Gamma 1-heavy chain deposition disease accompanied by IgG kappa in serum, urine, and bone marrow

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Abstract A 32-year-old Japanese woman presented with hypertension, nephrotic syndrome, microhematuria, and severe hypocomplementemia. Her serum creatinine concentration increased from 1.46 mg/dL (129.0 μ mol/L) to 3.46 mg/dL (305.8 μ mol/L) over 1 month. Renal biopsy revealed Congo red-negative nodular glomerulosclerosis accompanied by mesangial proliferation. There was extensive staining of immunoglobulin (Ig) G in the glomerular and tubular basement membranes and expanded mesangial regions. Staining was negative for IgA, IgM, and kappa and lambda light chains and positive for the gamma 1 IgG subclass. Staining for constant domains of the gamma heavy chains showed a deletion of the first constant domain (CH1). Electron microscopy revealed electron-dense deposits in the glomerular and tubular basement membranes and mesangium. These findings indicated gamma 1-heavy chain deposition disease (HCDD). Serum and urine immunoelectrophoresis revealed an IgG kappa monoclonal band, whereas bone marrow biopsy revealed

monoclonal plasmacytosis with positive staining for kappa chains. HCDD associated with kappa light chain is extremely rare. We report the first case of HCDD with IgG kappa detected in the serum, urine, and bone marrow.

Keywords Heavy chain deposition disease · Immunoglobulin G1 kappa · Hypocomplementemia · Plasma cell dyscrasia · Renal failure

Introduction

Renal heavy chain deposition disease (HCDD) is a rare disorder characterized histopathologically by the presence of nodular glomerulosclerosis and glomerular and tubular deposition of monoclonal heavy chains without associated light chain deposition [1–3]. In a majority of HCDD cases, serum monoclonal immunoglobulin (Ig) G corresponding to the deposited heavy chains was found to be associated with a lambda light chain [1, 2, 4–8]. Here we report the first case of HCDD with IgG kappa detected in the serum, urine, and bone marrow.

Case report

A 32-year-old Japanese woman developed fever and cough with epigastric pain. Three weeks after the onset of these symptoms, she was admitted to a local hospital because of anasarca. Her blood pressure was 198/128 mmHg and serum creatinine was 1.46 mg/dL (129.0 μ mol/L). Urinalysis revealed heavy proteinuria and hematuria. Administration of antihypertensive agents and a diuretic did not result in a significant improvement in her edema. Ten weeks after the first onset of symptoms, she was referred to

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our hospital for further management. She was followed up as an outpatient suspected of being in the recovery phase of acute glomerulonephritis because of preceding cold-like symptoms, hypertension, edema, impaired renal function, hematuria, proteinuria, and hypocomplementemia. However, her edema did not improve; furthermore, her serum creatinine concentration increased to 3.46 mg/dL (305.8 μ mol/L) over a 1-month period. She was eventually admitted to our hospital.

On admission, her height and body weight were 167 cm and 87 kg, respectively; her weight had increased by 13 kg over the previous month. Her blood pressure was 128/92 mmHg, pulse rate was 78 beat/min, and body temperature was 36.7 °C. Urinalysis revealed proteinuria of 8.1 g/day and 20–29 red blood cells per high power field,

with hyaline casts and granular casts. Laboratory tests revealed the following: serum creatinine, 3.7 mg/dL (327.0 μ mol/L); total protein, 4.0 g/dL (40 g/L); serum albumin, 2.1 g/dL (21 g/L); C3, 0.28 mg/mL (0.28 g/L); C4, 0.041 mg/mL (0.041 g/L); CH50, 5 U/mL; IgG, 429 mg/dL (4.29 g/L); IgA, 208 mg/dL (2080 mg/L); and IgM, 38 mg/dL (380 mg/L). Other laboratory test results were as follows: leukocyte count, $7.40 \times 10^3/\mu$ L ($7.40 \times 10^9/L$); erythrocyte count, $3.91 \times 10^6/\mu$ L ($3.91 \times 10^{12}/L$); hemoglobin, 11.3 g/dL (113 g/L); hematocrit, 34.2 %; platelet count, $386 \times 10^3/\mu$ L ($386 \times 10^9/L$); serum urea nitrogen, 47 mg/dL (16.7 mmol/L); serum total cholesterol, 306 mg/dL (7.9 mmol/L); and serum triglycerides, 296 mg/dL (3.3 mmol/L). Hepatobiliary function was normal. Serological examinations were negative for antinuclear,

Fig. 1 **a** Serum immunoelectrophoresis showing the immunoglobulin G kappa monoclonal band. **b** Urine immunoelectrophoresis showing the immunoglobulin G kappa monoclonal band. **c** Serum immunofixation electrophoresis showing the immunoglobulin G kappa monoclonal band

Fig. 2 Biopsy specimen of the bone marrow (a, b) and kidney (c–j). **a** Immunohistochemistry of the bone marrow biopsy stained for kappa. **b** Immunohistochemistry of the bone marrow biopsy stained for lambda. **c** A glomerulus showing a marked increase in mesangial matrix with hypercellularity, nodule formation, and capillary aneurysms (periodic acid–Schiff stain, original magnification $\times 200$). **d** Immunofluorescence for immunoglobulin G1. Strong staining is observed for the expanded glomerular mesangial regions, glomerular basement membrane, and tubular basement membrane. **e–g** Immunofluorescence for immunoglobulin G heavy chain constant domains. Negative staining for CH1 (**e**). Positive staining of both CH2 (**f**) and CH3 (**g**) in the same regions as IgG1. **h** Electron-dense deposits in the mesangium (arrowhead) and in the glomerular basement membrane (arrow) (electron microscopy, original magnification $\times 4140$). **i** Electron-dense deposits (asterisk) in the tubular basement membrane (electron microscopy, original magnification $\times 3450$). **j** Electron-dense deposits in the glomerular basement membrane with no fibrils or tubules (electron microscopy, original magnification $\times 9200$)

band (Fig. 1a, b). Monoclonal IgG κ was detected by serum immunofixation electrophoresis (Fig. 1c). Bone marrow biopsy revealed monoclonal plasmacytosis (fewer than 10 % infiltration) with positive staining for kappa (Fig. 2a, b).

Renal biopsy obtained 15 glomeruli, none of which had global sclerosis. All the glomeruli showed proliferation with a diffuse increase in mesangial matrix that formed nodular lesions (Fig. 2c). Capillary aneurysms were also observed. Congo red staining was negative. There was extensive staining of IgG in the expanded mesangial regions and glomerular and tubular basement membranes. Staining for IgA, IgM, and kappa and lambda light chains was negative. Staining for C1q was positive at the same location as IgG, whereas staining for C3 and C4c was negative. IgG subclass staining was positive for gamma 1 at the same location as IgG (Fig. 2d). Staining for CH2 and CH3 was positive along capillary walls and on the tubular basement membrane. In these areas, staining for CH1 was negative (Fig. 2e–g). Electron microscopy revealed electron-dense deposits in the mesangium and glomerular and tubular basement membranes, with obliteration of the podocyte foot processes (Fig. 2h, i). The deposits had not formed fibrils or tubules (Fig. 2j). These findings were consistent with a diagnosis of gamma 1-HCDD.

Because the results of bone marrow biopsy did not meet the criteria for multiple myeloma, neither chemotherapy nor peripheral blood stem cell transplantation was considered. However, the patient had persistent anorexia and vomiting. Three months after the onset of edema, her serum creatinine was 9.1 mg/dL (804.4 μ mol/L) and her serum urea nitrogen was 54 mg/dL (19.2 mmol/L). Because esophagogastroduodenoscopy did not disclose erosion or an ulcer, uremia was suspected and hemodialysis treatment was initiated. However, there was no improvement in her symptoms. We then suspected neuromuscular dysfunction of the stomach as the cause of her symptoms

antineutrophil cytoplasmic, and antglomerular basement membrane antibodies; human immunodeficiency and hepatitis B and C virus infections, and cryoglobulin. Serum and urine immunoelectrophoresis revealed an IgG κ monoclonal

because an upper gastrointestinal series revealed a decline in bowel peristalsis; in addition, a low coefficient of variation of R–R intervals on electrocardiography revealed an autonomic disturbance and a nerve conduction study showed minor deterioration of motor and sensory nerve conduction velocity. She was treated with 125 mg/day of methylprednisolone for three consecutive days, followed by 30 mg/day of prednisolone. Her appetite improved after steroid treatment, which also caused an increase in her C3 levels to 0.53 mg/mL (0.53 g/L), C4 levels to 0.115 mg/mL (0.115 g/L), and CH50 levels to 15 U/mL. However, her renal function did not improve. She was subsequently discharged from our hospital and has been receiving hemodialysis on an outpatient basis since then. The steroid was tapered and withdrawn during the following 2 years. No relapse of anorexia and vomiting was reported.

Discussion

HCDD is an entity of the renal monoclonal immunoglobulin deposition disease, which also includes light chain deposition disease (LCDD) and light and heavy chain deposition disease (LHCDD) [2, 3, 8, 9]. These diseases are characterized by prominent renal involvement with diabetes-like nodular glomerulosclerosis and monotypic deposits of light chains and/or heavy chains. These deposits have a nonorganized, granular, electron-dense appearance on electron microscopy images [1–3]. In cases of HCDD, the deposited gamma heavy chains belong to a single subclass, with gamma 1–4 and alpha heavy chain subtypes having been reported [1, 2, 4–8, 10–15]. The clinical presentations include hypertension, proteinuria, hematuria, and renal insufficiency.

In the current case, the diagnosis of HCDD was based on the pathologic findings of Congo red-negative nodular glomerulosclerosis and deposition of IgG heavy chains that did not stain for light chains. The deposited heavy chains had a deletion of CH1, consistent with the findings in previous reports [1–3, 8, 12, 13].

Deletion of CH1 is not sufficient for deposition of heavy chains. In heavy chain disease, where heavy chains are detected in the serum but are not deposited in tissues, the variable regions of heavy chains (VH) are partially or entirely deleted together with CH1 [16]. Because the VH are preserved with minor amino acid alterations in patients with HCDD, it is considered that both CH1 deletion and physicochemical alterations in the VH are required for tissue deposition [17, 18].

HCDD associated with kappa light chain is extremely rare. On the other hand, kappa light chain deposition is seen in approximately 80 % of LCDD cases [9]. Only two cases of HCDD with kappa light chain have been reported

[10, 15]. One case showed IgG kappa monoclonal Ig in the bone marrow [10], and the other showed this Ig in the serum and bone marrow [15]. Our case is the first, to the best of our knowledge, in which IgG kappa was detected in the serum, urine, and bone marrow. However, it remains unknown whether differences in the composition of light chains contribute to prognosis in patients with HCDD.

The current case had a marked decrease in serum C4 levels, a finding as rare as gamma 1-HCDD. Hypocomplementemia is usually caused by the presence of gamma 1 or gamma 3 subtypes of heavy chains [2, 6–8, 10–13, 19]. In previous reports, all gamma 3-HCDD cases had severe hypocomplementemia with a marked decrease in C4 levels [7, 8, 11, 13, 19], whereas gamma 1-HCDD cases had decreased C3 but normal or slightly decreased C4 levels [2, 6, 10, 12]. It is also interesting that despite severe hypocomplementemia, C3 and C4 were not detected in the kidney in our case. Of the seven previously reported cases of gamma 1-HCDD, immunofluorescence revealed positive staining for C1q and C3 in four, whereas staining for complements was negative in the other three cases [2, 6, 10, 12]. It remains unknown whether extensive activation of complements contributed to the rapid deterioration in renal function in our case.

Our patient also had severe gastrointestinal dysfunction and neuropathy. Heavy chains deposited in autonomic nerves may also have contributed to the gastric neuropathy. Indeed the prevalence of peripheral neuropathy has been reported to be 20 % in LCDD cases [9], with several reports showing heavy chains deposited in organs other than the kidney, such as skin, skeletal muscle, and synovial tissue [7, 14, 20].

No standard treatment of HCDD has been established to date. Some reports showed a diminishing effect of prednisolone with or without melphalan on the nodular lesions that are a characteristic of HCDD [6, 19, 21]. In these cases, serum creatinine levels were less than 2 mg/dL when the initial treatment was started. Therefore, it is speculated that reduction of heavy chain secretion by chemotherapy may be an effective treatment for HCDD. Although the digestive symptoms were improved by administration of prednisolone, renal function failed to recover in our case. In four LCDD patients with impaired renal function, improvement was observed after administration of bortezomib [22], which may be an effective alternative treatment for HCDD. Hematologists consulted for the treatment of HCDD in our patient suggested that intensive chemotherapy should be avoided because she could develop multiple myeloma in the future and would require peripheral blood stem cell transplantation.

Long-term follow-up is necessary because one case of HCDD developed systemic amyloidosis within 10 years [21]. Therefore, careful long-term follow-up is necessary in

patients with HCDD. Our patient will be closely monitored for possible development of systemic amyloidosis and multiple myeloma.

Although the precise clinical course of HCDD is not well known, some cases have a rapid deterioration in kidney function [5, 8, 10, 15]. In fact, our patient proceeded to end-stage renal disease in only 3 months. Therefore, it is important to consider HCDD in patients with rapidly progressive renal failure.

Conflict of interest All the authors have declared no competing interest.

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