Probable light- and heavy-chain deposition disease in a patient with nodular diabetic glomerulosclerosis

Noriko Nakamura · Ritsuko Katafuchi ·
Izumi Watanabe · Yusuke Kuroki ·
Itsuko Ishida · Kei Hori

Received: 21 June 2013 / Accepted: 28 January 2014 / Published online: 13 February 2014
© Japanese Society of Nephrology 2014

Abstract We report a case of probable light- and heavy-chain deposition disease (LHCDD) in a diabetic patient, a rare and educational case. The patient was a 71-year-old man having a long history of uncontrolled diabetes mellitus with retinopathy. He showed heavy proteinuria and renal insufficiency, and did not have paraproteins. Renal biopsy revealed nodular glomerulosclerosis with severe mesangial widening and microaneurysm. Immunofluorescence (IF) showed weak staining of kappa light chain, IgG and C1q along glomerular basement membrane (GBM). At first, we interpreted these IF findings to be nonspecific, thus we diagnosed as diabetic nodular glomerulosclerosis. Later, we recognized one of a few case reports of monoclonal immunoglobulin deposition disease (MIDD) in diabetic patients, and reconsidered the first diagnosis. The added electron microscopy (EM) showed obvious electron-dense materials in GBM, while tubular basement membrane deposits were not identified. A concurrence of LHCDD and diabetic nodular glomerulosclerosis may be suggested in this case. Like this case, IF staining in MIDD is often weak, so it is difficult to diagnose MIDD accurately without EM. Reports of MIDD in diabetic patients are extremely rare, possibly due to being often overlooked. This case emphasizes that overall pathological examination including IF and EM is important for the accurate differentiation of nodular glomerulosclerosis, even in diabetic patients.

Keywords Light- and heavy-chain deposition disease · Nodular glomerulosclerosis · Diabetic glomerulosclerosis

Introduction

Light- and heavy-chain deposition disease (LHCDD) is a subtype of monoclonal immunoglobulin deposition disease (MIDD) which is characterized by the deposition of monoclonal light chain and heavy chain in various organs [1, 2]. MIDD includes light-chain deposition disease (LCDD), heavy-chain deposition disease (HCDD) and LHCDD [1–3]. LCDD is the most prevalent and reports of LHCDD and HCDD are extremely rare [2, 3]. The major clinical features are proteinuria and renal insufficiency, and not all cases have paraproteins or a background of hematological diseases [2, 4, 5]. The most characteristic pathological finding is nodular glomerulosclerosis similar to diabetic glomerulosclerosis [6], and it is necessary to differentiate from other nodular glomerular diseases. The key steps of the diagnosis are immunofluorescence (IF) and electron microscopy (EM). IF shows the staining of kappa or lambda light chains and/or heavy chains with interrupted linear pattern along the glomerular basement membrane (GBM) and tubular basement membrane (TBM), and EM shows electron-dense deposits in a endothelial side of GBM and along TBM [6].

The diagnosis of MIDD is sometimes difficult because its clinicopathological features are nonspecific and the staining of IF is often subtle. Particularly in diabetic patients, MIDD have a fear of being confused with diabetic glomerulosclerosis without careful pathological examinations.

N. Nakamura (✉) · I. Watanabe · Y. Kuroki · I. Ishida · K. Hori
Kidney Unit, Munakata-Ishikai Hospital, 5-5-3 Taguma,
Munakata, Fukuoka 811-3431, Japan
e-mail: norikokr0902@yahoo.co.jp

R. Katafuchi
Department of Nephrology, National Hospital Organization
Fukuoka-Higashi Medical Center, Fukuoka, Japan

Fig. 1 Light microscopy shows nodular glomerulosclerosis characterized by mesangial hypercellularity, microaneurysm and GBM thickening due to double contour (**a** Periodic acid–Schiff stain, original magnification $\times 400$, **b** Periodic acid–silver methenamine, original magnification $\times 400$). Electron microscopy shows the deposition of electron-dense material in the endothelial side of GBMs (**c**)

Here, we describe a case of probable LHCDD with diabetic nodular glomerulosclerosis.

Case report

A 71-year-old man admitted to our hospital with a 8-month history of generalized edema. He had a long history of uncontrolled type 2 diabetes mellitus with retinopathy. Three years before visiting our hospital, his HbA1c was 8.5 % (normal range 4.3–5.8 %), serum creatinine was 1.0 mg/dl and urinalysis was normal.

On admission, physical examination showed generalized edema and anemia of palpebral conjunctivae. His blood pressure was 180/68 mmHg. Urine protein excretion was 6.3 g/day, which was nonselective (selectivity index 0.26). There was no Bence-Jones protein. Urine sediment showed 10–15 RBCs/HPF and no cast. Laboratory data showed hemoglobin 8.9 g/dl, white blood cell count 6800/ μ l, platelet count 202000/ μ l, total protein 3.6 g/dl, serum albumin 2.0 g/dl, serum creatinine 1.5 mg/dl, blood urea nitrogen 23 mg/dl and serum cholesterol 249 mg/dl. Immunoglobulin (Ig) quantitation showed IgG 582 mg/dl, IgA 211 mg/dl and IgM 100 mg/dl. There was no monoclonal protein by serum and urine immunoelectrophoresis. Serological investigations were negative for antinuclear antibodies, rheumatoid factor, anti-DNA antibody, hepatitis B and C. Complement assay showed complement 3 62 mg/dl, complement 4 23 mg/dl and complement hemolytic activity 33.6 U/ml. Renal sonography showed

normal-sized kidneys (right 12.1 cm, left 11.9 cm in long diameter). A percutaneous renal biopsy was performed.

Light microscopy (LM)

Sections contained 15 glomeruli, one of which was obliterated by global sclerosis. Severe mesangial widening due to mesangial cell proliferation and increase in matrix was observed in 13 glomeruli, 12 of which were associated with nodular lesions, 8 with microaneurysm and 6 with segmental GBM thickening due to double contour as shown in Fig. 1a, b. The nodules were positive with both periodic acid–Schiff stain (PAS) and periodic acid–silver methenamine (PASM). There was moderate-to-severe tubular atrophy, moderate interstitial infiltration and severe fibrosis. Interlobular arteries showed marked fibrous intimal thickening. Arterioles showed hyaline change in places. Congo red staining was negative. First diagnosis of diabetic glomerulosclerosis, nodular type was made.

Immunofluorescent study (IF)

There was staining of kappa light chain, IgG and C1q with interrupted linear pattern along GBM as shown in Fig. 2a–c. IgM, IgA, C₃ and lambda light chain were negative. The presence or absence of staining along TBM was unknown because neither report about it nor photograph of TBM was available. We had not paid much attention to the staining of TBM.

Fig. 2 Immunofluorescent staining for IgG (**a**), C1q (**b**), kappa light chain (**c**) and lambda light chain (**d**)

Enzyme-labeled antibody method

To clarify the staining along TBM, we tried enzyme-labeled polymer method using paraffin-embedded sections. Primary antibody for IgG, kappa light chain and lambda light chain were Dako A0423, SIGNET 416-01, SIGNET 418-01, respectively. For the secondary antibody reaction, peroxidase-conjugated Histofine-Simplestain kit (Simplestain MAX-PO (MULTI), Nichirei, Tokyo, Japan) for primary antibodies is applied.

All the stainings for IgG, kappa light chain, lambda light chain were negative along TBM.

Electron microscopy (EM)

There is severe increase in mesangial matrix and proliferation of mesangial cells as well as infiltration of monocytes in the capillary lumen. In addition, the deposition of electron-dense material was seen in the endothelial side of GBMs as shown in Fig. 1c. No ultrastructural organization was observed. There was no electron-dense material along TBM.

Based on these EM and IF findings, the final diagnosis LHCDD superimposed with nodular diabetic glomerulosclerosis was suspected.

Clinical course

After the biopsy, he was treated with renin-angiotensin system inhibitors, calcium antagonists and diuretics, and received diet therapy with low salt and reduced protein intake. His blood sugar control was maintained at a level of HbA1c (Japan Diabetes Society) 6.5 % with diet therapy. But massive proteinuria (around 6 g/day) continued and renal function was progressively deteriorated. Five years later, he underwent peritoneal dialysis. Six months after dialysis initiation, paroxysmal ventricular tachycardia became frequently occurred and cardiomegaly and reduced cardiac function were detected with echocardiography. Around the same time, he was affected by one-sided facial nerve paresis of unknown cause. In addition, abnormal red blood cells such as anisocytosis, poikilocyte and Howell Jolly body were found in his peripheral blood, and myelodysplastic syndrome was suspected. Bone marrow

examination was not done. Three months later, he admitted because of a fracture of the femoral neck by a traffic accident and afterwards, severe pneumonia and fungal peritonitis occurred. His general condition rapidly worsened and about a year after admission he died from respiratory failure caused by pneumonia.

Discussion

The diagnosis of MIDD is sometimes difficult because the clinicopathological features are often nonspecific and can simulate many other diseases [4]. Common clinical findings are proteinuria and renal insufficiency, and not all cases have detectable monoclonal proteins or a background of hematological diseases like multiple myeloma. In fact, up to 20 % had no paraproteins by serum or urine [3, 5], and one-third had no hematological diseases by bone marrow examination [5]. The cases without any suggestive findings except for proteinuria and renal insufficiency have a fear of not considering MIDD as a possible diagnosis.

Nodular glomerulosclerosis is the most characteristic pathological feature of MIDD, and differential diagnosis is diabetic glomerulosclerosis, amyloidosis, membranoproliferative glomerulonephritis, immunotactoid glomerulopathy and fibrillary glomerulonephritis. Among them, many light-microscopy similarities between MIDD and diabetic glomerulosclerosis are described [6, 7]. In MIDD, the nodules are acellular with the expansion of mesangium, sometimes accompanied by mild mesangial hypercellularity. The nodules are PAS positive and Congo red negative. The GBMs appear focally thickened with or without double contours. Crescent formations and capillary microaneurysms have been described [7, 8]. These findings greatly resemble diabetic glomerulosclerosis. Some differences have been reported [6, 9]: the nodules are more evenly distributed in MIDD, the nodules are PAS positive but PASM negative in MIDD, whereas positive with both PAS and PASM in diabetic glomerulosclerosis, and exudative lesions as “capsular drops” and “hyaline caps” are not observed in MIDD. However, LM does not allow complete discrimination between them. The key steps of the diagnosis are IF and EM. IF shows the staining of kappa or lambda light chains and/or heavy chains with interrupted linear pattern along the GBM and TBM. Especially, the TBM deposits are noted to be strongly stained by IF, thus it is important for the diagnosis of MIDD [9]. On the other hand, the staining in GBM is often weak [6, 9] and in some cases there is a discrepancy between IF and EM findings [5, 6, 9]. In fact, several IF-negative cases have been reported despite the presence of large amounts of electron-dense deposits [5]. Moreover, in diabetic patients, the abnormal light chains are frequently glycosylated, which may impair

IF detection [6]. EM is essential for not overlooking MIDD.

In our case, the patient showed nephrotic-range proteinuria and renal insufficiency, but did not have paraproteins or a background of hematological diseases at the time of biopsy. LM revealed nodular glomerulosclerosis with severe mesangial widening, GBM thickening with double contour and microaneurysm, which was very similar to diabetic glomerulosclerosis. The nodules were positive with both PAS and PASM. IF showed subtle staining of kappa light chain, IgG and C1q along the GBM, and in addition, EM showed the deposition of electron-dense materials in the endothelial side of GBM, however, we did not understand the meaning of these findings at that time. We interpreted them as nonspecific findings. Thus, we first diagnosed as diabetic glomerulosclerosis, nodular type. As a result, LHCDD remained untreated for seven years. During that period, he developed cardiac disease (arrhythmia, cardiomegaly and cardiac dysfunction), facial nerve paresis and myelodysplastic syndrome. These might be extrarenal organ involvements related to immunoglobulin deposits, but we could not conclude because of not performing autopsy. Several years later, we recognized one of the few case reports of MIDD in diabetic patients [10] and we reconsidered the first diagnosis and suspected a possibility of LHCDD. However, there is one problem in making diagnosis of LHCDD, that is, no electron-dense deposit along TBM by EM. An additional immune-staining using paraffin-embedded section for light chains and IgG showed no staining along TBM. We could not explain why TBM deposits were not detected in this case although GBM deposits were clearly identified by EM. According to previous reports, in one of six cases of LHCDD reported by Masai et al. [2], TBM deposits were not detected. But in other five cases of LHCDD reported by Lin et al. [3], TBM deposits were identified in all cases. A case of LHCDD in a diabetic patient reported by Satirapoj et al. [10], similar to this case, also revealed both kappa and IgG deposits along the TBM. Although we could not make a clear reason of the lack of TBM deposits, the diagnosis of LHCDD cannot be denied because of the absence of the staining of light- and heavy-chain along TBM. We suspected a concurrence of LHCDD and diabetic nodular glomerulosclerosis based on GBM deposits by IF and EM in this case. It is unclear as to which the main cause of heavy proteinuria was, LHCDD or nodular diabetic glomerulosclerosis, in this case. The patient presented with sudden onset of nephrotic syndrome and relatively rapid progression to end-stage renal failure. Thus we speculate coexisting LHCDD with nodular diabetic glomerulosclerosis accelerated his renal damage.

MIDD in diabetic patients is rarely reported, possibly due to being often overlooked or misdiagnosed. We recognized only 5 case reports of MIDD in diabetic patients.

Satirapoj et al. [10] described a case of LHCDD having a history of uncontrolled diabetes mellitus with retinopathy that was characterized by heavy proteinuria, renal insufficiency and no paraproteins. Renal biopsy revealed nodular glomerulosclerosis. IF showed the staining of kappa light chain and IgG along GBM and TBM. EM showed the amorphous electron-dense material in GBM and TBM. In this case, the 7 courses of melphalan and prednisolone treatment have improved her renal function. The other 4 cases were reported by Lin et al. [3] in their study of 34 cases of MIDD, but no details were described.

We reported a case of probable LHCDD in a diabetic patient. Nodular glomerulosclerosis, even in diabetic patients, should be viewed with suspicion of non-diabetic nodular glomerular diseases like MIDD, and careful pathological examination including both IF and EM is essential for accurate diagnosis.

Conflict of interest The authors have declared that no conflict of interest exists.

References

1. Preud'homme JL, Aucouturier P, Touchard G, et al. Monoclonal immunoglobulin deposition disease (Randall type). Relationship with structural abnormalities of immunoglobulin chains. *Kidney Int.* 1994;46:965–72.
2. Masai R, Wakui H, Togashi M, et al. Clinicopathological features and prognosis in immunoglobulin light- and heavy-chain deposition disease. *Clin Nephrol.* 2009;71(1):9–20.
3. Lin J, Markowitz GS, Valeri AM, et al. Renal monoclonal immunoglobulin depositin disease: The disease spectrum. *J Am Soc Nephrol.* 2001;12:1482–92.
4. Pozzi C, Locatelli F. The patient with insidious chronic renal failure and the patient with the nephrotic syndrome—two manifestations of a protean and not so rare disease. *Nephrol Dial Transplant.* 1996;11:1876–80.
5. Pozzi C, D'Amico M, Fogazzi GB, et al. Light chain deposition disease with renal involvement: clinical characteristics and prognostic factors. *Am J Kidney Dis.* 2003;42(6):1154–63.
6. Schwartz MM. Monoclonal immunoglobulin deposition diseases. In: Jennete JC, Olson JL, Schwartz MM, Silvia FG, et al editors. *Heptinstall's Pathology of the Kidney.* 6th ed. Baltimore: Williams & Wilkins Publishers; 2007. p. 869–877.
7. Sinniah R, Cohen AH. Glomerular capillary aneurysms in light-chain nephropathy. *Am J Pathol.* 1985;118:298–305.
8. Nakamoto Y, Kawamura K, Mamiya S, et al. Kappa light chain nodular glomerulosclerosis with conspicuous crescent formation and tubulointerstitial injury. Reports of a case. *Acta Pathol Jpn.* 1992;42(6):439–47.
9. Ronco PM, Alyanakian MA, Mougenot B, et al. Light chain deposition disease: a model of glomerulosclerosis defined at the molecular level. *J Am Soc Nephrol.* 2001;12:1558–65.
10. Satirapoj B, Paueksakon P. A concurrence of light and heavy chain deposition disease and diabetic nephropathy. *J Med Assoc Thai.* 2007;90(10):2204–8.