CASE REPORT

Nephrotic Syndrome Related to Early Gastric Cancer

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Nephrotic syndrome results in a prolonged, heavy increase in glomerular permeability to proteins. Nephrotic syndrome caused by malignant neoplasms accounts for 7.9% to 10.9%. Nephrotic syndrome can improve following resection of gastric malignancies. However, the relationship between early gastric cancer and nephrotic syndrome has not been elucidated. We report a case of early gastric cancer with nephrotic syndrome that improved after resection of the primary gastric lesion by endoscopic submucosal dissection. (Korean J Helicobacter Up Gastrointest Res 2015;15:249-253)

Key Words: Nephrotic syndrome; Early gastric cancer; Endoscopic submucosal dissection

INTRODUCTION

Nephrotic syndrome is a foreseeable complication that results from a prolonged, heavy increase in glomerular permeability to proteins. Its typical feature is heavy proteinuria (>2 g/m²/day).

Glomerular diseases are rare in malignant diseases. Nephrotic syndrome caused by malignant neoplasms accounts for 7.9% to 10.9% of these cases.1,2 The first reported case, described by Lee et al.,3 found that 11% of patients with nephrotic syndrome had a carcinoma. It is recommended that all patients over 50 years of age with new-onset nephrotic syndrome be screened for cancer.

Nephrotic syndrome was reported to improve following resection of malignant tumors in patients with gastric cancer.2,3 Many cases of advanced gastric cancer treated with surgical tumor resection have been reported. However, the relationship between early gastric cancer and glomerulonephritis has not been elucidated. The present report documents a patient with early gastric cancer and concurrent nephrotic syndrome in whom endoscopic submucosal dissection of the cancer resulted in complete remission of nephrotic syndrome.

CASE REPORT

A 72-year-old man was referred to hospital due to an abnormal finding on endoscopy, which revealed a 2.2 cm elevated erythematous lesion on the anterior wall of the antrum (Fig. 1A). Histopathological examination of the biopsy showed a tubular adenoma with high-grade dysplasia. Abdominal CT and colonoscopy were performed to rule out other malignancy, but non-specific findings. Initial laboratory analysis was as follow: white blood cell count 9,090/mm³, hemoglobin 15.7 g/dL, and platelet count 221,000/mm³. The blood chemistry analysis showed AST 29 IU/L, ALT 22 IU/L, total protein 8.1 g/dL, albumin 5.0 g/dL, total cholesterol 213 mg/dL, BUN 20 mg/dL, and creatinine 1.1 mg/dL. The urinalysis revealed trace proteinuria and no glucosuria. The patient was consequently scheduled for endoscopic submucosal dissection (ESD).

One week before admission for ESD (one week after the initial laboratory analysis performed), the patient developed facial and leg edema. On the day of ESD, a number of abnormal findings were noted: white blood cell count 8,700/mm³, hemoglobin 16.3 g/dL, and platelet count 221,000/mm³. The blood chemistry analysis showed AST 34 IU/L, ALT 22 IU/L, total protein 8.1 g/dL, albumin 5.0 g/dL, total cholesterol 213 mg/dL, BUN 20 mg/dL, and creatinine 1.1 mg/dL. The urinalysis revealed trace proteinuria and no glucosuria. The patient was consequently scheduled for endoscopic submucosal dissection (ESD).
noted, with increased BUN (33 mg/dL), increased serum creatinine (1.9 mg/dL), and hyponatremia (sodium 130 mEq/L). Urinalysis revealed high-grade proteinuria (4+), and 24-hour urinary protein excretion was 5,902.4 mg/dL, but no hematuria. A serum antinuclear antibody test was negative. Serum complement levels, including C3 and C4, were normal, as were immunoglobulin levels, including IgG, IgA, and IgM. Hepatitis B and C markers and tumor markers were normal. The patient had no previous history of hypertension or any autoimmune disorder or any other renal disease which cause nephrotic syndrome. He did not take any medications which provoke nephrotic syndrome. Based on the presence of the bilateral lower extremity edema and short-term 10 kg weight gain, we diagnosed nephrotic syndrome.

The lesion in the stomach was completely resected by ESD, which was performed using an insulation-tipped knife. (KD-601L; Olympus, Tokyo, Japan) (Fig. 1B, C). The resected specimen was about 2.2 cm sized and histopathological diagnosis was confirmed as early gastric cancer, type IIa (papillary adenocarcinoma). It was confined to the mucosa and no lymphovascular invasion without tumor emboli before being completely removed and clear resection margin. A kidney biopsy was performed to determine the exact cause of the nephrotic syndrome, and histopathological results were suggestive of IgM nephropathy (Fig. 2).

The patient was treated with diuretics and supportive care, not invasive treatment such as dialysis and no use of steroid or immunosuppressive agent. Interestingly, two weeks after the ESD, the patient’s edema improved, along with a reduction in the proteinuria. At a 30-month follow-up after ESD, all the laboratory tests showed normal results (white blood cell count 8,860/mm³, hemoglobin 13.4 g/dL, platelet count 288,000/mm³, AST 32 IU/L, ALT 27 IU/L, total protein 7.7 g/dL, albumin 4.1 g/dL, total cholesterol 192 mg/dL, BUN 38 mg/dL, and creatinine 1.1 mg/dL), and the urinalysis showed no proteinuria or glucosuria. No peripheral edema was noted. In addition, there was no evidence of recurrence in endoscopy.

**DISCUSSION**

Usually, a diagnosis of paraneoplastic glomerulonephritis should be considered if the glomerulonephritis happens in the presence of malignant tumor, complete remission after ablation of malignant tumor, and recurs in association with the recurrence of malignant tumor. But, in fact, this diagnosis maybe difficult because delayed diagnosis of malignant tumor, the existence of other causes of glomerulonephritis, and the unusual occurrence of certain paraneoplastic glomerulonephritis after complete ablation of malignant tumor.

Reported cases of paraneoplastic glomerulonephritis associated with common solid tumors based on data published by Bacchetta et al. and many case reports published over the past 2 years. The prevalence of renal involvement in patients with cancer has been analyzed in both autopsy and clinical series. Data from the autopsy series were conflicting because of the technical limitations of postmortem study. In the clinical series, the prevalence (range, 7~34%) was
Fig. 2. (A) Focally increased mesangial cellularity with scattered interstitial infiltration of eosinophils (H&E, ×400). (B) Granular deposits of IgM in mesangial spaces and along some capillary walls (immunofluorescence study, ×400). (C) Some electron-dense deposits in mesangial spaces (arrow; uranyl acetate and lead citrate, ×10,000). (D) Tubuloreticular inclusions in endothelial cells (arrow; uranyl acetate and lead citrate, ×30,000).

overestimated because the threshold of proteinuria was low, and hematuria was detected by qualitative dipstick tests only.\textsuperscript{1} The prevalence of cancer in patients with glomerulopathy is easier to establish. The first study to investigate this issue, published by Lee et al.,\textsuperscript{1} found that 11\% of patients with nephrotic syndrome had a carcinoma. Analysis of the Danish Kidney Biopsy Registry, which included all biopsies performed in Denmark since 1985, showed that the risk for cancer at 1 year and 1~4 years after a diagnosis of glomerulopathy increased 2.4 and 3.5-fold, respectively, compared with the risk in the general population.\textsuperscript{3}

Nephrotic syndrome is an uncommon manifestation in patients with extrarenal cancer.\textsuperscript{1} Enríquez et al.'s study\textsuperscript{9} of 21 patients with cancer and nephrotic syndrome found membranous glomerulonephritis in 81\% of cases, none of which were associated with membranoproliferative glomerulonephritis.

The pathogenesis of paraneoplastic syndrome includes the involvement of tumor specific antigens, viral antigens and/or re-expressed fetal antigens, host-antibody response of the shedding of tumor antigen, and circulating tumor antigen-antibody complexes, which may inhibit or suppress tumor-specific cell-mediated immunity.\textsuperscript{4} Until
today, exact pathological mechanism of cancer-nephrotic syndrome association remains unproved, but, carcinoma related nephrotic syndrome also may result of immune reactions occurred by glomerular deposition of circulatory antigen-antibody complex. Many trials have been made to detect tumor related antigens or their specific antibodies in kidneys of malignant tumor patients. However, antigens/antibodies have been demonstrated in only a few cases of paraneoplastic glomerulopathy. The tumor antigens implicated in the formation of immune deposits are carcinoembryonic antigens, prostate-specific antigens, renal tubular epithelial antigen, and other unidentified tumor products. The presence of tumor antigens and their corresponding antibodies in patients with paraneoplastic glomerulopathies is not indications of their involvement in the initial pathogenetic process leading to the formation of immune deposits. These components can become passively deposited because of increased glomerular permeability to proteins as a result of the initial action. One study suggested an relationship between malignant tumor with nephrotic syndrome and continuous virus infections, which cause glomerulonephritis first and malignancies subsequently.

The diagnosis of paraneoplastic glomerulopathy should rely on three criteria. First, remission occurs after complete removal of the tumor by surgery, chemotherapy, or other treatments. Second, renal relapse accompanies the recurrence of the neoplasia. Third, a pathophysiological link is established between cancer and membranous nephropathy, including the detection of tumor antigens (such as carcinoembryonic antigens and prostate-specific antigens) and antitumor antibodies within subepithelial immune deposits. However, the presence of these antigens does not mean they are causative, because they can be passively deposited as a result of increased glomerular permeability to proteins.

In several studies on gastric cancer, nephrotic syndrome showed signs of regression after endoscopic or surgical resection of the gastric cancer. In these studies, the advanced and early gastric cancer cases, nephrotic cancer was shown to regress in the case of complete surgical removal of the tumor, and for only the case of case did the nephrotic cancer show signs of regression after complete endoscopic removal. So, the relationship between early gastric cancer that performed ESD and glomerulonephritis not enough to elucidated, still more studies are needed.

Because the general prognosis of nephrotic syndrome due to IgM nephropathy is less favorable compared to other types of nephrotic syndrome because it is less responsive to steroid treatments, this is still a controversial area of the treatment.

In this case, cause of nephrotic syndrome was IgM nephropathy. In several studies, most common clinical feature of IgM nephropathy is nephrotic syndrome (about 77%) and the general prognosis of nephrotic syndrome due to IgM nephropathy is less favorable compared to other types of nephrotic syndrome because it is less responsive to steroid treatments, but this is still a controversial area of the treatment.

It is well known that clinical remission after surgical removal of a tumor or chemotherapy-induced complete remission of the disease indicates a relationship between malignancy and glomerulopathy. The current report documents a patient with early gastric cancer and concurrent nephrotic syndrome in whom ESD of the cancer resulted in complete remission of nephrotic syndrome.

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