

Immunoglobulin heavy chain gene rearrangement in heavy chain deposition disease suggests it is a plasma cell disease: a case report

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Abstract

Heavy chain deposition disease (HCDD) is characterized by the deposition of truncated monoclonal immunoglobulin heavy chains along glomerular basement membranes. Truncated heavy chains are thought to be associated with plasma cell disease (PCD), but previous bone marrow cytology tests showed that only 30% of HCDD cases are related to PCDs. We report the first known use of immunoglobulin heavy chain (IGH) gene rearrangement to diagnose a patient with γ 3-HCDD, although bone marrow morphology test identified no abnormalities. Our findings provide strong evidence for a correlation between PCDs and HCDD, which could help understand the genetic background underlying abnormal heavy chains and assess disease prognosis. Further, concordant with previous findings, bortezomib-based chemotherapy had a good therapeutic effect in our patient. We summarize the experience of diagnosing and treating a case of HCDD, and combine this with a literature review to further explore the correlation between PCDs and HCDD, which has important clinical value.

Keywords

Immunoglobulin heavy chain gene rearrangement test, heavy chain deposition disease (HCDD), case report, plasma cell disease, genetic background, bortezomib

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Introduction

Heavy chain deposition disease (HCDD) is a rare disorder characterized by proteinuria, hematuria, and hypertension; about 30% of patients show acute kidney injury, and HCDD accounts for 0.05%–0.33% of renal biopsy findings.^{1,2} Poor renal prognosis has been reported for this disease, and patients have been reported to have an overall survival of only 55 months even when using immunosuppressant treatments.³ Bridoux and colleagues found that during HCDD development, the truncated CH1 domain of the free heavy chain cannot bind to the light chain, and that its high tissue affinity leads to kidney injury upon deposition along the glomerular basement membrane.^{4–6} However, it is still unclear how truncated heavy chains are produced.

We encountered a patient with HCDD and potential plasma cell disease (PCD) in whom we undertook hematological examinations to show that immunoglobulin heavy chain (IGH) gene rearrangement may explain the cause of abnormal heavy chains from a molecular biological perspective. This finding could be beneficial in fully assessing the disease and its prognosis.

Case presentation

The 62-year-old female patient was admitted to our hospital for edema of both lower limbs and foamy urine for 3 weeks. She had a history of hypertension for 1 year. On admission, her blood pressure was 148/86 mmHg, and moderate symmetrical sunken edema of the lower limbs was evident. Blood biochemical and imaging findings are shown in Table 1.

Figure 1 shows a pathological map of our patient's kidney biopsy. Nodular sclerosis was found upon optical microscopy. Electron microscopy revealed a 'line-like' deposition of dot-like and powder-like electron dense matter along the glomerular

basement membrane and tubular basement membrane, suggestive of HCDD. We performed a paraffin repair and IGH retaining assay, and the final diagnosis was γ 3-HCDD.

Bone marrow puncture and bone marrow biopsy revealed no abnormalities. However, serum and urine free light chain levels were elevated. To further clarify the correlation between HCDD and abnormal lymphoproliferative disease, we used the IGH gene rearrangement assay. This was positive for *IGH*, *IGK*, and *IGL*-related genes, suggesting the existence of a potential B lymphocyte tumor.

Our patient received eight cycles of bortezomib-based chemotherapy. Her lower extremity edema disappeared during the second month of an 8-month follow-up, proteinuria reduced from 2.56 g/24 hours to 0.3 g/24 hours, serum and urine free light chain κ and λ decreased to near normal levels (serum κ , 18.58 mg/L; serum λ , 9.71 mg/L; urine λ , 2.68 mg/L; and urine κ , 18.46 mg/L), serum albumin increased to normal levels, and stable renal function was observed. She has also only needed assessment as an outpatient.

Written informed consent was obtained from the patient and her family for her anonymized data to be published in this article. The reporting of this study conforms with CARE guidelines.⁷

Discussion

HCDD is accompanied by abnormal plasma cell hyperplasia in 30% of cases,⁸ and bortezomib-based chemotherapy, a first-line drug for multiple myeloma, has been reported to show excellent efficacy for many HCDD patients. Accordingly, HCDD is often thought to be a PCD; however, for the remaining 70% of HCDD patients without abnormal plasma cell hyperplasia, it remains unclear how truncated heavy chains are produced and

Table 1. Biochemical, imaging, and genetic examination results for our patient on admission.

Parameter	Patient value	Normal reference range
White blood cells ($\times 10^9/L$)	6.05	3.5–9.5
Platelets ($\times 10^9/L$)	159	125–350
Hemoglobin (g/L)	105↓	115–150
Urine protein	2+	Negative
Urine red blood cell count ($10^4/mL$)	30000	<8000
Normal urine red blood cell	60%	
24-hour urine total protein (mg)	2568↑	0–150
$\beta 2$ -microglobulin/blood	1.5↑	0.8–1.8
Urine free light chain κ (mg/L)	117↑	0.39–15.10
Urine free light chain λ (mg/L)	13↑	0.81–10.10
Urine free light chain κ/λ	9↑	0.461–4.00
Blood free light chain κ (mg/L)	27.8↑	3.30–19.40
Blood free light chain λ (mg/L)	38.8↑	5.71–26.30
Blood free light chain κ/λ	0.7165	0.26–1.65
Complement C3 (g/L)	0.67↓	0.9–1.8
Complement C4 (g/L)	0.080↓	0.1–0.4
Serum creatinine ($\mu\text{mol/L}$)	67.0	46–92
Albumin (g/L)	34.5↓	40–55
Thyroid function (T3, T4, TSH, TT3, and TT4)	normal	normal
Autoimmune test (anti-ANA and anti-ENA)	normal	normal
Cancer biomarkers (CEA, AFP, CA125, CA199, and CA153)	normal	normal
Pathology of abdominal fat biopsy	negative	negative
Blood and urine immunofixation electrophoresis	negative	negative
Systemic lymph node scan	negative	negative
Bone marrow puncture and biopsy	negative	negative
Bone scanning	negative	negative
Bone marrow flow cytometry	negative	negative
<i>IgH</i> gene rearrangement	<i>IGH</i> (+), <i>IGK</i> (+), <i>IGL</i> (+), <i>IGH(DH-JH)</i> (–)	–

T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; TT3, total triiodothyronine; TT4, total thyroxine; ANA, antinuclear antibodies; ENA, extractable nuclear antigens; CEA, carcinoembryonic antigen; AFP, alpha-fetoprotein; CA, cancer antigen.

↑, higher than the normal reference range; ↓, lower than the normal reference range.

whether bortezomib chemotherapy is a suitable treatment.

IGH genes comprise a recombination of V, D, and J genes, which can exist in a broad array of combinations. Malignant tumor cells have a common clone of origin, but normal B cells contain a unique length of the *IgH* variable region.⁹ Thus, evaluations of the clonal nature of

tissue samples contribute to the diagnosis of B lymphoma tumors. *IGH* gene rearrangement tests use PCR to detect the monoclonality of *IG* genes in B lymphoma with a detection limit of 1%.¹⁰ Plasma cell tumors are characterized by monoclonal abnormal multiplication, and have the same rearranged gene fragments, so specific bands are detected after amplification.¹¹

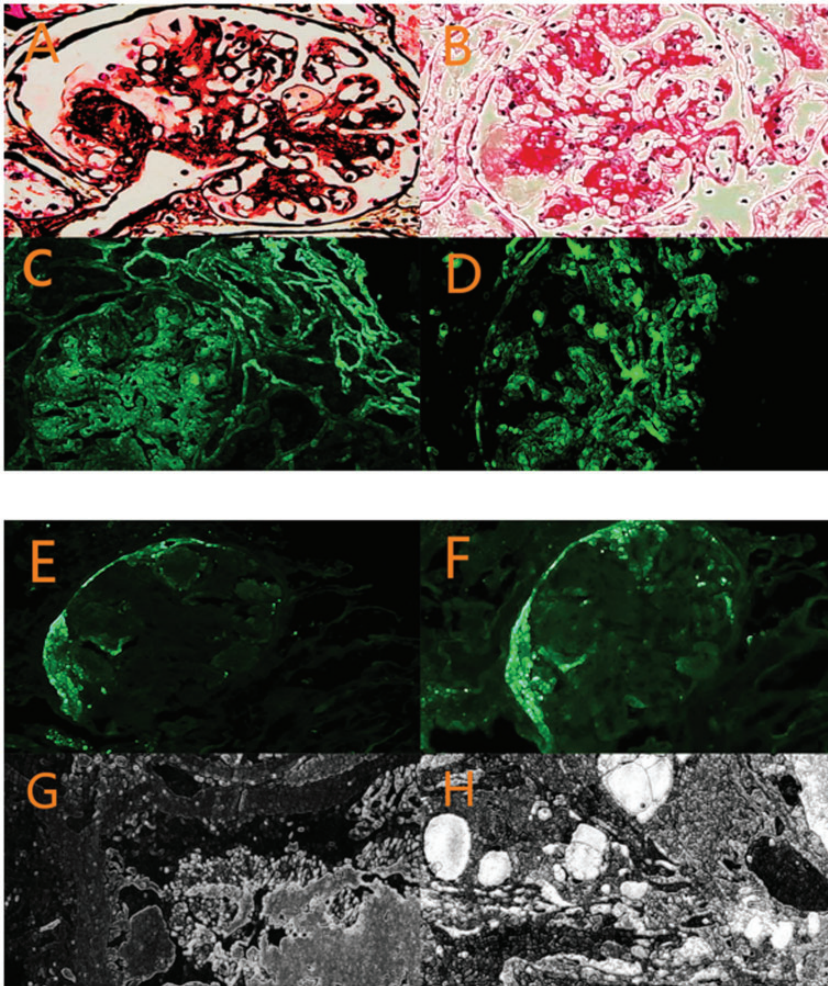


Figure 1. Pathological findings from the renal biopsy. (a) Glomerular mesangial cell and stroma showing mid-to-severe proliferation, with nodular changes. Periodic acid–silver methemamine staining, $\times 400$ magnification. (b) The glomerular capillary loop was lobulated, with a narrow and occluded lumen and thickened basement membrane. Periodic acid–silver methemamine staining, $\times 200$ magnification. (c) IgG deposits along the glomerular mesangial area and segmental capillary loops, with mass- and line-like deposits. Line-like deposits are also observed at the renal tubular basement membrane (TBM). (d) Immunofluorescence analysis showing immunoglobulin γ deposition. $\times 200$ magnification. Scale bar: $2 \mu\text{m}$. (e, f) Immunofluorescence analysis showing negative light chain kappa (κ) and lambda (λ). Scale bar: $2 \mu\text{m}$. (g, h) Glomerular basement membrane (GBM) showing segmental thickening, with extensively fused foot processes. Granular amorphous deposits are visible inside the GBM and outside the TBM. Scale bar: $2 \mu\text{m}$.

Thus, *IGH* gene rearrangements can be helpful in distinguishing tumoral hyperplasia from lymphoid tissue reactive hyperplasia.¹²

In B lymphoma tumors, the positivity rates of detection are 90% for both *IGH*

and *IGK*, and the positivity rate of combined detection is greater than 95%. *IGH* (*DH-JH*) assessment detects the incomplete rearrangement of *IGH*, and *IGL* detection complements and validates the *IGK*

rearrangement.¹³ Hence, *IGH* gene rearrangement can improve the early diagnosis of lymphoma from the level of cytology directly to the molecular level with a positivity rate of 83.3%.¹³ This technology has previously been applied to the diagnosis and prognosis of lymphoma and myeloma,¹⁴ but to our knowledge has never been used in patients with HCDD.

Considering the high sensitivity of *IGH* gene rearrangements and to further clarify the correlation between HCDD and PCDs, we used this technique for our patient. *IGH*, *IGK*, and *IGL*-related genes were positive, suggesting the existence of potential PCDs. This is the first known report showing *IGH* gene rearrangement in a patient with HCDD. Our results suggest that HCDD is a potential PCD, although normal bone marrow aspiration and flow cytometry were observed.

Hematopoietic stem cell transplantation, methylprednisolone, cyclophosphamide, and melpharone-based chemotherapy have previously been the main treatments for HCDD.¹⁵ In 2014, the application of bortezomib for patients with HCDD was first reported, and this showed good efficacy.¹⁶ Bortezomib is a proteasome inhibitor that inhibits the degradation of ubiquitinated proteins, destabilizes the internal environment, and leads to cell death. It has been used as a first-line drug for multiple myeloma since 2008.^{5,6} A multi-center study showed that patients with HCDD receiving bortezomib-based chemotherapy had an improved average kidney survival time of more than 85 months compared with immunosuppressive therapy which had a median survival of 55 months.¹⁷

Bortezomib-based chemotherapy also had a good therapeutic effect in our patient. The good clinical outcomes for myeloma treatment with bortezomib, resulting in abnormal plasma cell death, support our hypothesis that genetic abnormalities of *IGH*, *IGK*, and *IGL* genes lead to the

production of abnormal heavy chains, but further studies are needed to confirm this.

In summary, our findings from *IGH* gene rearrangement testing offers a higher sensitivity for HCDD than bone marrow morphology tests alone. Our findings from this testing of our current patient indicate that HCDD is a plasma cell disease. Moreover, *IGH* gene rearrangement testing can reveal the genetic background of the truncated heavy chain in patients with HCDD, so we recommend its use in such cases. Bortezomib-based chemotherapy should also be considered for patients with HCDD to achieve a good clinical response.


Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

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