Light chain proteinuria revealing mu-heavy chain disease: an atypical presentation of Waldenström macroglobulinemia in two cases

Heavy chain diseases (HCD) are rare mature B-cells proliferative disorders first described in 1964[1] and characterized by the production of a paraprotein consisting of truncated heavy chains devoid of bound light chains. Normal immunoglobulin is composed of two heavy chains and two light chains joined by disulfide bonds at the heavy chain constant domain 1 (CH1). In the absence of light chains, the heat shock protein BiP binds to CH1 and retains the heavy chain in the endoplasmic reticulum.[2] In HCD various mutations are responsible of splicing error leading to complete or partial deletion of CH1 and preventing therefore the binding of heavy chains to light chains as well as BiP.[3,4] Three HCD involving the main immunoglobulin (Ig) classes have been described: α-HCD, γ-HCD and μ-HCD which is the least common. A single case of δ-HCD has been reported. μ-HCD is often associated with a B-cell lymphoid disorder such as chronic lymphocytic leukemia with hepatosplenomegaly. It has also been described in association with myelodysplasia, cirrhosis and auto-immune disease.[5]

Waldenström macroglobulinemia (WM) is a lymphoplasmacytic lymphoma secreting monoclonal IgM, mainly κ, which is strongly associated with the *MYD88* L265P somatic mutation.[6] Patients may be asymptomatic or may present symptoms related either to bone marrow infiltration and/or to IgM gammopathy physico-chemical properties (including hyperviscosity, auto-immune hemolytic anemia, cryoglobulinemia, anti-MAG neuropathy). Serum-free light chains (sFLC) rarely reach high levels in WM and complications related to light chains, like nephropathy or amyloidosis, are uncommon[7] compared to multiple myeloma.

We report here two cases with IgM κ monoclonal gammopathy visible as a small peak on serum protein electrophoresis (SPEP) and in contrast to a high level of sFLC revealing μ-HCD associated with WM.

Case 1. In December 2018, a 79 year-old man with chronic renal failure of unknown cause presented with acute renal failure (creatinine 1,160 μmol/L) associated with nephrotic syndrome (proteinuria 2,9 g/24 hours and albumin 27 g/L) leading to end-stage renal failure requiring hemodialysis and normocytic non-regenerative anemia. The blood count was as following: hemoglobin 6 g/dL, platelets 208,000/mm^3, neutrophils 3,100/mm^3, lymphocytes 900/mm^3. Kidney biopsy showed interstitial fibrosis and tubular atrophy associated with linear Congo red-negative deposits of κ-light chains along the basement membrane suggestive of Randall-type monoclonal immunoglobulin deposition disease (MIDD). sFLC-κ were elevated at 2,585 mg/L with a κ/λ ratio of 57/36. γ globulins were at 6,5 g/L and no peak was detected on SPEP but immunofixation was positive for monoclonal IgM κ (Figure 1A). Serum immuno-selection confirmed the presence of μ-heavy chain (μ-HC) (Figure 1B). Bone marrow aspiration and biopsy showed lympho-plasmocytic infiltration with 19% of lymphoid and plasma cells on aspiration and 25% of CD19$^+$ CD20$^+$ cells with monotypic expression of κ-light chain on flow cytometry. Immuno-histochemistry on biopsy identified

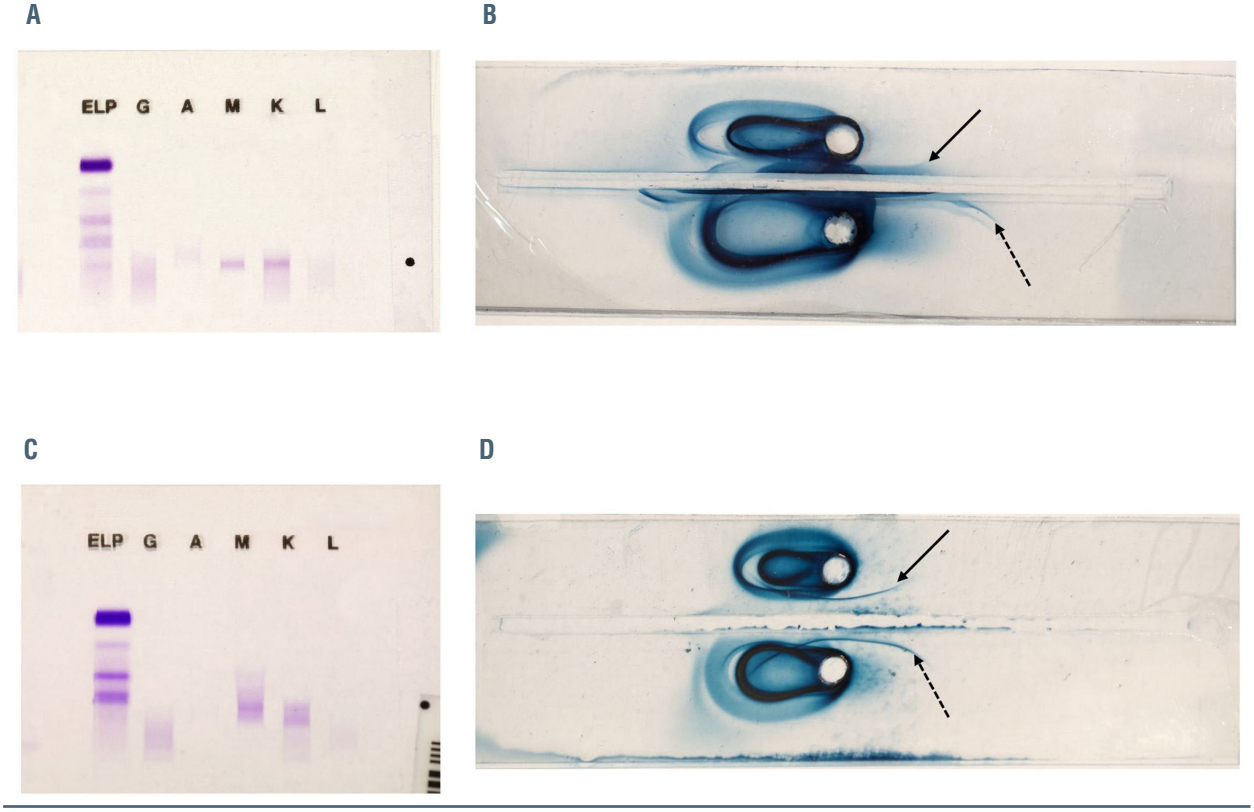

Figure 1. Immunological tests. On the left side, serum protein electrophoresis and immuno-fixation for patient 1 (A) and patient 2 (C) who had both monoclonal IgM κ. On the right side, immuno-electrophoresis with immuno-selection for patient 1 (B) and patient 2 (D). Black arrow indicate precipitine line consisting of μ-heavy chain (continuus arrow for patients, dotted arrow for positive control)

a κ monotypic population consisting of 20% of mature plasma cells CD138$^+$ and lymphoid cells CD20$^+$ CD79a$^+$ CD5$^+$ CD10$^-$ CD23$^-$. The screening for L265P mutation of *MYD88* was positive. No adenomegaly nor splenomegalia was found on whole-body computed tomography scan. Cardiac markers were increased (troponin 199 ng/L and NT-pro BNP 13,664 ng/L) and echocardiography suggested infiltrative cardiomyopathy confirmed by cardiac magnetic resonance imaging. Although imaging features could not distinguish between amyloid and Randall-type light chain deposition (LCD), endomyocardial biopsy was not performed because of histological evidence of MIDD in the kidneys. This infiltrative cardiomyopathy was attributed to probable Randall-type LCD. A treatment combining rituximab 375 mg/m^2 + cyclophosphamide 750 mg/m^2 + dexamethasone 20 mg was initiated allowing partial hematological response after seven cycles. Weekly subcutaneous injections of bortezomib 1.3 mg/m^2 were then added, leading to a κ/λ ratio normalization after one cycle of bortezomib, so that cyclophosphamide was discontinued. At date of follow-up in October 2020, the patient had received 13 cycles of rituximab and eight courses cycles of bortezomib and had achieved a sustained complete hematological response.

Case 2: In March 2019, a 74 year-old woman presented at a rheumatologic clinic for diffuse pains associated with joints swelling leading to the diagnosis of articular chondrocalcinosis. In the context of osteo-articular pains, a SPEP was performed revealing hypogammaglobulinemia at 2,7 g/L. sFLC-κ were elevated at 3,260 mg/L with a κ/λ ratio of 14/61. The blood count was as following: hemoglobin 12 g/dL, platelets 374,000/mm^3, neutrophils 7,660/mm^3, lymphocytes 2,790/mm^3. There was no hypercalcemia. Urine protein-to-creatinine ratio was at 29 mg/mmol (corresponding to 0,29 g/24 hours of proteinuria) and renal function was normal. Urine protein immuno-electrophoresis revealed Bence Jones proteinuria. β-2-microglobuline was 2,6 mg/L. Free light chain multiple myeloma was suspected and bone marrow aspiration was performed which revealed lymphocytic infiltration consisting of 54% of mature lymphocytes associated with 3% plasma cells frequently containing vacuoles. This cytologic aspect of low-grade lymphoma was suggestive of Waldenström disease. Flow cytometry on bone marrow confirmed this diagnosis with a large monoclonal κ B-cell population CD19$^+$, CD20$^+$, CD22$^+$, FMC7$^+$, CD200$^+$, CD5$^-$, CD23$^-$, CD10$^-$, CD43$^-$, CD38$^-$. L265P mutation of *MYD88* was detected.

A whole-body computed tomography scan and ^{18}fluorodeoxyglucose-positron emission tomography scan showed no lytic bone lesion or hepatosplenomegaly or lymphadenopathy. Monoclonal IgM κ was detected on serum immunofixation (Figure 1C) and immuno-selection confirmed the presence of μ-HC (Figure 1D).

In the absence of clinical impact, no specific treatment was introduced other than sodium bicarbonate to prevent cast nephropathy.

Few cases of γ-HCD at diagnosis or during the evolution of WM have been described[8] and Wahner-Roedler *et al*. reported in 1992 three cases of WM among the 27 first cases of μ-HCD.[11] Unlike γ-HCD and α-HCD, μ-HCD is characterized by secretion of sFLC most often κ in the urine in one-half to two-thirds of patients with a risk of cast nephropathy or amyloidosis.[4,5] However, the abnormal Ig is not detected by SPEP in two-thirds of μ-HCD.[5]

These two new cases illustrated an uncommon presentation of WM like light-chain multiple myeloma with hypogammaglobulinemia, elevated sFLC and proteinuria revealing finally μ-HCD. The dissociation between the sFLC level and the absence of a peak on SPEP was unusual. Moreover, the presence of vacuolated plasma cells in the bone marrow was highly suggestive of μ-HCD. In order to detect heavy chains devoid of light chains on immuno-electrophoresis, immuno-selection techniques and the use of specific anti-light chains anti-serum are required. The serum samples were electrophoresed in agar containing anti-κ and anti-λ antibodies trapping free lights chains and complete immunoglobulins. The throughs contained anti-μ antiserum revealing mobile free μ-HC through precipitin line (Figure 1B and D). Bone marrow aspiration, immune phenotyping of B cells and the presence of monoclonal IgM on immunofixation easily clarified the diagnosis of WM, in conjunction with the *MYD88* mutation. Of note, this is to our knowledge the first report of such a mutation in patients with μ-HCD. The association of these two conditions raises the question of the underlying pathophysiology and may suggest a continuum between WM and μ-HCD: the secretion of truncated monoclonal IgM would be secondary to alteration of immunoglobulin gene within lympho-plasmocytic cells. Unfortunately we did not have sufficient biological sample to perform DNA sequencing.

sFLC are part of the monitoring of multiple myeloma especially oligo-secretory myeloma and light-chain myeloma as well as amyloid light-chain amyloidosis. It has been recently suggested that sFLC could be a reliable marker in WM for prognosis and therapeutic response[10,11] but currently, the routine use is not recommended in WM. Although μ-HCD is a rare condition and renal complications are even more infrequent, it could be cost-effective to screen for proteinuria or even to measure sFLC and light chain proteinuria at diagnosis of lymphoplasmatic lymphoma, especially if the paraprotein is not detected on electrophoresis, because of the possible harmful renal and systemic consequences of sFLC increase. Indeed, cases of cast nephropathy[12] and systemic amyloidosis[13] associated with μ-HCD have been reported and here we described the first case of MIDD.

Patient 1 presented Randall-type LCD disease with no HCD disease. Even though both conditions, HCD disease and HCD are due to *CH1* deletion, μ-HC protein never causes kidney or another organ damage. This difference could be explained by the fact that in μ-HCD, the CH1 deletion is associated with deletions of a variable region which seems to be involved in tissue precipitation. Indeed, it has been reported that sequence analysis of HCD disease proteins revealed amino acid substitutions in the variable region responsible for charge and hydrophobicity modifications.[4]

Because of the rarety of this condition, there is no prospective studies and therefore no guidelines for the management of μ-HCD which is based on case reports. In asymptomatic patients such as patient 2, simple monitoring seems reasonable. For symptomatic patients, the chemotherapy targets the underlying clone as proposed in the monoclonal gammopathy of clinical significance field.[15] In this report the use of rituximab associated with bortezomib and cyclophosphamide + dexamethasone allowed a complete response in patient 1.

In summary, low levels of IgM protein with the presence of light chain proteinuria and high level of sFLC in WM patients are highly suggestive of μ-HCD, even more if bone marrow examination reveals vacuolated plasma cells, and should alert physicians to the possibility of kidney damage. Finally, our report suggests that μ-HCD associated with lymphoplasmatic proliferation and *MYD*

mutation can be regarded as particular subgroup of WM.

Hélène Vergneault,[1] Djaouida Bengoufa,[2] Aline Frazier-Mironer,[3] Isabelle Brocheriou,[4] Samuel Bitoun,[1] Camille Villesuzanne,[1] Alexis Talbot,[1,5] Stéphanie Harel,[1] Bertrand Arnulf[1] and Bruno Royer[1]

[1]Immuno-hematology Department, Saint-Louis Hospital, APHP; [2]Immunology Laboratory, Saint-Louis Hospital, APHP; [3]Rheumatology Department, Lariboisière Hospital, APHP; [4]Pathology Laboratory, La Pitié Salpêtrière Hospital, APHP and [5]INSERM U976 Équipe 5, Institut de Recherche Saint Louis, Université de Paris, Paris, France

Correspondence: BRUNO ROYER - bruno.royer@aphp.fr

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References

1. Franklin EC, Lowenstein J, Bigelow B, Meltzer M. Heavy chain disease. A new disorder of serum γ-globulins: report of the first case. Am J Med. 1964;37(3):332-350.
2. Hendershot L, Bole D, Köhler G, Kearney JF. Assembly and secretion of heavy chains that do not associate posttranslationally with immunoglobulin heavy chain-binding protein. J Cell Biol. 1987; 104(3):761-767.
3. Bakhshi A, Guglielmi P, Siebenlist U, Ravetch JV, Jensen JP, Korsmeyer SJ. A DNA insertion/deletion necessitates an aberrant RNA splice accounting for a mu heavy chain disease protein. Proc Natl Acad Sci U S A. 1986;83(8):2689-2693.
4. Seligmann M, Mihaesco E, Preud'homme J-L, Danon F, Brouet J-C. Heavy chain diseases: current findings and concepts. Immunol Rev. 1979;48(1):145-167.
5. Fermand J-P, Brouet J-C. Heavy-chain diseases. Hematol Oncol Clin North Am. 1999;13(6):1281-1294.
6. Treon SP, Xu L, Yang G, et al. MYD88 L265P somatic mutation in Waldenström's macroglobulinemia. N Engl J Med. 2012;367(9):826-833.
7. Uppal NN, Monga D, Vernace MA, et al. Kidney diseases associated with Waldenström macroglobulinemia. Nephrol Dial Transplant. 2019;34(10):1644-1652.
8. Presti BC, Sciotto CG, Marsh SG. Lymphocytic lymphoma with associated γ heavy chain and IgM-γ paraproteins: an unusual biclonal gammopathy. Am J Clin Pathol.1990;93(1):137-141.
9. Wahner-Roedler DL, Kyle RA. μ-heavy chain disease: presentation as a benign monoclonal gammopathy. Am J Hematol. 1992; 40(1): 56-60.
10. Leleu X, Xie W, Bagshaw M, et al. The role of serum immunoglobulin free light chain in response and orogression in Waldenstrom macroglobulinemia. Clin Cancer Res. 2011;17(9):3013-3018.
11. Itzykson R, Le Garff-Tavernier M, Katsahian S, Diemert M-C, Musset L, Leblond V. Serum-free light chain elevation is associated with a shorter time to treatment in Waldenstrom's macroglobulinemia. Haematologica. 2008;93(5):793-794.
12. Preud'homme JL, Bauwens M, Dumont G, Goujon JM, Dreyfus B, Touchard G. Cast nephropathy in mu heavy chain disease. Clin Nephrol. 1997;48(2):118-121.
13. Kinoshita K, Yamagata T, Nozaki Y, et al. Mu-heavy chain disease associated with systemic amyloidosis. Hematol Amst Neth. 2004; 9(2):135-137.
14. Khamlichi AA, Aucouturier P, Preud'homme JL, Cogné M. Structure of abnormal heavy chains in human heavy-chain-deposition disease. Eur J Biochem. 1995;229(1):54-60.
15. Witzig TE, Wahner-Roedler DL. Heavy chain disease. Curr Treat Options Oncol. 2002;3(3):247 254.