

## Do We Have to Perform a Renal Biopsy? Clinical Dilemmas in a Case with Nephrotic Syndrome

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**ABSTRACT:** Renal biopsy is one of the pivotal diagnostic tools used in the field of nephrology. A morphological analysis of the kidney may also be of value for the overall management of patients with diabetic nephropathy. However, the indications for renal biopsy differ considerably among nephrologists, and no global consensus regarding performing this procedure among diabetic patients with various renal manifestations has yet been achieved. In this report, we would like to describe our serendipitous experience with a male type 2 diabetic patient presenting with nephrotic syndrome complicated by concurrent gastric carcinoma. We also discuss several conundrums that arose in the current case, which had an impact on our diagnostic and therapeutic decisions.

**KEYWORDS:** diabetic nephropathy, nephrotic syndrome, paraneoplastic glomerular injury, membranous nephropathy, renal biopsy

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### Introduction

Renal biopsy is one of the pivotal diagnostic tools used in the field of nephrology. There are numerous diseases that can cause nephrotic syndrome, nephritic syndrome, and acute kidney injury, which have vastly different prognostic and therapeutic implications, illustrating the importance of histopathological examinations in the differential diagnosis.<sup>1</sup> However, the indications for renal biopsy differ considerably among nephrologists, and a global consensus regarding performing this procedure is lacking.<sup>2</sup> In this report, we describe our serendipitous experience with a male type 2 diabetic patient presenting with nephrotic syndrome complicated by concurrent gastric carcinoma. We also discuss several conundrums that arose in the current case, which had an impact on our diagnostic and therapeutic decisions.

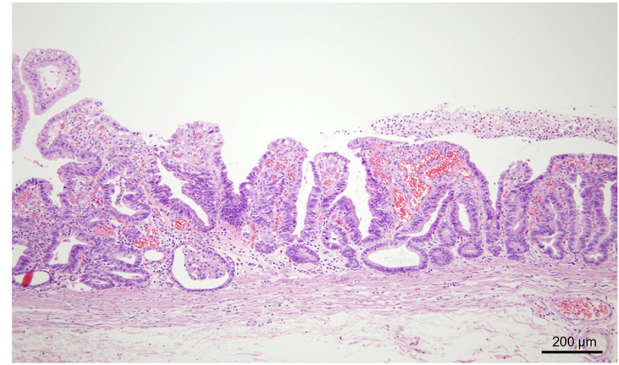
### Case Report

A 64-year-old male was referred to our unit with complaints of progressive swelling of his legs and weight gain of approximately

5 kg. Thirteen years before, he was found to have type 2 diabetes. Thereafter, he had received combination treatment with oral voglibose and nateglinide, which had kept his HbA1c levels between 6 and 7%. His serum creatinine (sCr) levels had increased gradually during the last two years. He had noticed the symptoms about three months before the referral, when his level of blood sCr was 1.7 mg/dL. He denied the use of any drugs, and his medical histories included hypertension and hyperlipidemia for more than 10 years.

His physical examination at the referral was unremarkable except for periorbital and leg edema. The laboratory data obtained on admission are summarized in Table 1. Tests for hepatitis B virus surface antigens and antibodies to the hepatitis C virus were negative. Renal sonography showed that the renal dimensions of the right kidney measured 113 × 60 mm, while those of the left kidney measured 115 × 66 mm, and the degree of renal cortex echogenicity was normal. The patient's urine was 3+ for protein and contained 8.9 g of protein in a 24 hour specimen. His proteinuria selectivity index

and creatinine clearance were 0.325 and 78.8 mL/minute, respectively. An ophthalmologic analysis revealed the patient to have simple diabetic retinopathy. On the other hand, the latex-agglutination test for fecal occult blood was positive (124 ng/mL) despite the absence of remarkable findings in the diagnostic thoracoabdominal computed tomography scan, and thus, endoscopic analyses of the upper and lower gastrointestinal tracts were performed. The presence of sigmoid colon polyps, which consisted of adenomatous tissue, was confirmed, while the gastric biopsy specimens revealed the presence of a well-differentiated adenocarcinoma confined to the submucosa. Endoscopic mucosal resection (EMR) was finally performed three months after the referral, confirming that the neoplastic tissue was of type 0–IIc based on the Paris endoscopic classification of superficial neoplastic lesions,<sup>3</sup> with a well-differentiated adenocarcinoma (Fig. 1), 7 × 6 mm in size. Eight months after the EMR, he was negative at occult fecal blood test but continued to exhibit nephrotic syndrome with a urine protein level of 3.69 g/g · Cr, an sAlb of 2.7 g/dL, and an sCr level of 2.04 mg/dL, and he was thus subjected to a pathological evaluation.



**Figure 1.** A photomicrograph of the EMR specimen. A type 0–IIc lesion with a well-differentiated adenocarcinoma with negative lymphovascular involvement was found (hematoxylin and eosin stain). The scale bar is indicated.

**Table 1.** Laboratory data on admission.

White blood cells	9400/μl	(3900–9800)
Hb	11.3 g/dl	(13.5–17.6)
Platelet count	25.3 × 10 <sup>4</sup> /μl	(13.0–36.9)
Fibrinogen	716 mg/dl	(129–271)
D-dimer	2.2 μg/ml	(0–1.5)
Blood urea nitrogen	31 mg/dl	(8–20)
Creatinine	1.8 mg/dl	(0.63–1.03)
Total protein	5.9 g/dl	(6.9–8.4)
Albumin	2.6 g/dl	(3.9–5.1)
Sodium	142 mmol/l	(136–148)
Potassium	5.7 mmol/l	(3.6–5.0)
Chloride	110 mmol/l	(96–108)
Calcium	8.8 mg/dl	(8.8–10.1)
Phosphorus	4.0 mg/dl	(2.4–4.6)
Aspartate aminotransferase	15 IU/l	(11–30)
Alanine aminotransferase	13 IU/l	(4–30)
C-reactive protein	0.24 mg/dl	(0–0.14)
IgG	856 mg/dl	(870–1700)
IgA	276 mg/dl	(110–410)
IgM	94 mg/dl	(33–160)
CEA	1.0 ng/ml	(<5)
CA19–9	8 U/ml	(<37)
FBS	151 mg/dl	(70–109)
HbA1c	6.70%	(4.3–5.8)

**Note:** The reference ranges for each parameter used at our institute are indicated in the brackets.

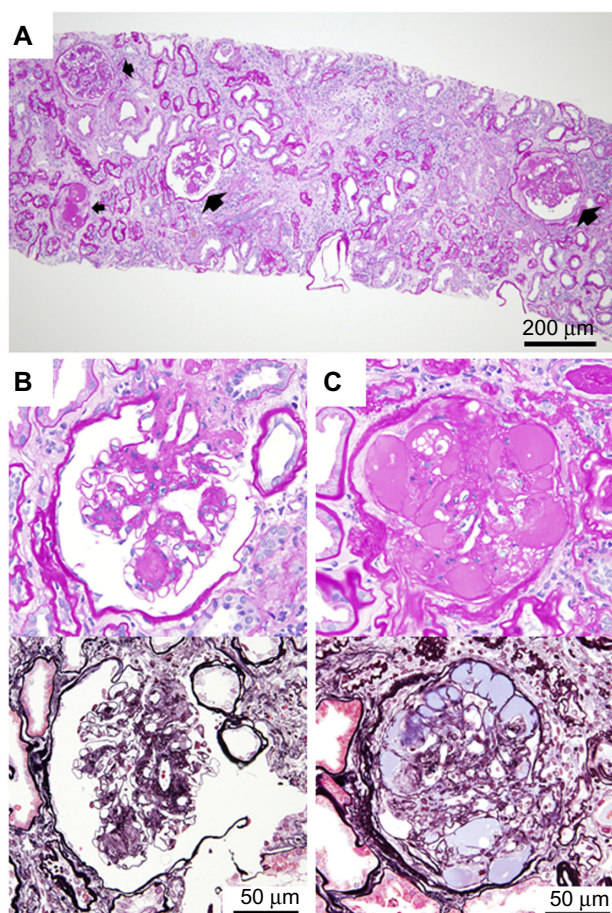
**Abbreviations:** Hb, hemoglobin; Ig, immunoglobulin; CEA, carcinoembryonic antigen; CA, carbohydrate antigen; FBS, fasting blood sugar.

The renal biopsy consisted of three cores of renal parenchyma with 32 glomeruli, almost half of which were globally sclerotic. There were glomeruli with hyalinotic lesions, globally widened mesangial regions, and a number of rounded acellular mesangial nodules; and also interstitial infiltration of lymphocytes, atrophic changes in the tubule structure, interstitial fibrosis, and arteriolar hyalinization were identified (Fig. 2). Immunofluorescence staining failed to demonstrate the linear staining of IgG along the glomerular capillary wall. Instead, the presence of focal deposits of IgM in the depending portions of the areas of hyalinosis was confirmed. Electron microscopy failed to show the presence of electron-dense deposits on the subepithelium of the glomerular basement membrane, which is a suggestive finding of membranous nephropathy.<sup>4</sup>

Based on the renal pathological findings, combined with the patient's clinical pictures, he was finally diagnosed to have nephrotic syndrome due to diabetic nephropathy, and treatment with olmesartan medoxomil at 20 mg/day, amlodipine besilate at 5 mg/day, and furosemide at 80 mg/day, which had been started after the referral, as well as the oral hypoglycemic agents described above, was continued. Despite the absence of any exacerbation of the blood pressure control, his renal function gradually declined and a periodic hemodialysis program finally commenced 21 months after the renal biopsy.

## Discussion

Performing a renal biopsy for proteinuric diabetics has usually been considered when the presence of a renal disease other than diabetic nephropathy is suggested by clinical signs, such as rapid deterioration of the renal function, microscopic or macroscopic hematuria, and proteinuria in newly diagnosed diabetics without retinopathy or neuropathy.<sup>5–7</sup> On the other hand, the association of chronic renal insufficiency, nephrotic syndrome, and diabetes with microangiopathic complications such as retinopathy makes a diagnosis of diabetic nephropathy probable, diminishing the need for a renal biopsy.<sup>5,8,9</sup> However, several recent studies have suggested a morphological analysis



**Figure 2.** The renal biopsy findings. (A) A low power view showing the diffuse distribution of glomeruli with various stages of diabetic glomerular injuries, including glomeruli with hyalinotic lesions (narrow arrow), a moderate increase in mesangial matrix and thickening of the capillary wall (medium arrow), as well as nodule formation (wide arrows) (periodic acid-Schiff stain). Two sections of the same glomerulus with nodular lesions (B) and enormous exudative lesions with some bubbles, probably representing plasma proteins/lipids (C) (upper panel, periodic acid-Schiff stain; lower panel, periodic acid methenamine silver-Masson trichrome stain). The scale bar is indicated in each panel.

of the kidney to be of value for the overall management of patients with diabetic nephropathy,<sup>5–10</sup> implying the diagnostic potential of such a procedure in the overall assessment for diabetics with various renal manifestations. Considering the clinical picture of our patient at the referral, one might have straightforwardly attributed the nephrotic syndrome to diabetic nephropathy without pathological confirmation, and might even argue that the patient's renal pathological findings were not surprising. However, the clinical significance of the current case should be considered carefully in terms of the fact that the concurrent gastric carcinoma was found before arriving at the conclusion that the nephrotic syndrome was etiologically linked to diabetic glomerular injuries.

Nephrotic syndrome has been a focus of studies as one of the pivotal manifestations of the glomerular damage associated with various kinds of neoplasms,<sup>11–13</sup> while membranous

nephropathy, one of the most common causes of adult nephrotic syndrome worldwide,<sup>14</sup> is the most common paraneoplastic glomerulopathy associated with solid tumors.<sup>11–13</sup> The main problem is to determine how thorough the search for neoplasia should be in such nephrotic subjects. Experts recommend performing basic routine cancer screening procedures, including chest radiography, an occult blood survey of stool specimens, colonoscopy, and measurements of the carcinoembryonic antigen (CEA) and prostate-specific antigen levels, especially in older patients with newly diagnosed membranous nephropathy without any other obvious causes. In addition, further investigations, such as bronchoscopy, gastroscopy, and CT, may be in order after the first-line assessment.<sup>11,13</sup> However, although some of these examinations may be carried out in the ordinary clinical setting,<sup>7,15</sup> the extent of the workup depends on the judgment of the primary physician. On the other hand, the validity of such a policy among the nephrotic patients whose renal pathological diagnoses are lacking or those with glomerulopathy other than membranous nephropathy remains to be established. We believe, however, that there are some subsets of nephrotic patients who would benefit from the screening for malignancies, as described in the current report. Otherwise, we might have overlooked the concurrent gastric carcinoma in the present case if we had simply ascribed the nephrotic syndrome to diabetic nephropathy regardless of the presence or absence of the pathological confirmation and had failed to perform upper gastrointestinal endoscopy, which led us to promptly identify the disease.

Fecal immunochemical tests are recommended as the first-choice modality for colorectal cancer screening in average-risk populations,<sup>16</sup> although the current evidence is insufficient to recommend for or against routine surveys to detect gastric or esophageal carcinoma in patients with characteristics similar to those of our patient, ie, positivity for fecal occult blood with negativity on colonoscopy, based on a population-based colorectal cancer screening program.<sup>17</sup> Nevertheless, it has been shown that performing upper gastrointestinal endoscopy in patients with a positive fecal occult blood test alone is not exceptional, even in the field of gastroenterology.<sup>18</sup> We believe that the flexible application of such procedures should be mandatory in nephrotic subjects with these characteristics.

An alternative concern raised from the current case is the role of a renal histological analysis in cancer patients with various renal manifestations, including nephrotic syndrome. In patients with carcinomas that are incurable at the moment of diagnosis, a renal biopsy may not be indicated.<sup>11</sup> Although the relationship between malignancies and nephrotic glomerulopathies is somewhat difficult to prove, it may be suggested by clinical characteristics, such as a close temporal link and parallel evolution, including improvement, resolution, and relapse.<sup>11–13,15</sup> Moreover, we should bear in mind that the time to remission of nephrotic syndrome after successful treatment of a malignancy can often be months to years.<sup>11,12,19</sup> Nevertheless, the persistence of nephrotic syndrome with a progression





of chronic renal failure in the current patient obliged us to perform a histological survey in view of the possibility of finding a potentially reversible glomerular lesion.<sup>7</sup> One may argue that pathological assessment of the kidney is not warranted in the milieu of chronic renal insufficiency<sup>20</sup>; however, there was a clinical benefit to performing a renal biopsy in the present patient, because it led us to conclude that the presence of a latent relationship between nephrotic syndrome and gastric malignancy was unlikely, and that our patient was incidentally complicated with gastric carcinoma. In the current case, we faced, as do most physicians at various times, diagnostic dilemmas, not only as to whether to perform a renal biopsy but also with respect to how long it is possible to wait to perform a renal biopsy despite progressive deterioration of the patient's renal function. Obviously, further experience with similar cases is required to resolve such conundrums. The establishment of an optimal management strategy for diabetic patients with both malignancies and various renal manifestations is therefore a matter requiring continuous and careful attention.

### Author Contributions

TA drafted the manuscript. NO, ET, and OS made contributions to the acquisition of the clinical data. EK and DN provided a detailed review of the contents and structure of the manuscript, resulting in significant changes to the original document. All authors have read and approved the final manuscript.

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