six cases of ovarian carcinoma associated paraneoplastic nephrotic syndrome has been reported worldwide, but no cases have been reported in Korea. Here, we report a case of paraneoplastic nephrotic syndrome in a patient with an ovarian carcinoma. The patient presented with ascites, proteinuria and hypoalbuminemia. An initial computed tomography (CT) scan and ultrasonography evaluations showed no specific findings suggestive of an ovarian tumor. Despite treatment for nephrotic syndrome, the symptoms became more aggravated. There after, follow up evaluation at Yonsei University Medical Center, including serum CA 125, pelvis MRI and peritoneal fluid examination were performed. On the pelvis MRI, a left ovarian mass was detected with an ascitic fluid collection. The serum CA 125 level was elevated to 2211 U/ml. The peritoneal fluid cytological examination showed malignant cells suggestive of an ovarian carcinoma.

Combination chemotherapies including paclitaxel plus carboplatin, topotecan plus gemcitabine and oxaliplatin plus capecitabine were administered to the patient, and complete remission was achieved on image and tumor marker studies. There was complete recovery from the nephrotic syndrome with no evidence of ascites and proteinuria. These findings suggest that nephrotic syndrome caused by paraneoplastic

syndrome can be resolved only after the complete control of the underlying malignancy.

**Key Words:** Paraneoplastic syndrome, nephrotic syndrome, ovarian carcinoma.

### INTRODUCTION

Nephrotic syndrome is a rare manifestation of malignancy associated with paraneoplastic syndrome. In 1960, Lee et al.<sup>1</sup> first reported paraneoplastic nephrotic syndrome in malignant tumors.

Paraneoplastic nephrotic syndrome has been reported to be associated with various malignancies. However, an ovarian carcinoma associated with nephrotic syndrome has rarely been reported with only 6 cases worldwide. And has never been reported in Korea. We report here, a case of an ovarian carcinoma associated with paraneoplastic nephrotic syndrome.

### CASE REPORT

A 59-year-old woman was referred to the Yonsei Cancer Center, Yonsei University College of Medicine in May 2001 due to ascites, progressive proteinuria and abdominal pain. She had been diagnosed with nephrotic syndrome at another hospital in October 2000. The initial laboratory studies showed a serum albumin level of 2.4 g/dl, a total cholesterol level of 358 mg/dl and a protein level showing > 300 mg/dl on urinalysis. Twenty four hour urine collection studies showed protein excretion of 6,335 mg. A

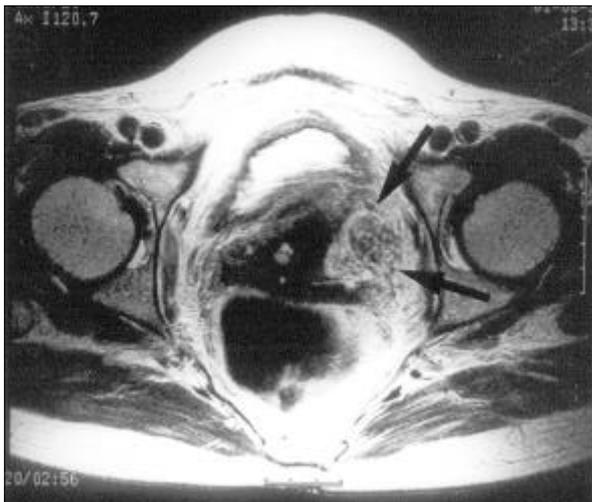
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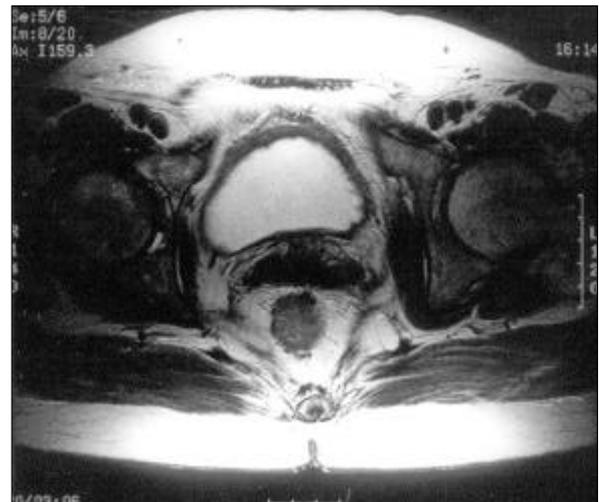
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renal biopsy showed type I membranous glomerulonephritis. Prior to admission, the patient had no history of either hypertension or diabetes mellitus, and the family history was unremarkable. Her vital signs were as follows: blood pressure 120/80 mmHg, pulse rate 80/min, respiration rate 17/min, and body temperature 36.5°C. On physical examination there was diffuse direct tenderness of the abdomen or rebound tenderness. No hepatomegaly or splenomegaly were noted, but there were ascites and pitting edema in both lower extremities. Laboratory testing revealed the following: white cell count (WBC) 8,650/mm<sup>3</sup>, hemoglobin 9.8 g/dl, hematocrit 29.2%, platelet count 547,000/mm<sup>3</sup>, serum calcium 8.4 mg/dl, phosphate 4.4 mg/dl, blood urea nitrogen 26.8 mg/dl, creatinine 1.9 mg/dl, total cholesterol 195 mg/dl, serum total protein 5.4 g/dl, albumin 2.8 g/dl, serum sodium 135 mmol/L, potassium 4.6 mmol/l, chloride 96 mmol/l, bicarbonate 31 mmol/l, and urine protein 3 positive. Twenty four hour urine collection studies showed protein and albumin excretion of 1117 mg and 924 mg, respectively. The twenty four hour urine creatinine clearance was 28.68 ml/min. To evaluate the possibility of malignant ascites, we checked the serum CA 125 level, which was found to be 2211U/ml. The abdominal pelvic magnetic resonance imaging (MRI) showed an enlarged left ovarian mass (Fig. 1). A peritoneal fluid cytological

examination showed malignant cells suggestive of ovarian carcinoma cells. At this time the patient was referred Hemato Oncology division for further therapy. The patient was given four cycles of taxol 135 mg/m<sup>2</sup> (Day 1) and carboplatin 300 mg/m<sup>2</sup> (Day 2) every 3 weeks, which resulted in a partial remission on the magnetic resonance image (Fig. 2) with a decreased CA 125 level of 378U/ml. Since then, the CA 125 level was elevated to 985U/ml and on a follow-up chest CT a moderate amount of pleural effusion in the left low lung field was observed (Fig. 3). The chemotherapy was changed to topotecan 1.25 mg/m<sup>2</sup> (Day 1-5) and gemcitabine 1,000 mg/m<sup>2</sup> (Day 1, 8) every three weeks. Complete remission, as observed on the follow-up MRI, was achieved after 4 cycles of this chemotherapy (Fig. 4), and 24 hour urine protein level has markedly decreased from 5595 mg to 187 mg. However, a follow-up evaluation after one month showed the 24 hour urine protein has increased again to 5,657 mg, and the serum CA 125 level had also increased to 306U/ml. The patient was retreated with a new combination chemotherapy, oxaliplatin 130 mg/m<sup>2</sup> (Day 1) and oral capecitabine 2,000 mg/m<sup>2</sup>/Day (Day 1-14) every three weeks. After 5 cycles of this new regimen, the CA 125 and 24 hour urine protein levels had decreased to 22.25 U/ml and 82 mg, respectively, which were within the normal ranges (Fig. 5). The patient has now followed-up



**Fig. 1.** An MRI at the time of diagnosis, shows ascites and peritoneal implants, including the left adnexa ovary, uterine fundus and bladder dome, with carcinomatosis (before chemotherapy).



**Fig. 2.** An MRI after 4 cycle of chemotherapy shows the absence of the left adenexal mass and ascites (after Taxol plus Carboplatin chemotherapy).

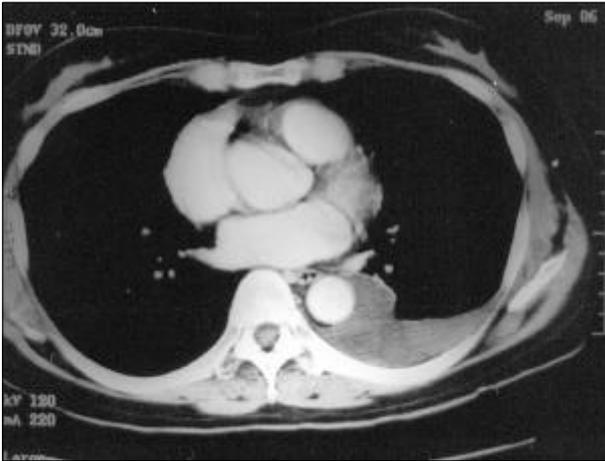


Fig. 3. The chest CT scan shows a moderate amount of pleural effusion in the left lower lung field (refractory state).



Fig. 4. Complete remission was achieved after 4 cycles of chemotherapy (after Topotecan plus Gemcitabine chemotherapy).

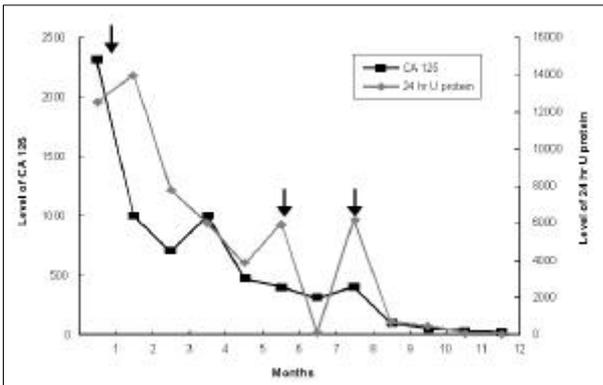


Fig. 5. CA-125 and 24 hour urine protein excretion changes after chemotherapy. 1st arrow: Taxol plus Carboplatin chemotherapy. 2nd arrow: Topotecan and Gemcitabine chemotherapy. 3rd arrow: Oxaliplatin and Capecitabine chemotherapy.

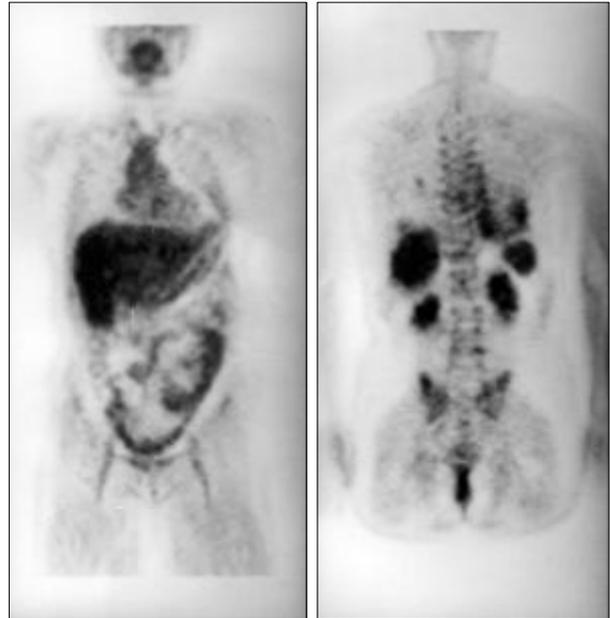


Fig. 6. No evidence of an increased uptake of the ovarian carcinoma in a PET-whole body scan (after Oxaliplatin plus Capecitabine chemotherapy).

with complete remission of the ovarian carcinoma and normal renal function (Fig. 6).

### DISCUSSION

Paraneoplastic syndrome presents with various manifestations in cancer patients, and may be due to immune reactions, related to a primary malignancy, such as growth factors or biologically active hormones. Tubular interstitial nephritis and glomerular nephropathies have also been reported in cancer patients. The main manifestations of glomerular disease are membranous glomerulonephritis or minimal change disease. On pathological examination, electron microscopy of renal glomerular membranous lesions generally demonstrates subepithelial deposits of immunoglobulins and complements which are important markers of this immune process. These are thought to be the main immune process in cancer related paraneoplastic nephrotic syndrome. Specifically, tumor associated and viral antigens have been found in immune complexes associated with some malignancies.<sup>2</sup> More than 50% of patients with a variety of cancers have glomerular deposits even in the

**Table 1.** Summary of Paraneoplastic Nephrotic Syndrome Associated with an Ovarian Carcinoma

Case & Reference	Age/Sex	Clinical onset of renal lesion	Discovery of malignancy	Type	Treatment	Normalize CA125/Proteinuria
1 <sup>1</sup>	65/F	Apr, 1960	Nov, 1961	MGN	Operation	Yes
2 <sup>7</sup>	65/F	Mar. 1986	Sep. 1986	MGN	Cisplatin 60 mg Adriamycin 60 mg Cytosan 600 mg	Yes
3 <sup>8</sup>	68/F	Apr. 2000	May. 2000	MGN	Operation Paclitaxel 175 mg/m <sup>2</sup> Carboplatin (AUC 6)	Yes
4 <sup>11</sup>	64/F	Oct, 1992	Oct, 1993	Amyloidosis	Operation	No*

\*Expired due to renal failure after the operation.  
MGN, Membranous glomerulonephritis.

absence of clinically significant renal disease.<sup>3</sup> Minimal change disease can be associated with Hodgkin's disease,<sup>4</sup> lymphoproliferative disease, pancreatic carcinoma,<sup>5</sup> and mesothelioma.<sup>6</sup> There is a parallel correlation between the activity of malignant lympho-proliferative disease and proteinuria level. The general approach to paraneoplastic syndrome requires careful diagnosis because this syndrome usually parallels the course of the underlying malignancy, or paraneoplastic symptoms, and may precede the symptoms and signs of the malignancy. In our case the nephrotic syndrome was diagnosed first with the ovarian carcinoma being diagnosed later. Topalak,<sup>7</sup> et al. reported a positive relation between the serum CA 125 levels and the amounts of ascites found in ovarian cancer patients with malignant ascites. The adult onset of nephrotic syndrome has been reported to be associated with an underlying cancer in about 10% of cases<sup>1</sup> but only a few cases of nephrotic syndrome, associated with an ovarian carcinoma, have previously been reported<sup>8</sup> (Table 1). It has been reported that malignancy associated nephrotic syndrome can be successfully resolved by treatment of the underlying malignancy.<sup>9,10</sup> In our experience, we noted that the patient achieved complete recovery from nephrotic syndrome after complete remission of the ovarian carcinoma had been achieved. The level of proteinuria correlates well with the clinical course of the cancer, and the twenty four hour urine

protein excretion level correlates with the serum CA 125 level.

The important point gained from our case were, when confronted with nephrotic syndrome, of questionable etiology, the clinician should always consider an underlying malignancy, and check the serum CA 125 level. As in this case, we experienced that successful chemotherapy can not only achieve remission, but can also result in the resolution of secondary nephrotic syndrome.

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