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CASE REPORT

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A case of heavy-chain deposition disease with good long-term renal survival and a literature review

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Abstract

Background Monoclonal immunoglobulin deposition disease (MIDD) is characterized by the deposition of nonamyloid monoclonal immunoglobulin and its free fragment light chain and/or heavy chain in systemic tissues and organs, and the kidney is most vulnerable organs. MIDD can be divided into three types: light-chain deposition disease (LCDD), light and heavy chain deposition disease (LHCDD), and heavy-chain deposition disease (HCDD), of which LHCDD and HCDD are rarer (Bridoux et al. in Kidney Int 2015;87:698–711; Preud'homme et al. in Kidney Int 1994;46:965–72). Poor outcome in most HCDD, but in this paper, we will report a case of HCDD with good long-term renal survival and review the literature for reference.

Case presentation A 32-year-old man presented to our department with skin laxity and nephritic syndrome, accompanied by an significant increase of serum creatinine and received short-term hemodialysis treatment. Both the blood and urine free light chain ratio increased significantly. Renal biopsy showed mesangial nodular glomerulosclerosis on light microscopy, and immunofluorescence staining showed positivity for γ-heavy chain (HC), with negative light chain (LC) staining; the diagnosis was considered HCDD. After six courses of bortezomib combined with dexamethasone chemotherapy and thalidomide 100 mg/day, the renal function gradually recovered, while also with proteinuria and hematuria significantly improved. The blood and urine free light chain ratio decreased to normal. Until now, the patient has been followed for four years, and long-term renal survival has been observed.

Conclusion Herein, we report a case presenting with proteinuria, hematuria, renal impairment, and skin laxity, and a renal biopsy showed linear IgG deposition in the glomerular basement membranes and tubular basement membrane. However, they ultimately proved to have HCDD. Bortezomib combined with dexamethasone, and oral thalidomide led to a good long-term renal survival. We also provide a review of currently available literature, and this is the first large-scale review summarizing the characteristics of HCDD up to date.

Keywords Heavy-chain deposition disease, Monoclonal immunoglobulin deposition disease, Acute renal failure, Skin laxity, Case report

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Background

Monoclonal immunoglobulin deposition disease (MIDD) can be divided into three types: light-chain deposition disease (LCDD), light and heavy chain deposition disease (LHCDD), and heavy-chain deposition disease (HCDD), of which LHCDD and HCDD are rarer [1, 2]. Heavy-chain deposition disease (HCDD) is typically characterized by marked renal involvement with diabetes-like nodular glomerulosclerosis and glomerular and tubular basement membrane deposition of monoclonal heavy chains (HCs) without light chains (LCs). These deposits have an unorganized, granular, electron-dense appearance on electron microscopy images [3–5]. Clinical manifestations include hypertension, proteinuria, hematuria, and renal insufficiency. No treatment has been established for the disease, and most cases have a poor prognosis, progress to end-stage renal disease over months to years, rely on dialysis, and have a high mortality rate [5–8].

Case presentation

A 32-year-old man who had no significant medical and family history was admitted to our hospital in August 2019 because of edema with proteinuria and hematuria. Physical examination revealed a blood pressure of 200/140 mmHg, excessive laxness of the skin on the face, neck, and abdomen (Fig. 1A and C), and mild edema of the lower limbs. Laboratory tests revealed hypoalbuminemia (29 g/L), proteinuria (3.07 g/day), hematuria (364 red blood cells per high-power field), and a serum creatinine level of 1.48 mg/dL. Levels of immunoglobulins and complements were within their normal ranges. Urine protein immunoelectrophoresis showed a monoclonal free κ-light chain; however, the results of serum protein immunoelectrophoresis were normal. Serum concentrations of free κ and λ were 322.50 and 37.1 mg/L, respectively, with κ:λ of 8.69 (standard value, 0.26–1.65). Urine concentrations of free κ and λ were 790 and 71.9 mg/L, respectively, with κ:λ of 10.90 (standard value, 0.46–4.00). Tests for antinuclear antibody, anti-DNA antibody, anti-SS-A/SS-B antibody, antineutrophil cytoplasmic antibody, antiglomerular basement membrane antibody (GBM), and antiphospholipase A2 antibody were all negative. Flow cytometric immunofluorescence analysis of bone marrow aspirate showed approximately 1.2% monoclonal plasma cells. During the disease course, anemia developed, the hemoglobin concentration was 65 g/L, and serum creatinine levels gradually increased. A renal biopsy showed a cortex containing 20 glomeruli, with moderate-to-severe proliferation of glomerular mesangial cells and matrix, nodular glomerulosclerosis, glomerular basement membrane thickening, segmental mesangial insertion, and double-track formation, showing 4 crescent formation. Some renal tubules showed basement membrane thickening, epithelial detachment, focal inflammatory cell infiltration and thickened walls of the fibrotic arterioles, and luminal narrowingin the renal interstitium (Fig. 2). Immunofluorescence showed IgG(+++), IgA(-), IgM(+), C3(++), Clq(-), κ(-), λ(-), IgG1(-), IgG4(-), PLA2R(-); a high-intensity (3+) linear pattern for IgG deposition in the glomerular and tubular basement membranes with no free light chains κ and λ. Immunohistochemistry also showed no free light chain κ and λ. Further inspection showed γ heavy-chain deposition in the glomerular and tubular basement membranes (Fig. 3). Electron microscopy showed segmental

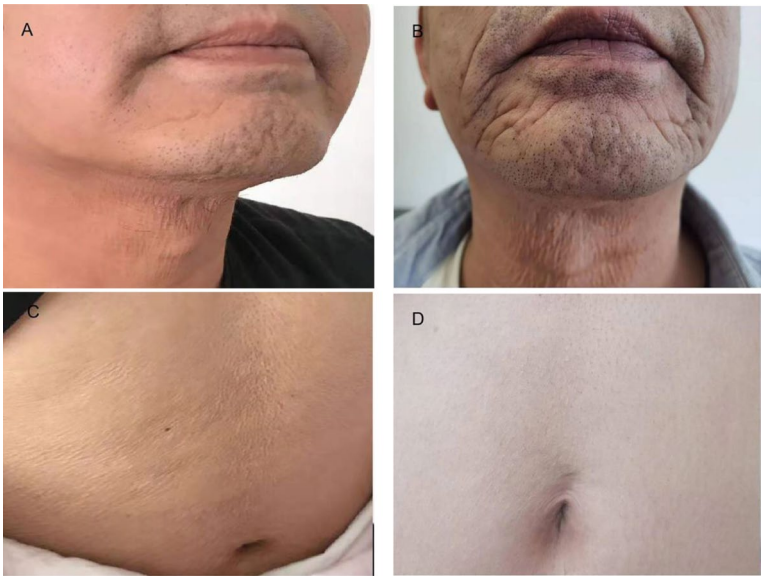

Fig. 1 Skin laxity in the face, neck and abdomen of the patient. **A** and **C** before treatment. **B** and **D** 44 months after the first treatment

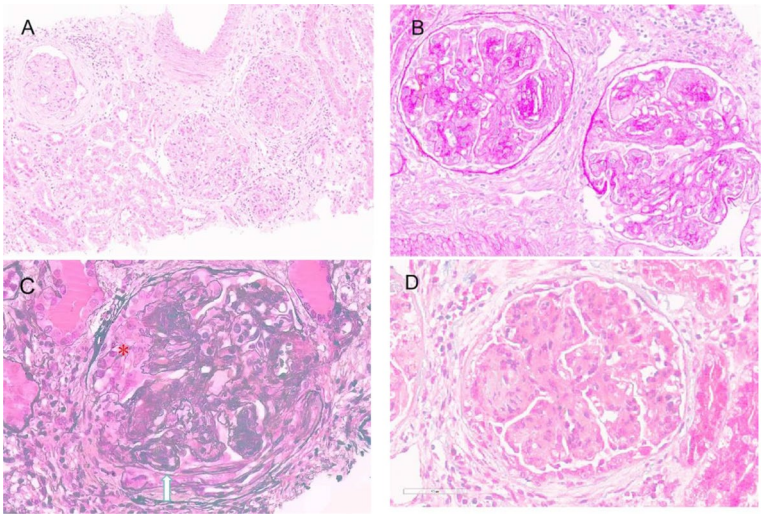

Fig. 2 Light microscopy. **A**. Hematoxylin-eosin staining (×100); **B**. Periodic acid-Schiff staining (×200); showing moderate-to-severe proliferation of glomerular mesangial cells and matrix; **C**. Periodic acid-silver methenamine (×200); showing crescent formation (*) and glomerular basement membrane thickening, segmental mesangial insertion, and double-track formation (white arrow); **D**. Masson's trichrome staining (×400); showing nodular glomerulosclerosis

thickening of the glomerular basement membrane, extensive fusion of foot processes, significant proliferation of mesangial cells and stroma, and nodule formation. More granular amorphous electron-dense materials were observed in the mesangial area, medial glomerular basement membrane, and lateral tubular basement membrane (Fig. 4). The patient was considered to have HCDD in combination with clinical features and pathological diagnosis. The patient went to a high-level hospital for a skin biopsy of the facial laxity, and light microscopy showed normal epidermis, a small amount of lymphocytes infiltrated the small vessels in the superficial dermis, and collagen showed no significant abnormality. Regrettably, immunofluorescence analysis was not performed. In October 2019, the patient started the first course of chemotherapy with bortezomib 2.4 mg combined with dexamethasone 30–40 mg, d1, d4, d8, and d11, and oral thalidomide 100 mg/day. The creatinine was 10.4 mg/dL, and hemodialysis was started. Ten days later, because of catheter-related infection, the right internal jugular catheter was removed, and hemodialysis was stopped. Afterward, the above regimen was continued for five courses, and thalidomide 100 mg/day was given orally for maintenance therapy. Proteinuria, hematuria, anemia, and renal function gradually improved with treatment. Until now, the patient maintained on thalidomide and oral antihypertensive drugs, after followed for four years, his blood pressure was stable, and the serum creatinine, albumin, and hemoglobin levels were 1.07 mg/dL, 41.2 g/L, and 189 g/L, respectively. serum free κ and λ concentrations were 22.00 and 23.2 mg/L, respectively, with κ:λ of 0.95. The patient was in good general condition, without peripheral nerve paralysis or other adverse reactions. His abdominal skin symptoms improved, but the skin manifestations in the face and neck were further aggravated (Fig. 1B and D).

Discussion and conclusions

The pathogenesis of HCDD is related to the deficiency of the HC constant region 1 (CH1 domain), which prevents HC binding to its chaperone protein in the endoplasmic reticulum, resulting in the secretion of a truncated HC by the B-cell or plasma-cell clone [9]. The deposition of pathogenic HCs in systemic tissues and organs causes dysfunction, most commonly involving the kidneys. According to our data, 80.8% of patients with HCDD showed CH1 fragment deletion of the HC, a few patients had CH2 fragment deletion, CH1 and CH2 fragments were deleted simultaneously, or VH and VH3 fragments were deleted (Table 1).

The authors searched PubMed and China National Knowledge Infrastructure using the following keywords: heavy-chain deposition disease, monoclonal immunoglobulin deposition disease, HCDD, MIDD. A total of 142 cases or series of reports had been published since the first report in 1993, of which six cases could not be counted, and one case involving only the eyes was excluded. A total of 136 reports were included in the statistics, including this patient. HCDD mainly occurred in the middle-aged and older population (>50 years old), without significant sex differences. 55.2% of the patients had onset of nephrotic syndrome, 85.8% had hematuria, mainly microscopic hematuria, and >90% had renal failure. Approximately 80% of patients had hypertension at onset, 90% had anemia and edema, 56.5% had myeloplasmacytosis, and approximately 8.7% had multiple

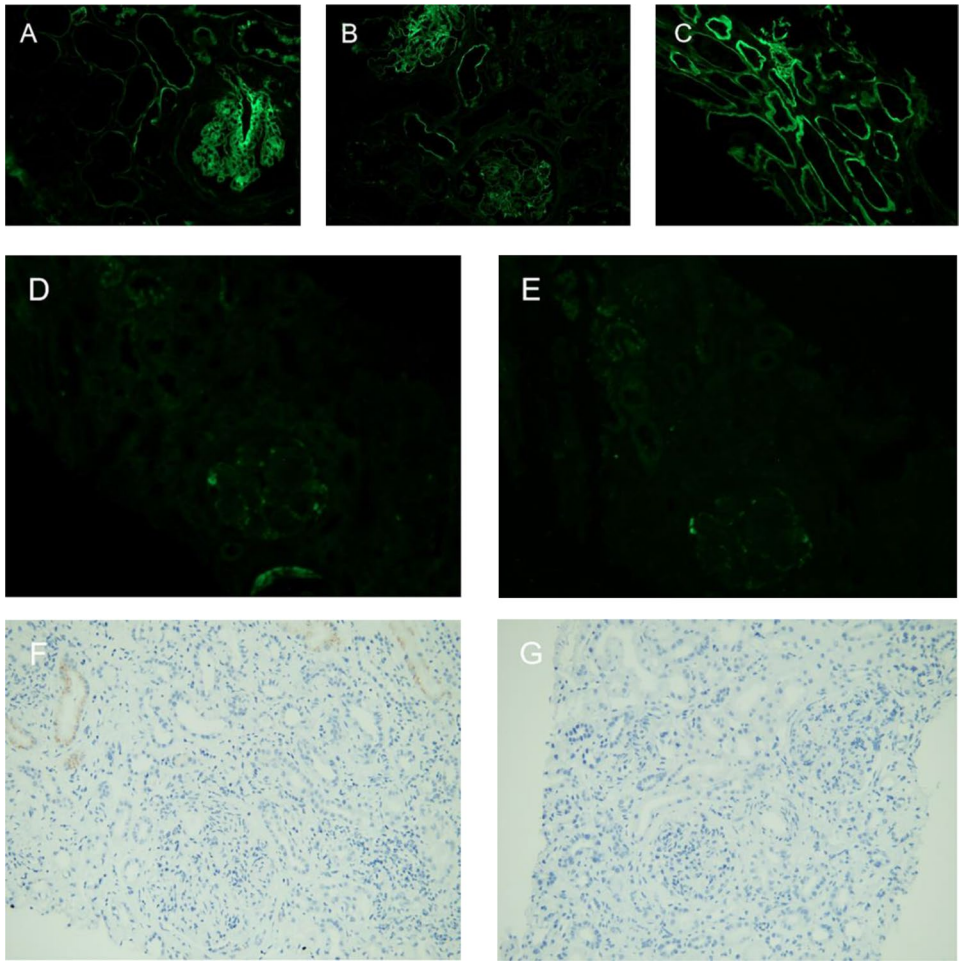

Fig. 3 Immunofluorescence staining shows: IgG(+++), IgA(-), IgM(+), C3(++), Clq(-), κ(-), λ(-), IgG1(-), IgG4(-), PLA2R(-). IgG in a linear deposition in glomerular and tubular basement membranes (**A**) (×200). Moderate positivity for γ heavy chain in a linear deposition in glomerular basement membrane (**B**) (×100) and tubular basement membrane (**C**) (×200). Free light chain κ (**D**) (×100) and λ (**E**) (×100) are negative. Immunohistochemistry κ (**F**) and λ (**G**) are negative

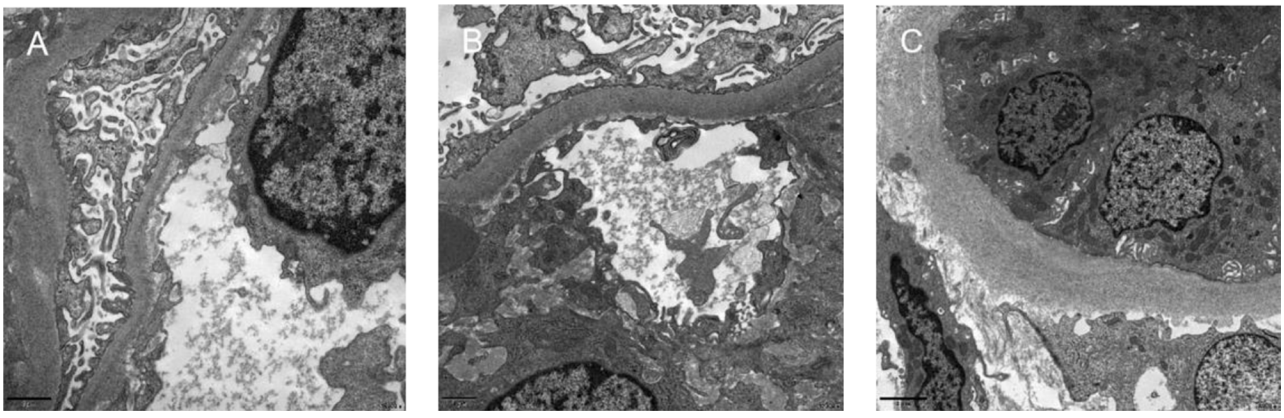

Fig. 4 Electron microscopy shows segmental thickening of glomerular basement membrane, extensive fusion of foot processes (**B** ×12,000), significant proliferation of mesangial cells and matrix, and nodule formation. The mesangial area, the medial basement membrane of the glomerulus (**A** ×15,000 and **B** ×12,000), and the lateral basement membrane of the renal tubule (**C** ×8000) showed a lot of granular amorphous electron density

Table 1 Pathology Summary of HCDD

			Light microscopy			Immunofluorescence					Electron microscopy			
Author	N	domain deletion	NGS	Interstitial fibrosis	arterios clerosis	Subclass	GBM deposits	Mesangium	TBM deposits	Vasular deposits	GBM deposits	Mesangium	TBM deposits	Vasular deposits
Nasr et al	7	NA	6/7	7/7	7/7	γ1 (2) ; γ2 (1) ; γ4 (1) ; γ (1) ; α (1)	NA	NA	NA	NA	6/7	7/7	7/7	NA
Bridoux et al	15	CH1 (11/11)	15/15	15/15	NA	γ1 (9) ; γ3 (1) ; γ4 (2) ; α (3)	15/15	NA	15/15	9/15	11/11	10/11	9/11	3/11
Zhang et al	25	NA	25/25	22/25	NA	γ1 (13) ; γ2 (2) ; γ3 (6) ; γ4 (2) ; γ1、γ4 (1) ; γ2、γ4 (1)	25/25	15/25	19/25	8/25	22/22	14/22	25/25	NA
Joly et al	22	NA	22/22	17/22	14/22	γ1 (14) ; γ3 (1) ; γ4 (3) ; α (4)	20/22	NA	22/22	NA	11/11	9/11	11/11	3/11
Nara et al	5	NA	3/5	5/5	4/5	γ1(3) ; γ4(1)	NA	NA	NA	NA	5/5	4/5	2/5	NA
Lin et al	6	NA	NA	NA	NA	γ1 (2) ; γ3 (1) ; γ4 (1) ; γ (1) ; α (1)	NA	NA	NA	NA	NA	NA	NA	NA
Case	50	CH1 (10/15) ; CH2 (1/15) ; CH1、CH2(2/15) ; V_H (1/15) ; V_H3 (1/15)	41/48	6/34	5/34	γ (7) ; γ1 (15) ; γ2 (4) ; γ3 (7) ; γ4 (6) ; α (5) ; μ (2) ; δ (1)	27/42	29/38	29/38	14/37	27/38	22/34	18/36	6/36
Total	130	CH1 (21/26) ; CH2 (1/26) ; CH1、CH2 (2/26) ; V_H (1/26) ; V_H3 (1/26)	112/122	72/108	30/68	γ (9) ; γ1 (58) ; γ2 (7) ; γ3 (16) ; γ4 (15) ; α (14) ; μ (2) ; δ (1) ; γ1、γ4 (1) ; γ2、γ4 (1)	87/104	44/63	85/100	31/77	82/94	66/90	72/95	12/58

Abbreviations NGS nodular glomerulosclerosis; GBM glomerular basement membrane; TBM tubular basement membrane; NA not applicable

myeloma. Five of these patients presented with AL or AH amyloidosis [10–14]. Patients with HCDD may present with amyloidotic changes after many years of follow-up and may present with cardiac, hepatic, and splenic symptoms [14]. In some patients, extrarenal manifestations were mainly presented as skin laxity (8.1%), manifested as excessive wrinkling and laxness of the skin on the face, neck, abdomen, and thighs, with reduced elasticity. Skin recoiled slowly on being released after stretching [15–21]. Skin biopsies showed decreased elastic fibers in the dermis, with heavy chain deposition confirmed by immunofluorescence in four of them [16, 17, 20, 21]. The development of cutis laxa may be a cutaneous manifestation of the secretory activity of HCDD [17]. Chavarot et al. [15] pointed out that in γ-HCDD, extrarenal manifestations such as cutis laxa may precede renal injury and are precious factors for an early diagnosis, which is crucial to avoid the progression of irreversible renal and elastic tissue damage. Extrarenal manifestations also involve the liver, heart, digestive tract, minor salivary gland, thyroid, and skeletal muscles [7], as well as lymphocytic vasculitis, emphysema, chronic obstructive pulmonary disease, hiatal hernia, and osteoarthropathy [15–18]. Most patients presented hypocomplementemia, and C3 mainly decreased, as well as C4 and/or CH50. In some patients, monoclonal bands of IgG κ or IgG λ were observed in the serum immune-solid phase electrophoresis, and monoclonal bands of κ or λ were observed in the urine immune-solid phase electrophoresis.

Pathologically, >90% of the renal biopsy showed nodular glomerulosclerosis by light microscopy, which may be accompanied by crescent formation, membrane proliferation-like changes, and capillary proliferation, and Congo red staining was negative. Some patients had associated interstitial fibrosis and arteriolosclerosis. Most were positively stained with IgG (86.9%) by immunofluorescence, and IgG1-4 subtypes were all present, of which the IgG1 subtype was the most common (46.9%). Followed by IgA deposition (10.8%), IgM and IgD deposition were rare. Some patients may have C3 and C1q deposition. Royal et al. found the only case of IgD HCDD by laser microdissection (LMD) and mass spectrometry (MS), which results in extensive focal glomerulosclerosis, tubular atrophy, and interstitial fibrosis, with poor renal recovery [22]. Immunofluorescence and electron microscopy showed that immune complexes were mainly deposited in the glomerular basement membrane, mesangial, tubular basement membrane, and small vessels in linear, powdered, or fine granular deposits. A few could be deposited in the Bowman's capsule and/or glomerular capillary walls. Electron microscopy showed extensive fusion and disappearance of foot processes in some patients (Table 1) [3–8, 10–44, 46].

Regarding treatment, the prognosis of patients treated with bortezomib combined with dexamethasone was

Table 2 Summary of clinical manifestations of HCDD

Author	N	Age(y)	Sex (M)	HT	Anemia	Edama	Serum Albumin	NS	Hematuria	sCr (mg/dL)	eGFR (ml/min)	Hypocomplementemia	Serum M-protein	MM	UP (g/d)
Nasr et al	7	53	5/7	7/7	NA	7/7	28	6/7	5/7	5.6 (2.5-15)	NA	NA	no (3)	2/7	11.5
													IgG (3)		
													IgA (1)		
Lin et al	6	53.8	1/2	6/8	NA	5/6	29.0±3.0	3/6	4/6	4.8±1.5	NA	3	IgGκ (1)	1/6	5.3±2.2
													IgAκ (1)		
													IgMλ (1)		
													γ (3)		
Bridoux et al	15	65(53-84)	7/15	14/15	NA	NA	NA	10/15	13/15	1.6(1.2-4.2)	36(9-68)	NA	IgGκ (2)	NA	4(0.4-18)
													IgAκ (2)		
													IgGλ (4)		
													IgGλ, λ (1)		
													IgGκ, κ (2)		
													IgAλ (1)		
Zhang et al	25	50.3±9.6	14/25	19/25	21/25	24/25	29.6±5.8	10/25	20/25	1.6 (0.9-6.5)	50.4±28.0	C3↓ (17)	IgGκ (1)	1/25	4.0±2.5
												C4↓ (6)	IgAκ (1)		
													IgGλ (8)		
Joly et al	23	59 (55-73)	12/23	17/23	NA	NA	26 (24-30)	14/23	19/23	1.63 (1.50-1.89)	37 (32-40)	NA	NA	1/23	3.6 (2-5)
Nara et al	5	45 (35-80)	2/5	3/5	NA	NA	NA	1/5	NA	1.0 (0.94-1.4)	51.7 (43.6-73)	NA	IgGλ (3)	0	2.1 (0.5-6.4)
													κ (1)		
													NA (1)		
Vignon et al	5	69 (58-84)	1/5	1/5	NA	2/5	33(25-36)	1/5	5/5	1.91 (1.50-3.62)	29 (13-50)	NA	IgAκ (4)	0	3.5 (0.7-9.0)
Case	50	56 (47.8-68)	22/50	34/41	33/36	32/32	27 (24-31)	29/48	31/32	RF 45/48	34 (19-52.7)	C3↓23/40	IgGλ 14	5/44	
												C4↓14/39	IgGκ 5		
												CH50↓10/12			
Total	136		66/136	101/127	54/61	71/75		74/134	97/113	RF45/48		C3↓ 43/71	IgGκ 11	10/115	
												C4↓23/70	IgGλ 30		
												CH50↓10/12			
Ratio %			48.5	79.5	88.5	94.7		55.2	85.8	RF 93.8				9.5	

Note Values for continuous data given as mean ± standard deviation or median(range); for categorical data, as count (percentage).Abbreviations: M male; HT hypertension; NS nephrotic syndrome; Scr serum creatinine; eGFR estimated glomerular filtration rate, using the CKD-EPI formula; MM multiple myeloma; NA not applicable

better than that of melphalan combined with methylprednisolone (MP) and other regimens, and the former had a higher renal survival rate than the latter. However, complications of peripheral neuropathy developed in some patients, and they had to reduce or stop bortezomib. A small number of patients with neuropathy could be controlled by gabapentin. In addition, Turner et al. [23] reported a case of HCDD with high anti-GBM antibodies, and the clinical and pathological findings were dominated by HCDD without crescentic nephritis. The patient achieved complete remission with daratumumab, was treated with stem cell transplantation, and recovered well. Zhang et al. [24] reported a case of HCV-positive HCDD with κ plasma-cell tumor in a patient with poor renal outcome and dependence on hemodialysis (Table 2) [3–8, 10–46]. After treatment, urinary protein and renal functions improved or remained stable in 46.8% of the patients, and more than half of the patients experienced continuous progression of renal function to end-stage renal disease several months to years later and required dialysis or even died.

This patient had clinical and pathological findings consistent with the diagnosis of HCDD. This patient was a young man who presented with nephritic syndrome with acute kidney injury, anemia, skin laxity, and a significant increase in serum and urine κ:λ free light chain ratio. Bone puncture showed a high proportion of plasma cells (1.2%); however, not meet the diagnostic criteria of multiple myeloma diagnosis. In this case, bortezomib combined with dexamethasone was used, which achieved good efficacy.

The limits of this case were that the patient's skin biopsy showed no abnormality, and an immunofluorescence examination was not performed; the former may be related to the insufficient depth of skin sampling. Based on the literature, his skin laxity might be associated with HCDD, although we could not reliably identify it by pathological section. After treatment, the patient showed improvement of abdominal skin laxity, but the skin manifestations in the face and neck were further aggravated, which was difficult to explain. Only one of the 10 cases of HCDD with skin laxity reported in the literature showed no improvement in skin symptoms four years after treatment, and 9 others were not described. It has been suggested that there is no effective medical treatment for the cutaneous manifestations of cutis laxa, and excess skin can be removed surgically [20].

In conclusion, we report a rare case of HCDD with an excellent renal recovery during a follow-up period of four years. We also summarized and reviewed previously reported cases. HCDD mainly occurs in the patients aged > 50 years, with no significant sex difference. Most patients showed proteinuria, hematuria, edema, hypertension, anemia, renal function, and hypocomplementemia at onset. More than half of the patients with HCDD experience continuous progression of renal function.

A small number of patients may present with multiple myeloma or amyloidosis, and extrarenal involvement is dominated by skin laxity. Light microscopy showed characteristic nodular glomerulosclerosis, and immunofluorescence revealed HC deposition but negativity for LC. Sensitive techniques such as immunoelectron LMD/MS can be used to evaluate renal biopsies when routine assessment fails to reach an accurate diagnosis [47, 48]. In conclusion, this is the first large-scale review summarizing the characteristics of HCDD.

Abbreviations

MIDD	Monoclonal immunoglobulin deposition disease
LCDD	Light-chain deposition disease
LHCDD	Light and heavy chain deposition disease
HCDD	Heavy-chain deposition disease
HC	Heavy chain
LC	Light chain
GBM	Antiglomerular basement membrane
LMD	Laser microdissection
MS	Mass spectrometry
MP	Methylprednisolone

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Author contributions
X.C. wrote the main manuscript text and H.C. prepared Figs. 1, 2, 3 and 4. W.Z. and X.Y. provided writing guidance; C.X. helped collect the patient's data and seek consent from patients' families; All authors reviewed the manuscript.

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Data availability
Data is provided within the manuscript.

Declarations

Ethics approval and consent to participate
It has been approved by the medical ethics committee of People's Hospital of Yueqing. (Serial number YQYY202300183).

Consent for publication
Written informed consent was obtained from the the patient for publication of this case report and any accompanying images.

Competing interests
The authors declare no competing interests.

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