Minimal Change Nephrotic Syndrome Complicated with Malignant Ascites in a Patient with Type II Diabetes

Taro Sugase, Tetsu Akimoto, Yoshitaka Iwazu, Tomoyuki Yamazaki, Akihiko Numata, Fumi Takemoto, Shigeaki Muto and Eiji Kusano

Abstract

A large number of renal biopsy studies have shown the concurrent presence of non-diabetic renal disease in diabetics. This report describes one such diabetic female patient with nephrotic syndrome due to minimal change glomerular disease who was successfully treated with prednisolone. Despite the remission of her nephrotic syndrome, she had gradual development of malignant ascites, which was finally interpreted to be linked to primary peritoneal carcinoma. It is necessary to bear in mind that malignancies may not only be the underlying etiology for paraneoplastic glomerular injuries, but also can be an independent pathogenic process, regardless of their nephrotic status during the overall management of the patients with ascites.

Key words: minimal change nephrotic syndrome, primary peritoneal carcinoma, diabetes, renal biopsy, malignant ascites

(Intern Med 51: 1885-1888, 2012)
(DOI: 10.2169/internalmedicine.51.7550)

Introduction

A large number of renal biopsy studies have shown the concurrent presence of non-diabetic renal disease in diabetics with variations in their prevalence and composition (1). This report describes one such diabetic female patient with nephrotic syndrome due to minimal change glomerular disease who was successfully treated with prednisolone (PSL). Despite the remission of her nephrotic syndrome, she was complicated with the gradual development of malignant ascites, which was finally interpreted to be associated with primary peritoneal carcinoma, a rare type of peritoneal cancer similar in numerous clinical aspects to ovarian carcinoma (2).

Case Report

An 82-year-old female was admitted in May 2010 presenting with complaints of progressive swelling of her legs. She had gained about 10 kg in the previous five weeks. Two years prior to admission, she was found to have type II diabetes, which was controlled with a rapid-acting type of recombinant human insulin. She neither smoked nor drank alcohol, and denied the use of any drugs. Her other medical histories included hypertension and hyperlipidemia for twenty-one years.

Her physical examination at admission was unremarkable except for periorbital and leg edema. A laboratory evaluation revealed the following results: white blood cells, 6,700/μL; hemoglobin, 14.2 g/dL; platelet count, 26.3×10^4/μL; fibrinogen, 618 mg/dL; D-dimer, 17.7 μg/mL; blood urea nitrogen, 27 mg/dL; serum creatinine, 0.58 mg/dL; total protein, 4.2 g/dL; serum albumin, 1.2 g/dL; sodium, 139 mmol/L; potassium, 4.3 mmol/L; chloride 107 mmol/L; calcium 7.1 mg/dL; phosphorus 4.4 mg/dL; aspartate aminotransferase, 62 U/L; alanine aminotransferase, 56 U/L; C-reactive protein, 0.04 mg/dL; immunoglobulin (Ig) G, 248 mg/dL; IgA, 418 mg/dL; IgM, 126 mg/dL; carcinoembryonic antigen (CEA), 2.8 ng/mL; carbohydrate antigen (CA) 19-9, 25 U/mL; and squamous cell carcinoma (SCC)-related antigen, 0.8 ng/mL. The patient’s fasting plasma glucose and HbA1c were 88 mg/dL and 5.9%, respectively. Tests for anti-neutrophil cytoplasmic antibodies (ANCA), anti-glomerular basement membrane (GBM) antibodies, hepatitis B virus surface antigen (HBsAg), anti-HBsAg antibodies, and antibodies to the
hepatitis C virus were all negative. Renal sonography revealed that both kidneys were of normal size, and the renal cortex echogenicity was normal. No radiological findings suggestive of vascular thrombosis were noted. Her urine was 3+ for protein and contained 5.9 g of protein in a 24-hour urine specimen. The proteinuria selectivity index was 0.012, and her creatinine clearance was 78.8 mL/min. The sediment contained 2 to 3 granular casts per low power field. The urinary excretion of β2-microglobulin and N-acetyl-beta-D-glucosaminidase were 2,633 μg/L and 36.9 Ug·Cr, respectively. An ophthalmological analysis failed to demonstrate any diabetic retinopathy.

At the end of May, a renal biopsy was performed (Fig. 1). The renal biopsy consisted of two cores of renal parenchyma with twenty glomeruli, and exhibited no glomerular changes except one glomerulus that was globally sclerotic. There was no intimal thickening, medial hypertrophy, or tubular atrophy. An immunohistochemical analysis failed to reveal any immune complex deposits among the observed glomeruli. Electron microscopy disclosed no apparent electron dense deposits within the GBM or mesangial area, while it demonstrated diffuse fusion of the foot processes of the glomerular visceral epithelial cells, consistent with minimal change glomerular disease. In the middle of June, the intravenous administration of unfractionated heparin (10,000 U/day), which had commenced on the day following admission in an attempt to maintain an active partial thromboplastin time between 1.5 and 2 times the control value, was changed to 1 mg/day warfarin, and oral PSL at a dose of 40 mg/day was initiated. Following this treatment, her leg edema was successfully controlled, and there were gradual improvements in her proteinuria and hypoalbuminemia, and her urinary protein level finally decreased to 0.15 g/g·Cr and the sAlb increased to around 3.5 to 3.9 g/dL at the follow-up (Fig. 2).

Nevertheless, an ultrasonographic survey of the abdomen was performed six months after the renal biopsy because of progressive appetite loss, abdominal pain, and protracted vomiting, in addition to bilateral mildly enlarged ovaries with ascites. Endoscopic examinations of the gastrointestinal tract failed to reveal any neoplastic lesions. A further work-up with a computed tomography (CT) scan revealed the presence of bilateral pleural effusion associated with a nodular lesion in the lower lobe of the left lung and the thickening of the parietal peritoneum without any aggravated lymphadenopathies (Fig. 3A). The laboratory data showed a significantly elevated serum CA-125 level (1,680 U/mL) with a normal level CEA (2.0 ng/mL). The cytological examination of the free peritoneal fluid revealed clusters of malignant cells consistent with adenocarcinoma (Fig. 3B). Based on these findings, the patient was presumptively diagnosed to have advanced stage primary peritoneal carcinoma (2). She was then treated with intraperitoneal carboplatin combined with intravenous paclitaxel (3), which resulted in a partial response. She is currently six months from her initial diagnosis of peritoneal carcinoma, and a decrease in her serum CA-125 to 23 U/mL was confirmed, without evidence of recurrent nephrotic syndrome.

**Discussion**

Performing a renal biopsy for diabetics with overt proteinuria has generally been considered when the presence of a renal disease other than diabetic nephropathy is suggested by clinical signs, such as a rapid deterioration of the renal function, microscopic or macroscopic hematuria, and proteinuria in newly diagnosed diabetics without retinopathy or neuropathy (1, 4, 5). On the other hand, a diagnosis of diabetic nephropathy can be made without pathological confirmation in the appropriate clinical setting, such as the presence of diabetic retinopathy, a long duration of diabetes, and hypertension. In this context, the information available concerning the qualitative and quantitative renal morphology in the patients with diabetic retinopathy is still limited, and to...
date the knowledge regarding the relationship between these findings and the clinical renal parameters is insufficient (1). Before arriving at the conclusion that nephrotic syndrome is etiologically linked to minimal change glomerular disease, the presence of alternative renal injuries, such as membranous nephropathy, which is one of the most common causes of nephrotic syndrome in adult patients (6), and nephrosclerosis due to a long history of hypertension, were suspected. Thus, there was a clinical benefit to performing a renal biopsy in the present patient, since it led us not only to diagnose her with minimal change nephrotic syndrome rather than of diabetic nephropathy, membranous nephropathy, or hypertensive nephrosclerosis, but also because initiating steroid treatment for nephrotic syndrome resulted in prompt remission. Moreover, several recent studies have suggested a morphological analysis of the kidney to be a valuable diagnostic procedure for the overall management of patients with diabetic nephropathy (1, 4, 5, 7). Therefore, the clinical significance of a renal biopsy in the overall assessment for proteinuric diabetics should be evaluated more carefully.

The combination of the clinical findings of the present patient, including malignant ascites compatible with adenocarcinoma and an elevated CA-125 level with a normal CEA level were suggestive of ovarian carcinoma (8), which is usually found as a large ovarian mass at the time of diagnosis (9). Although cases of ovarian carcinoma with normalized ovaries and disseminated peritoneal spread may not be exceptional (9), the diagnostic imaging performed in the
current patient revealed the bilateral mildly enlarged ovaries with the thickened parietal peritoneum. Primary peritoneal carcinoma is a relatively newly described disease entity, characterized by abdominal carcinomatosis without an identifiable primary tumor, ovaries of normal size or enlarged by a benign process, and an elevated level of CA-125 (2, 3, 9). The absence of surgical and pathological findings precluded us not only from diagnosing the present patient with primary peritoneal carcinoma in terms of the diagnostic criteria established by the Gynecologic Oncology Group (10), but also to exclude the possible complication with malignant mesothelioma, although the disease seems to occur predominantly in males and is usually associated with asbestos exposure (11). Nevertheless, the clinical findings and previous information described above led us to interpret that the gradually developed malignant ascites was associated with primary peritoneal carcinoma.

It has been widely acknowledged that ascites can develop as a result of not only liver disease, congestive heart failure or nephrotic syndrome, but also various malignancies including ovarian, endometrial, breast, esophageal, gastric, colorectal, lung, pancreatic, hepatobiliary, and primary peritoneal carcinoma (8, 12). One may argue that the presence of the peritoneal carcinoma in the current patient might be etiologically linked to the minimal change nephrotic syndrome, and it might have developed through a paraneoplastic mechanism. Interestingly, the presumable association between the development of minimal change nephrotic syndrome and ovarian carcinoma has been described anecdotaly (13). Although the relationship between malignancies and nephrotic glomerulopathies is difficult to prove, it has been suggested by clinical characteristics such as a close temporal link and parallel evolution, including improvement, resolution, and relapse (14-16). In this context, the fact that the malignant ascites had gradually developed despite the remission of nephrotic syndrome led us to consider that the presence of a latent relationship between minimal change nephrotic syndrome and peritoneal malignancy was unlikely, at least in the current patient. Instead, our patient seemed to be incidentally complicated with primary peritoneal carcinoma. Therefore, it is necessary to consider these neoplastic issues not only as the etiology underlying paraneoplastic glomerular injuries, but also as an independent pathogenic process, during the overall management of patients with ascites, regardless of their nephrotic status.

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

References