

A Case of Esophageal Cancer Showing Complete Remission of Nephrotic Syndrome after Esophagectomy

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Abstract. *Nephrotic syndrome associated with a malignant tumor may remit following resection of the tumor. This report documents a case of esophageal cancer with concurrent nephrotic syndrome in which a surgical resection of the tumor resulted in a complete remission of nephrotic syndrome. A 78-year-old male patient noticed edema of his lower legs in February 2009 and was diagnosed with nephrotic syndrome. An endoscopic examination revealed an indented lesion with a nearly semiannular low elevation on the posterior wall of the esophagus at 31 to 34 cm from the upper incisors, and a diagnosis of esophageal cancer was made. A two-stage operation was planned. In March 2009, a subtotal resection of the thoracic esophagus through a right thoracic approach and cervical external esophagostomy were performed, and in April 2009, antethoracic route esophagogastronomy was performed. The urinary protein levels were negative by the 86th day of hospitalization, and the patient progressively improved and was discharged on the 91st hospital day. There has been no recurrence of esophageal cancer or relapse of nephrotic syndrome at 12 months following the operation. In esophageal cancer patients with nephrotic syndrome, surgical treatment should be undertaken because the remission of nephrotic syndrome may be expected following tumor resection. For this purpose, selecting the appropriate operative procedures and careful perioperative management, including nutritional management, are of profound importance.*

Nephrotic syndrome caused by malignant neoplasms accounts for approximately 7.9 to 10.9% of these cases (1-2).

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Nephrotic syndrome has been reported to improve following the resection of a malignant tumor in patients with gastric (3-5) and colon cancer (6-7); however, such improvements have only been reported in a few cases of esophageal cancer with concurrent nephrotic syndrome. The present report documents a patient with esophageal cancer and concurrent nephrotic syndrome, in whom a surgical resection of the cancer resulted in a complete remission of nephrotic syndrome.

Case Report

A 78-year-old male patient presented with a chief complaint of edema of the lower legs and weight gain. The patient neither smoked nor consumed alcohol. The patient's family history was unremarkable. In February of 2009, the patient visited a nearby hospital because of his symptoms, and was diagnosed with hypoalbuminemia, proteinuria, and esophageal cancer. In March of 2009, the patient was referred to our institution and was admitted for surgical treatment.

At the time of admission, the patient was a moderately nourished man 151.6 cm in height, weighing 46.8 kg. The patient's body temperature was 36.4°C, and his blood pressure was 144/92 mmHg. The patient's pulse was 78 bpm and was regular. The conjunctiva showed no signs of anemia or jaundice. No abnormalities were found in the physical findings of the chest and abdomen, but a marked pitting edema was observed in the lower extremities.

The patient's blood biochemical tests at the time of admission revealed the total protein to be 5.1 g/dl; albumin, 2.1 g/dl; total cholesterol, 343 mg/dl; and triglycerides, 256 mg/dl, thus indicating marked hypoproteinemia, hypoalbuminemia, and a serum lipid abnormality. Proteinuria was observed (2.3 g/day), but no other abnormality was noted. The tumor marker carcinoembryonic antigen (CEA) was present at 0.5 ng/ml, within the normal limits, and squamous cell carcinoma antigen (SCC) was elevated to 2.4 ng/ml, which lies above the upper limit of the normal range (1.5 ng/ml). The patient's 24-hour

urinary protein excretion increased to 7.8 g following admission, and a diagnosis of nephrotic syndrome was made according to the diagnostic cut-off of 3.5 g/day or higher. Plain chest radiograms showed no abnormalities in the lung fields, bones, soft tissues or cardiac shadow.

Esophagographic examinations revealed irregular wall contours with a low raised lesion in the posterior wall of the midthoracic esophagus (Mt) (Figure 1). Upper gastrointestinal endoscopy showed an indented lesion with an irregular margin accompanied by a nearly semiannular low elevation on the posterior wall of the esophagus, located from 31 to 34 cm from the upper incisors. The lesion did not stain for Lugol's solution (Figure 2). A biopsy disclosed the lesion to be squamous cell carcinoma, and the diagnosis was 0-IIa plus IIc type esophageal cancer.

Computed tomography of the abdominothoracic region showed lymphadenopathy (1.2×1.5 cm) of the midthoracic no. 108 juxta-esophageal lymph node (Figure 3), but no findings were indicative of distant metastasis to other organs, such as the lung or liver. The diagnosis was T1b, N1, P0, M(-), clinical stage II esophageal cancer.

Treatment was planned to be carried out as a two-stage operation considering the degree of surgical invasiveness, because the patient had concurrent pronounced hypoalbuminemia. The first operation was performed on the 17th hospital day and consisted of a subtotal resection of the thoracic esophagus and a mediastinal lymphadenectomy through a right thoracic approach, as well as cervical external esophagostomy. The second operation was an esophagogastrostomy through an antethoracic route which was performed on the 40th hospital day. A gross pathological examination of the resected specimen revealed a 32×20 mm, 0-IIa plus IIc type superficial cancer of the esophagus (Figure 4). Histopathologically, the tumor was a highly differentiated squamous cell carcinoma with a tumor invasion depth of pSM3, with no invasion into the lymph and blood vessels, and had metastatic deposits in lymph node no. 108. A histological diagnosis confirming T1b, N1, P0, M(-), p stage II esophageal cancer was made.

After the second-stage operation, minor leakage from the site of the esophagogastric anastomosis was noted, which was conservatively cured with enteral nutritional support *via* an intestinal stoma. The urinary protein levels were negative by the 86th hospital day, and the patient progressively improved and was discharged on the 91st hospital day (Figure 5). After the proteinuria subsided, the hypoalbuminemia improved and the edema of the lower legs receded. There has been no recurrence of esophageal cancer or relapse of nephrotic syndrome as of 12 months following the operation.

The clinicopathological findings in this esophageal cancer case are described in accordance with the General Rules for Esophageal Cancer Study(8).

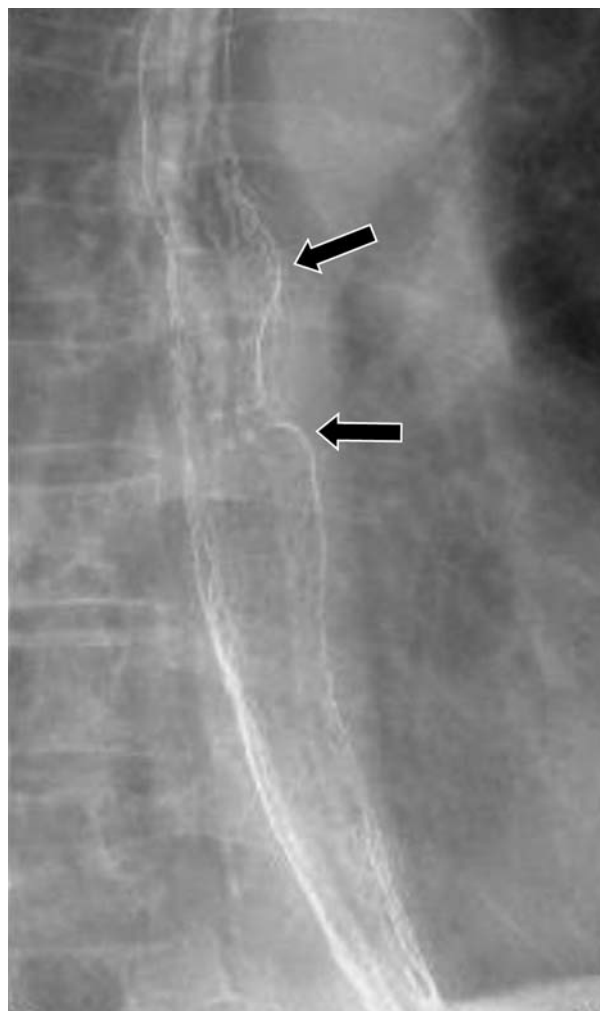


Figure 1. Esophagography. Irregular wall contours with a low raised lesion in the posterior wall of the midthoracic esophagus (Mt) were noted (arrows).

Discussion

Attention has become focused on the association of nephrotic syndrome with malignant tumors since Lee *et al.* (1) reported that malignant tumors were observed in 11 (10.9%) out of 101 patients with nephrotic syndrome in 1966. Most such malignant tumors are epithelial malignant tumors in the gastrointestinal and respiratory system. Non-epithelial malignant tumors in the hemopoietic system are uncommon. Esophageal cancer concurrent with nephrotic syndrome is rare, and has been reported in only 6 patients in Japan including the present patient, and in as few as 5 patients in Western countries (Table I). Of these patients, 10 were male with ages ranging from 50 to 78 years. The histological type of esophageal cancer was squamous cell carcinoma in all reported cases (9-18).

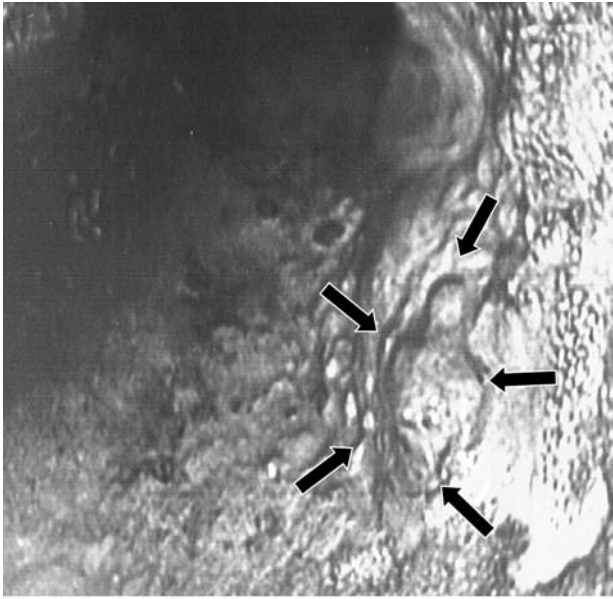


Figure 2. Esophagoscopy. An indented lesion with an irregular margin accompanied by a low elevation in the midthoracic esophagus wall was noted. The lesion did not stain for Lugol's solution, and was diagnosed as 0-IIa plus IIc type esophageal cancer (arrows).

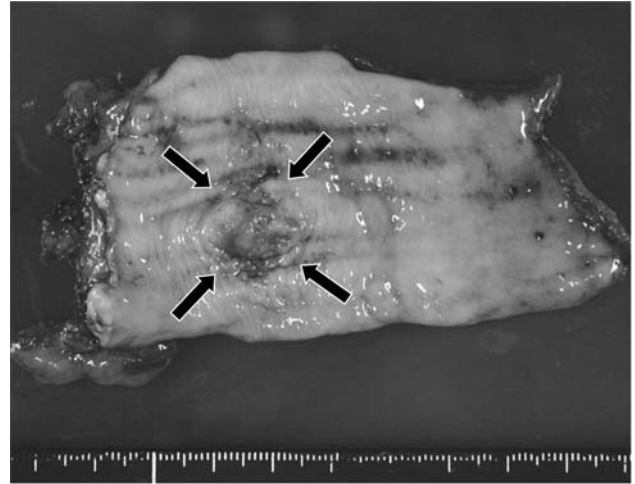


Figure 4. Macroscopic findings of the resected specimen. A gross pathological examination revealed a lesion measuring 32x20 mm in size, which was diagnosed as 0-IIa plus IIc type superficial esophageal cancer (arrow).

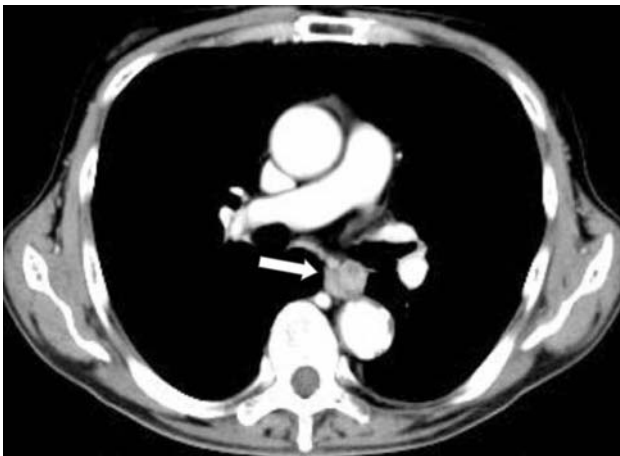


Figure 3. Chest CT scan. Lymphadenopathy of the midthoracic juxta-esophageal lymph node no.108 measuring 1.2x1.5 cm in size was present (arrow).

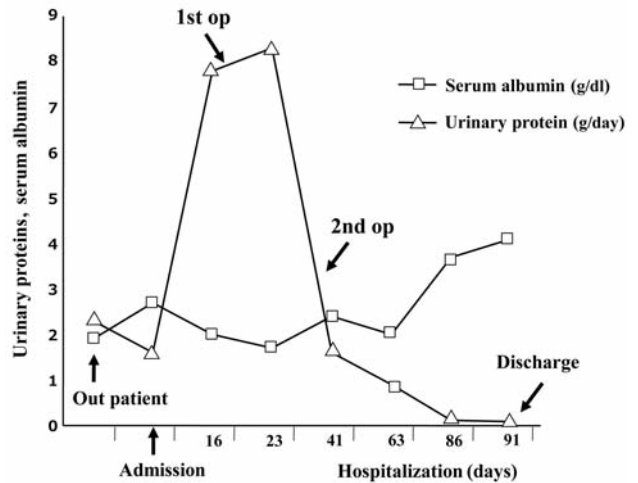


Figure 5. The pre- and postoperative serum albumin levels, and 24-hour urinary protein excretion over time.

Membranous glomerulonephritis (MGN) has been reported to be a histological feature of the kidney in 60 to 80% of nephrotic syndrome patients with concurrent epithelial malignant tumors (1, 15, 19). Of the 11 reported cases of nephrotic syndrome complicated by esophageal cancer, MGN was present at a frequency of 5 (56%) out of 9 cases with documented renal histopathological findings;

therefore, the trend was similar to that of overall epithelial malignant tumor cases. The pathogenic mechanism of MGN is attributed to the deposition of circulating immune complexes composed of tumor-derived causative antigen and corresponding antibody in the glomerular basement membrane, and is caused by various antigens, including tumor-associated antigens, re-expressed fetal antigens, viral antigens, and autologous non-tumor antigens (5, 7, 20). A report described the histological evidence of the normalization of glomerular lesions on a postoperative

Table I. Reported cases of esophageal cancer with concurrent nephrotic syndrome.

Author (ref)	Year	Age years/gender	Pathology		Treatment	Outcome
			Esophagus	Kidney		
Yoshida <i>et al.</i> (9)	1979	50/M	SCC	Minimal change	Steroid	Death (3 months)
Walker <i>et al.</i> (10)	1981	59/F	SCC	MPGN	Surgery	Improvement of nephrosis
Ducret <i>et al.</i> (11)	1981	61/M	SCC	Not described	Radiation	Death (6 months)
Heckerling <i>et al.</i> (12)	1985	65/M	SCC	MGN	Surgery	Improvement of nephrosis
Uezono <i>et al.</i> (13)	1989	68/M	SCC	Minimal change	Surgery	Improvement of nephrosis
Suzuki <i>et al.</i> (14)	1991	65/M	SCC	MGN	Surgery	Death (3 months)
Burstein <i>et al.</i> (15)	1993	65/M	SCC	MGN	Surgery	Improvement of nephrosis
Yedidag <i>et al.</i> (16)	1997	61/M	SCC	MGN	Steroid	Death (9 months)
Nagasaka <i>et al.</i> (17)	1999	76/M	SCC	MPGN	Surgery	Improvement of nephrosis
Muramoto <i>et al.</i> (18)	2009	54/M	SCC	MGN	EMR	Improvement of nephrosis
Present case	2010	78/M	SCC	Not described	Surgery	Improvement of nephrosis

SCC: Squamous cell carcinoma; MPGN: membranous proliferative glomerulonephritis; MGN: membranous glomerulonephritis; EMR: endoscopic mucosal resection; M: male; F: female.

kidney biopsy in a patient whose nephrotic syndrome remitted after a resection of the tumor (21). Muramoto *et al.* (18) reported that in a case of esophageal cancer with concurrent nephrotic syndrome showing elevated serum SCC antigen levels, the remission of nephrotic syndrome was achieved following the normalization of the serum SCC levels after tumor resection, thus suggesting that SCC might have been a causative antigen. In the present case, the serum SCC levels, which were elevated prior to the operation, returned to normal levels after the operation. This indeed suggests that SCC may be a causative antigen, as documented by Muramoto *et al.* (18), although the histological features of the renal glomeruli could not be obtained in the present case.

As the etiology of nephrotic syndrome has been more fully characterized in recent years, the importance of immunological abnormalities has become recognized, and the efficacy of steroid therapy and the use of immunosuppressants in the treatment of patients with nephrotic syndrome has also been reported (22). Conversely, in patients with nephrotic syndrome and a concurrent malignant tumor, steroid therapy and immunosuppressants have been associated with a response rate of no more than 30 to 40% (22, 23). If pharmacotherapy precedes these treatments, then there is concern that tumor growth will be exacerbated, thus leading to an increase in postoperative complications due to immunosuppression; therefore, several researchers have advocated that surgery should precede immunotherapy whenever a resection of the tumor is feasible (23). Asaoka *et al.* (4) reported that the remission of nephrotic syndrome associated with gastric cancer was achieved following a resection of the tumor in 17 (81%) out of 21 patients, of 11 esophageal cancer patients with concurrent nephrotic syndrome. Furthermore, the prognosis was unfavorable in all three patients who were not surgically

treated and who died within 1 year, whereas in the remaining eight patients whose tumors were resected, nephrotic syndrome remitted in all but one patient, who died of septicemia following the operation. Among the seven patients with a remission of nephrotic syndrome, there were two who survived for at least 2 years after the operation, thus indicating that the surgery led to an overall improvement in the prognosis (12, 18). These findings indicate that surgical treatment should be positively undertaken upon obtaining consent from the patient, and that a full explanation should be provided about esophageal cancer with nephrotic syndrome and where remission of nephrotic syndrome may be expected following tumor resection.

Surgical treatment for esophageal cancer is extremely invasive as it requires a two-cavity thoracic-abdominal approach (24, 25). Therefore, it is essential to provide sufficient doses of albumin during the perioperative period in patients with cancer complicated by nephrotic syndrome with severe hypoalbuminemia, as seen in the present case, and at the same time a surgical procedure that is as minimally invasive as possible should be performed. Suzuki *et al.* (14) recommended a two-stage operation as a safer method. In the present case, the complete removal of the primary lesion was performed during the first operation and reconstruction of the gastrointestinal tract was performed at the second operation. Although minor postoperative leakage was noted, the operative results were favorable; namely, the patient was cured in a relatively short period with enteral nutritional support *via* a prior constructed intestinal stoma.

In conclusion, it is important to select an appropriate operative method, and careful perioperative management, including nutritional management, should be included in the treatment of patients with esophageal cancer and concurrent nephrotic syndrome.

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