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Original contribution

Importance of frequency and morphological characteristics of nodular diabetic glomerulosclerosis in diabetic nephropathy☆,☆☆

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Summary The Renal Pathology Society proposed a pathological classification for diabetic nephropathy (DN) (RPS 2010). We retrospectively examined the renal structural-functional relationships using the RPS 2010 classification in 49 DN cases. We also evaluated the importance of the percentage of glomeruli with nodular diabetic glomerulosclerosis and their morphological characteristics (cellular, cellular and extracellular matrix [ECM] or ECM types) in the pathology of DN. The classes of DN (RPS 2010) were significantly correlated with the duration of diabetes mellitus (DM), degree of proteinuria, a decreased estimated glomerular filtration rate (eGFR), and the stages of Japanese clinical DM and chronic kidney disease (CKD). When the percentage of glomeruli with nodular glomerulosclerosis (IIIA <25%, IIIB 25–50%, IIIC 50–75%, and IIID >75%) was added to class III in this classification, the classes of DN had a greater correlation with the levels of proteinuria. The morphological characteristics of nodular glomerulosclerosis such as cellular, cellular and ECM, or ECM type were associated with several clinical parameters including the duration of DM, degree of proteinuria, a decreased eGFR, and/or the stages of clinical DM and CKD. Mesangial red blood cell fragments that is indicative of microvascular injury was found in cellular or cellular and ECM types of nodular glomerulosclerosis. The RPS 2010 classification is useful as a DN pathological classification that indicates a good correlation with the clinical characteristics of DN. In addition, the frequency and morphological characteristics of nodular diabetic glomerulosclerosis is important for the evaluation of the pathology in DN.

1. Introduction

Diabetic nephropathy (DN) is one of the most common causes of end-stage renal disease (ESRD) worldwide [1]. The increased prevalence of diabetes mellitus (DM) has led to an increase in patients with DN and ESRD [2]. In Japan, the annual incidence of starting dialysis due to DN has been the predominant cause since 1998, indicating DN as one of

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the most important causes of ESRD [3]. The percentage of patients with DN was 44.2% among new dialysis patients, and 36.6% among all dialysis patients at the end of 2011 according to the Japanese society for dialysis therapy renal data registry [3].

Several studies have shown cross-sectional relationships between histological and clinical findings in DM type 1 or type 2 patients with DN [4-8]. The importance of renal pathology in DN has been recognized, and the pathological classification is considered to be important for evaluating the stage of DM, the mechanisms of renal dysfunction and proteinuria, and the natural history of DM. The development of DN is considered to be accompanied with the glomerular microvascular injuries, and mesangial red blood cell (RBC) fragments in glomeruli are morphologically indicative of microvascular injury in DN [9]. Nodular glomerulosclerosis is one of the most characteristic pathological findings of advanced DN, and mesangiolysis-associated nodular glomerulosclerosis can be a useful prognostic indicator for DN [10].

A pathological classification of DN was proposed by the Renal Pathology Society [11]. This classification is considered to be an important first step toward the development of a clinically useful classification system for DN [12], and several recent studies have demonstrated the clinical utility of this classification [13-17].

The present study aimed to confirm the usefulness of the pathological classification for DN (RPS 2010) in the relationship for clinical characteristics for DN. In addition, we also examined the importance of the evaluation of the frequency and the morphological characteristics of nodular diabetic glomerulosclerosis including the presence of mesangial RBC fragments in the pathology of DN.

2. Materials and methods

2.1. Patients and clinical features

We retrospectively examined renal biopsy cases of DM (n = 62) from a series of biopsies in our department from 2008 to 2016. The study protocol was approved by the Human Ethics Review Committee of Nippon Medical School. DN was defined by a previous clinical history of DM with the presence of proteinuria and/or a decreased renal function and biopsy-proven kidney disease caused by DM. Cases concomitant with non-DM renal diseases were excluded. Among our 62 cases of DM, 13 had diseases concomitant with non-DM renal diseases, such as IgA nephropathy, membranous nephropathy and microscopic polyangiitis. We therefore examined the clinicopathological characterization of 49 cases of DN.

The clinical characteristics at the time of biopsy were collected, including age, duration of DM at the time of the biopsy, gender, HbA1c, 24-h urinary protein (g/day), the estimated glomerular filtration rate (eGFR) (mL/min/1.73 m^2), the Japanese clinical DM stage [18], and the chronic kidney disease (CKD) stage.

2.2. Pathological classification

For each biopsy specimen, light microscopy, immunofluorescence and electron microscopy were routinely performed. Sections for light microscopy were stained with hematoxylin–eosin, periodic acid–Schiff, Masson's trichrome and periodic acid methenamine silver. All the patients were categorized according to the RPS 2010 pathological classification of DN [11]. The glomerular classifications were as follows: class I (Figs. 1A and 2A): glomerular basement membrane thickening (>395 nm in females and >430 nm in males) by electron microscopy; class IIA (Figs. 1B and 2B): mild mesangial expansion in <25% of the observed mesangial areas; class IIB: severe mesangial expansion in >25% of the observed areas; class III (Figs. 1–E and 2C–E): at least one glomerulus had nodular diabetic glomerulosclerosis (Kimmelstiel-Wilson lesion; K-W lesion); and class IV (Figs. 1F and 2F): global glomerulosclerosis in >50% of the glomeruli. All biopsy samples included more than 10 glomeruli.

2.3. The frequency and the morphological characteristics of nodular diabetic glomerulosclerosis

We focused on the frequency and the morphological characteristics of nodular diabetic glomerulosclerosis in DN. We examined the percentage of glomeruli with nodular diabetic glomerulosclerosis among the total glomeruli in each case of our class III cases and compared to be clinical characteristics. We also divided class III into 4 classes according to the percentage of glomeruli with nodular diabetic glomerulosclerosis as follows: IIIA, <25%; IIIB, 25% – 50%; IIIC, 50% – 75%; and IIID, 75–100%. We also examined the correlation between the DN classification (RPS 2010) with the frequency of nodular diabetic glomerulosclerosis and the clinical characteristics.

In order to clarify the importance of the morphological characteristics of nodular diabetic glomerulosclerosis in the evaluation of the pathology for DN, we divided nodular diabetic glomerulosclerosis into 3 morphological subtypes: the cellular type, the cellular and extracellular matrix (ECM) type, and the ECM type. The cellular type was primarily occupied by the cellular component in nodular lesions (Figs. 1C and 2C). The cellular and ECM type was characterized by cellular component in the peripheral area and increased ECM in the central area of nodular lesions (Figs. 1D and 2D). In the ECM type of nodular diabetic glomerulosclerosis, the ECM widely accumulated without cellular component in nodular lesions (Figs. 1E and 2E). In our DN cases, nodular lesions were noted in all 24 cases of class III and 8 of 10 cases of class IV. Regardless of the number of nodular lesions in each glomerulus, we calculated the percentage of cellular, cellular and ECM, and ECM type of nodular lesions among