

Severe nephritis as initial sign of Waldenström's macroglobulinemia

Thomas Knoop,^{1,2} Kristin Kampevold Larsen,³ Friedemann Leh,³ Anette Lodvir Hemsing,¹ Ingrid Anna Teigen,⁴ Håkon Reikvam^{1,5}

¹Department of Medicine, Haukeland University Hospital; ²Institute of Medical Science, University of Bergen; ³Department of Pathology, Haukeland University Hospital; ⁴Department of Pharmacology, Haukeland University Hospital; ⁵Institute of Clinical Science, University of Bergen, Bergen, Norway

Abstract

Waldenström's macroglobulinemia (WM), characterized with monoclonal immunoglobulins of type M and lymphoplasmacytic lymphoma, is a rare clonal B-cell disorder. WM usually present as an indolent lymphoma, and renal involvement is, in contrast to multiple myeloma, very rarely seen. We present a patient presenting with severe nephritis and nephrotic range proteinuria of more than 9 g/day as initial manifestations of WM. Furthermore, we discuss diagnostic and therapeutic approaches for this rare manifestation of the disease, in the light of recent research and treatment recommendations.

Introduction

Waldenström's macroglobulinemia (WM), defined as the presences of monoclonal immunoglobulins of type M (IgM) and $\geq 10\%$ clonal lymphoplasmacytic cells in the bone marrow, is a malignant lymphoid B-cell disorder.¹⁻³ WM is a rare disease, with an incidence of about 5/1,000,000/year.¹ The median age at diagnosis is 70 year, with a slightly preponderance towards males.¹ The disease is characterized by increased levels of circulating monoclonal IgM, produced and secreted by the malignant clone.¹ WM usually present as an indolent lymphoma, although hyper-viscosity, neuropathy, bone marrow failure and general B-symptoms could occur.² However, in contrast to multiple myeloma (MM), where organ failure including renal failure, is a common manifestation of the disease,⁴ kidney involvement in WM is uncommon.⁵

In the present case report we describe a

rare initial manifestation of WM; a patient presenting with acute renal failure and massive proteinuria. We discuss the case in light of the existing literature regarding kidney involvement in WM.

Case Report

The patient was a 65 years old woman, which primary medical history included a mild aortic valve stenosis and conservative treated arthrosis in hip and knee joints. She had no previous history of renal disease, and displayed a normal ranged creatinine value eight months prior to admission. The past months before hospitalization she had experienced general fatigue with increased need for sleep, reduced appetite with metallic taste in the mouth, and increased dyspnea and headache, most pronounced in the morning. Simultaneously she had increased diuresis and foaming urine.

At the time of hospitalization, she was in decreased general condition and was noticed to be pale in the skin. As expected, a systolic heart murmur was detected, but with a normal respiratory and abdominal examination. Her vital sign demonstrated a blood pressure of 225/140 mmHg, pulse 97/min and respiration rate 15/min.

Initial blood and urine samples were collected, and the main findings are given in Table 1. The blood test confirmed anemia, acute kidney failure, extensive proteinuria, although hyperproteinemia with elevated monoclonal IgM and kappa light chains. Interestingly, serum albumin was within normal range, despite of proteinuria of ~ 9 g/day. ANCA, anti-nuclear antibodies (ANAs), anti-Sm antibody, anti-dsDNA antibody, anti-cyclic citrullinated peptide (CCP) antibody, and anti-glomerular basement membrane (GBM) antibody were negative and serum complement levels were normal. Hence there were no suspicions of other causes of glomerulonephritis.

Based on the clinical examination and initial blood and urine tests, we suspected her nephropathy to be related to her monoclonal IgM and light chain component of isotype kappa. Initial treatment included fluid therapy and antihypertensive treatment with nifedipine and carvedilol.

Bone marrow aspirate and biopsy was performed. The smear confirmed infiltration of lymphoid cells, and immunophenotyping revealed a clonal expansion with the following features; CD45+/ CD19+/ CD20+/+ CD5-/ CD10-/ CD11c-/ CD38-/ CD43-/ CD200+ /CD31(+)/CD200+/ LAIR-/ IgM-/ CD81-/ kappa light chain+. The immunophenotype were consistent with lymphoplasmacytic lymphoma /WM.⁶

Correspondence: Håkon Reikvam, Department of Clinical Science, University of Bergen, N-5021 Bergen, Norway.
Tel.: 55.97.50.00 - Fax: 55.97.29.50.
E-mail: Hakon.Reikvam@med.uib.no

Key words: Nephrite; hypertension; proteinuria; Waldenström's macroglobulinemia.

Acknowledgments: we thank the patient for the opportunity to present this case report.

Funding: the study was supported by Helse Vest and the Norwegian Cancer Society.

Contributions: TK, HR, conceptualization, methodology, data curation, writing, review and editing, and project administration; KKL, FL, methodology and visualization; ALH, methodology and writing; IAT, formal analysis.

Received for publication: 9 July 2019.

Revision received: 7 November 2019.

Accepted for publication: 11 November 2019.

This work is licensed under a Creative Commons Attribution NonCommercial 4.0 License (CC BY-NC 4.0).

©Copyright: the Author(s), 2019
Licensee PAGEPress, Italy
Clinics and Practice 2019; 9:1184
doi:10.4081/cp.2019.1184

The diagnosis was confirmed by biopsy (Figure 1), demonstrating infiltration of lymphoid cells in the majority of the bone marrow compartments. Molecular genetic confirm mutation in the *MYD88* gene.⁷

Based on these findings we concluded with the diagnosis of WM. However, the pathophysiology behind her nephropathy was yet to be resolved. Therefore, a kidney biopsy was performed after initial control of the hypertension. The biopsy revealed a heterogeneous picture with nodular mesangial expansion and segmental membranoproliferative pattern. Some glomeruli showed ischemic changes and there were tubular atrophy of moderate grade and diffuse interstitial fibrosis. Several arteries and arterioles showed thickening of the wall with narrowing of the lumina and intimal edema. Immunohistochemistry revealed positivity for kappa light chains and IgM along the glomerular capillary walls and along the outer aspect of the tubular basement membrane. Kappa light chains and IgM were also detected in walls of small vessels along with changes consistent with thrombotic microangiopathy (Figure 2). Staining for amyloid with congo red was negative. Electron microscopy examination confirmed fine granular electron dense deposits along the glomerular basement

membrane and also non-fibrillary subendothelial deposits. Electron microscopy also showed segmental double contours of the glomerular basement membrane with interposition of mesangial cells consistent with a membranoproliferative pattern (Figure 3). Cryoglobulins, hepatitis screen, lupus markers and complement levels were all initially ruled out as potential causes of membranoproliferative glomerulonephritis.

Hence the diagnosis of severe nephritis related to both tubulointestinal and membranoproliferative character secondary to paraproteinemia related to WM was made. After initial supportive therapy with fluid and antihypertensive treatment, anti-WM therapy was initiated with bortezomib-dexamethasone-rituximab (VD-Ritux) regimen.⁸ This regimen was selected based on reduced or absence of nephrotoxicity of the pharmacological agents, and rapid and sustaining documented effect of the treatment approach.⁸ The patient tolerated and responded well to the treatment (Figure 4). Her levels of IgM and kappa light chain markedly decreased, in parallel with improvement of kidney function and the proteinuria resolved.

She is currently followed in the outpatient department of hematology and nephrology, without signs of active disease.

Discussion and Conclusions

A quantitative test for proteinuria should be performed on all patients complaining of foamy urine. Nephrotic syndrome is defined by the loss of >3.0 g protein in urine per day, and proteinuria should be followed by reduced serum albumin and edema. In contrast, nephritic syndrome is a clinical syndrome defined by the association of hematuria, proteinuria, renal failure and often arterial hypertension. The classical triad of nephritic syndrome includes hematuria, hypertension and azotemia with subsequent renal failure. In the present case report we describe a patient with both signs of nephritic and nephrotic syndrome.

While renal pathology is common in MM patients, affecting about 40% of the patients,⁴ nephropathy in WM is quite uncommon, although until 5% of WM can have renal involvement related to their WM.^{5,9,10} The varieties of WM related pathology include process associated with the tumor burden itself, the IgM paraproteinemia or a light chain fraction. The pathophysiology of the renal involvement in WM could be multifactorial, and involve; amyloidosis, monoclonal IgM deposition and cryoglobulinemia, direct lymphoplasmacytic lymphoma involvement, light-

chain deposition and cast nephropathy, thrombotic microangiopathy (TMA) or other rare cases.⁹ This is in contrast to MM, where the majority of renal involvements seem to be related to cast nephropathy. In addition hypercalcemia could contribute to renal insufficiency in MM, however hyper-

calcemia are seldom seen in WM.¹

Histologically, the nephropathy associated with WM could be divided in two; i) predominantly glomerular lesions or ii) primary tubulointestinal lesion, although overlap between these two forms can be seen.^{5,9,10} The former include membranopro-

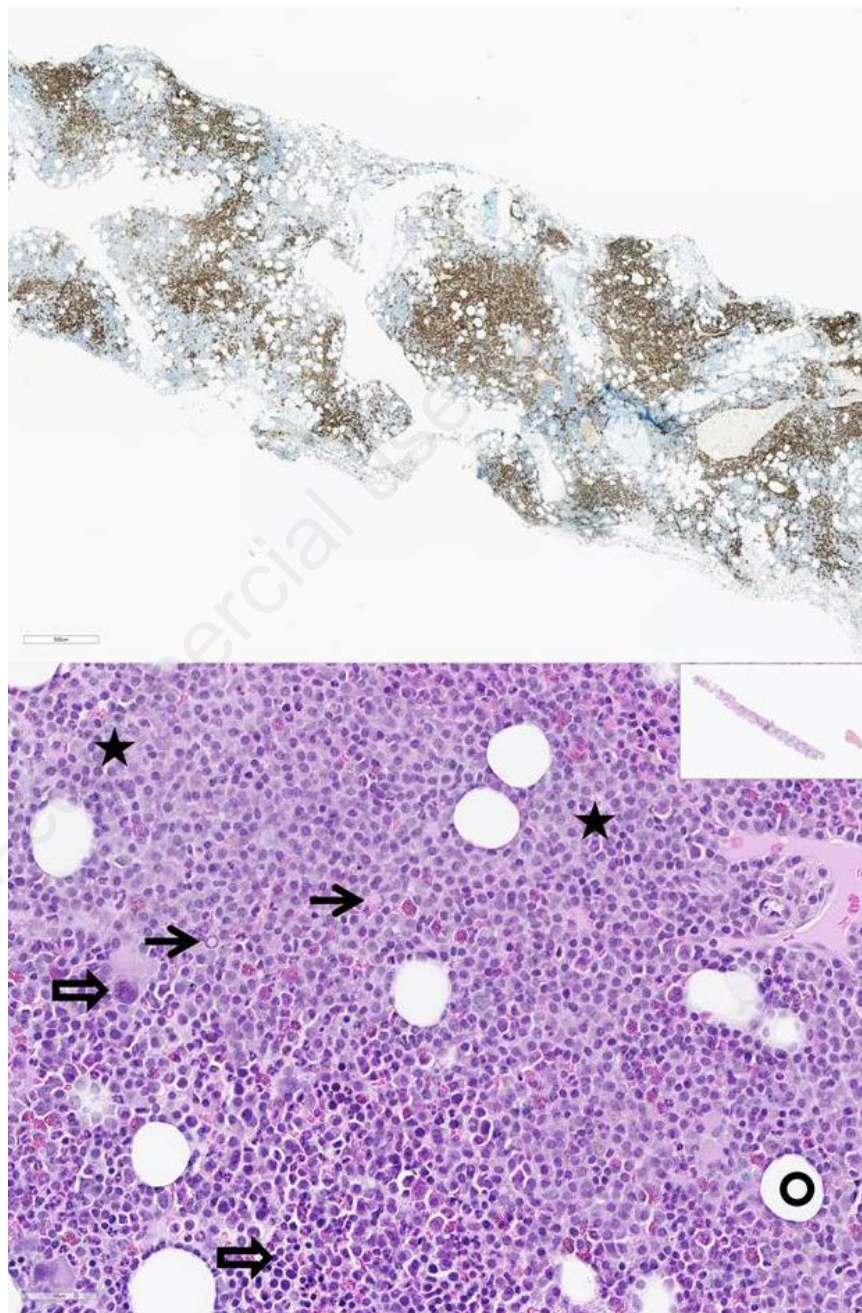


Figure 1. Bone marrow biopsy. Upper section: Bone marrow biopsy, immunohistochemically stained for CD138, demonstrates infiltration of positive stained cells (brown) consistent with diagnosis of lymphoplasmacytic lymphoma. Lower section: Bone marrow biopsy, hematoxylin and eosin (H-E) stained. The bone marrow is hypercellular, showing a reduced number of fat cells (circle). Beside areas with hematopoiesis (open arrows), there are areas dominated by infiltration of lymphoplasmacytic lymphoma cells (asterisks), among these a few cells demonstrating Dutcher bodies (closed arrows).

liferative glomerulonephritis with or without cryoglobulinemia, light chain deposition, AL-amyloidosis and thrombotic microangiopathy. The later include direct lymphoplasmacytic infiltration; light chain cast nephropathy, acute tubular injury or acute interstitial nephritis.^{5,9,10}

The kidney biopsy from our patients demonstrated a mixed pattern, involving both glomerular lesions and tubulointestinal damage (Figure 2). The severe treatment refractory hypertension and relatively high degree of proteinuria at the same time, is a very uncommon presentation of kidney disease associated with WM. The extensive renal pathology, involving both the glomerulus and tubulointestinal system, could explain the severe symptoms seen in our patients.

Bone marrow infiltration was probably the main reason for the anemia. Fluid overload, i.e. hypervolemia, could also have contributed to the decreased hemoglobin. All biochemical markers of hemolysis, i.e. lactate dehydrogenase (LDH), haptoglobine, bilirubin, and reticulocyte count were within normal range values (Table 1). To our knowledge, the patient did not take any drugs prior to admission potentially causing

Table 1. Blood and urine samples at the time of diagnosis.

Blood tests	Values	References
Hemoglobin	7.4 g/dL	11.7-15.3
Leukocytes	13.2x10 ⁹ /L	3.5-11.0
Reticulocytes	0.035x10 ¹² /L	0.030-0.100
Thrombocytes	333x10 ⁹ /L	165-387
Creatinine	245 µmol/L	45-90
CRP	23 mg/L	<5
Troponin T	42 ng/L	<15
NT-proBNP	2323 ng/L	<211
Protein	87 g/L	62-78
Albumin	41 g/L	39-48
LDH	172 (U/L)	105-205
Bilirubin	5 µmol/L	<19
Haptoglobine	2.05 g/L	0.50-2.10
β2-mikroglubuline	11.7 mg/L	<2.0
IgG	2.77 g/L	6.0-15.3
IgA	0.33 g/L	0.8-4.0
IgM	37.5 g/L	0.3-2.3
Kappa light chains	1080 mg/L	6.7-22.4
Lambda light chains	29.2 mg/L	8.3-27.0
Ratio kappa/lambda light chains	37.0	0.31-1.56
Urine tests	Values	References
Protein/creatinine	922 mg/mmol	<20.0
Albumin/creatinine	626.4 mg/mmol	0.0-2.5

CRP, C reactive protein; NT-proBNP, N-terminal B-type natriuretic peptide; LDH, lactate dehydrogenase; Ig, Immunoglobulin.

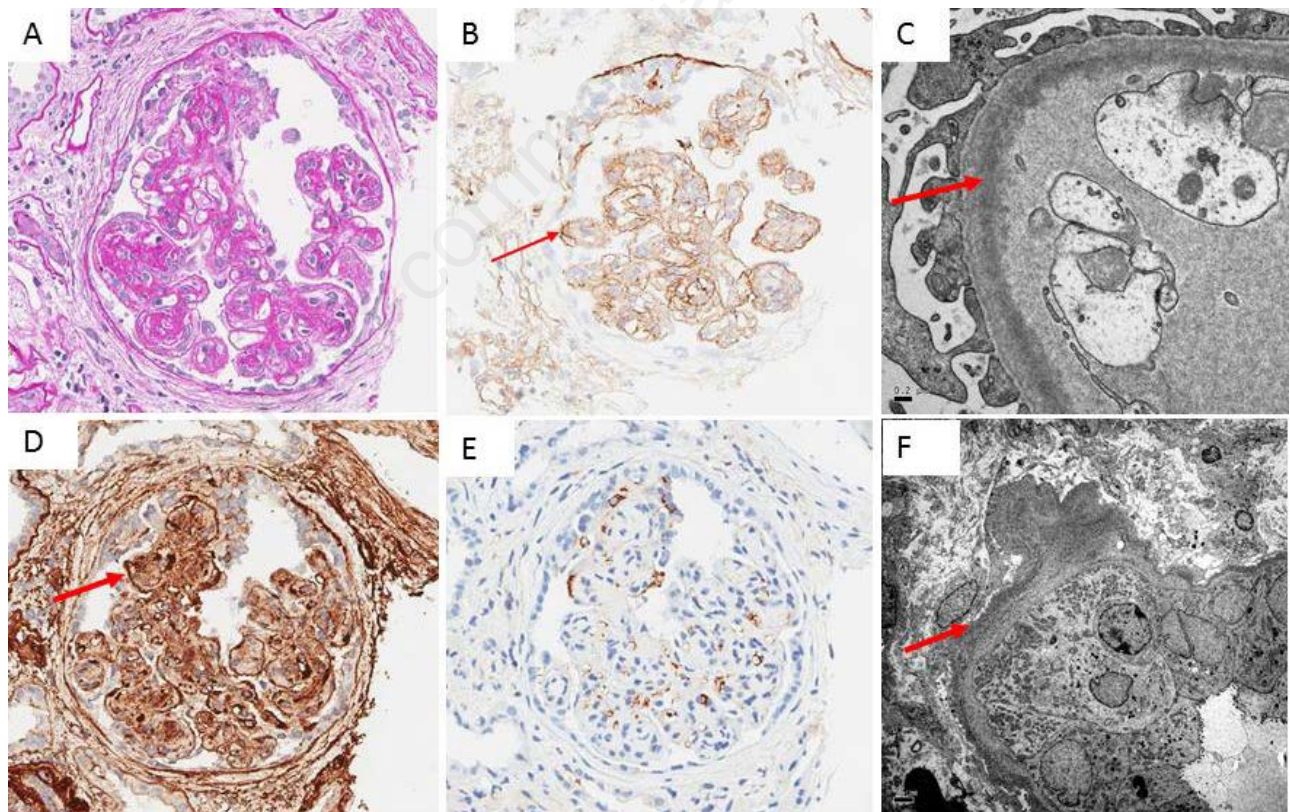


Figure 2. Kidney biopsy. A) Light microscopy showing glomerulus with nodular mesangial expansion and segmental membranoproliferative pattern (Periodic Acid-Schiff staining). B) Immunohistochemistry showing membranous staining for IgM. C) Electron microscopy showing granular electron dense deposits along the glomerular membrane. D) Immunohistochemistry showing membranous staining for kappa light chain. E) Immunohistochemistry showing negative staining for lambda light chain along the glomerular basal membrane. F) Electron microscopy showing granular electron dense deposit along the tubular basement membrane.

thrombotic microangiopathy.

Given the severity of hypertension, a screen for secondary causes was performed. Thyroid function tests and plasma concentrations of normetanephrine and metanephrine were all normal. To our knowledge, the patient did not have a history of gestational hypertension or diabetes.

Different treatment regimens have been used to treat WM, and several of them have demonstrated excellent outcome.² Most of the regimens involve rituximab, a monoclonal antibody against CD20, which is expressed on lymphocytoplasmocytic cells. No clear guidelines regarding treatment of WB associated with kidney disease exist. However, avoidance of drugs with potential nephrotoxic effects should be endeavored. In the present case we chose treatment with bortezomib and rituximab, which are considered to have minimal kidney associated side

effects, and could be given without dose reduction in the case of kidney failure.⁸ Plasma exchange could be considered as part of the treatment approach in the clinical setting of hyperviscosity,² which the present patient was lacking. However, to avoid hyperviscosity and IgM flares, as can be seen with onset of rituximab therapy,^{2,8} rituximab was avoided from the first treatment cycle with the VD-Ritux regimen. She received the total of five cycles of the VD-Ritux regimen, and bortezomib was given twice weekly the two first cycles, however weekly from the third cycle, to reduce the risk of neuropathy, as a recognized common side effect of bortezomib.⁸ Ibrutinib, an inhibitor of Bruton's tyrosine kinase (BTK) expressed in B-cells, have demonstrated very promising results in treatment of WM, special in *MYD88* mutated cases.¹¹ However, ibrutinib is usually not recom-

mended as first line treatment, at least not for younger and fit patients who can tolerate chemo-immunotherapy treatment.² The last years of research has paved the way to more personalized treatment approaches for WM patients, focusing on increasing depth and duration of response alongside lower toxicity rates.¹² Special mutation status seems to be important, and *MYD88* mutated patients in general have good treatment responses,¹² and this was also the fact for our patient.

In the present case report we describe a previously healthy woman presenting with both nephritic and nephrotic features as debut symptoms from her WM. The case illustrates a rare case of severe nephropathy and renal failure associated with WM, and illustrates the importance of prompt diagnosis and treatment start to resolve normal kidney function.

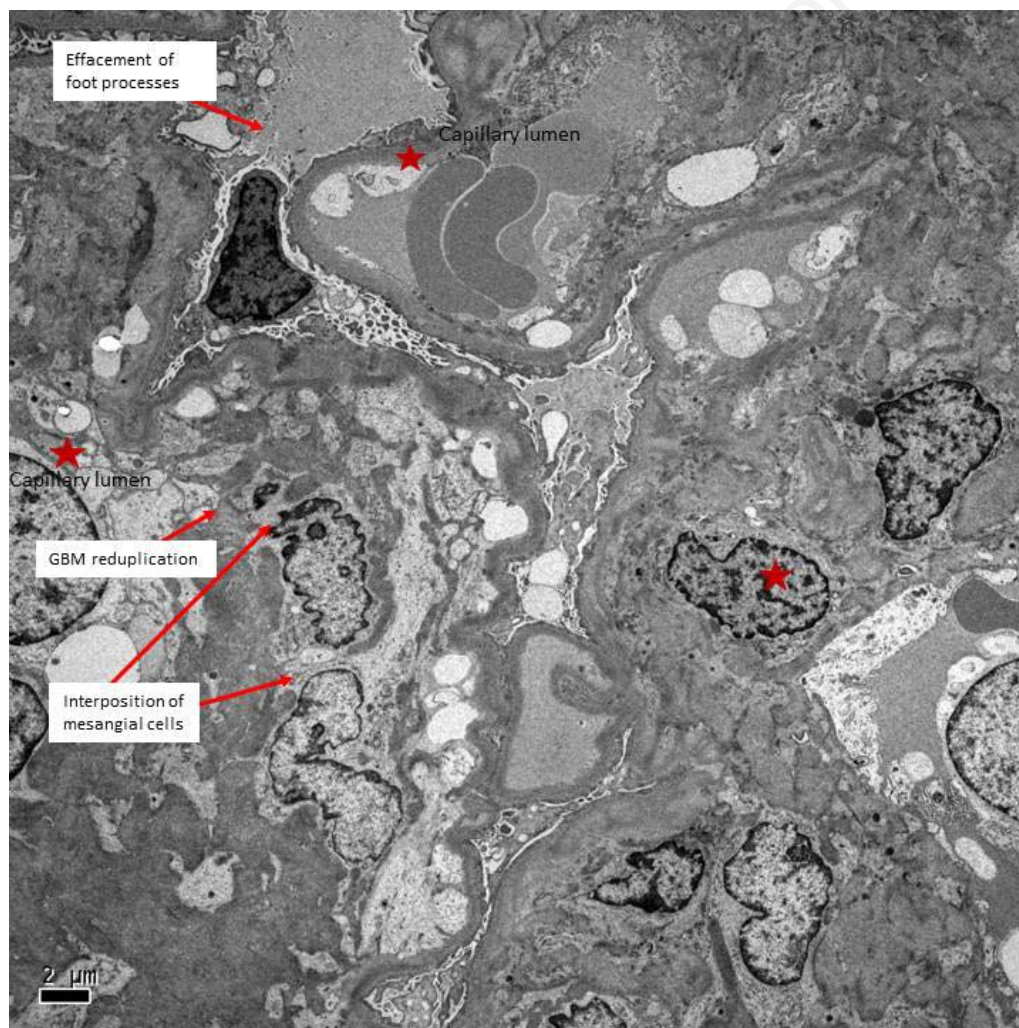


Figure 3. Detailed electron microscopy examination of kidney biopsy. Electron microscopy examination confirms fine granular electron dense deposits along the glomerular basement membrane and also non-fibrillary subendothelial deposits. Electron microscopy also shows segmental double contours of the glomerular basement membrane (GBM) with interposition of mesangial cells consistent with a membranoproliferative pattern. There is extensive podocyte foot process effacement.

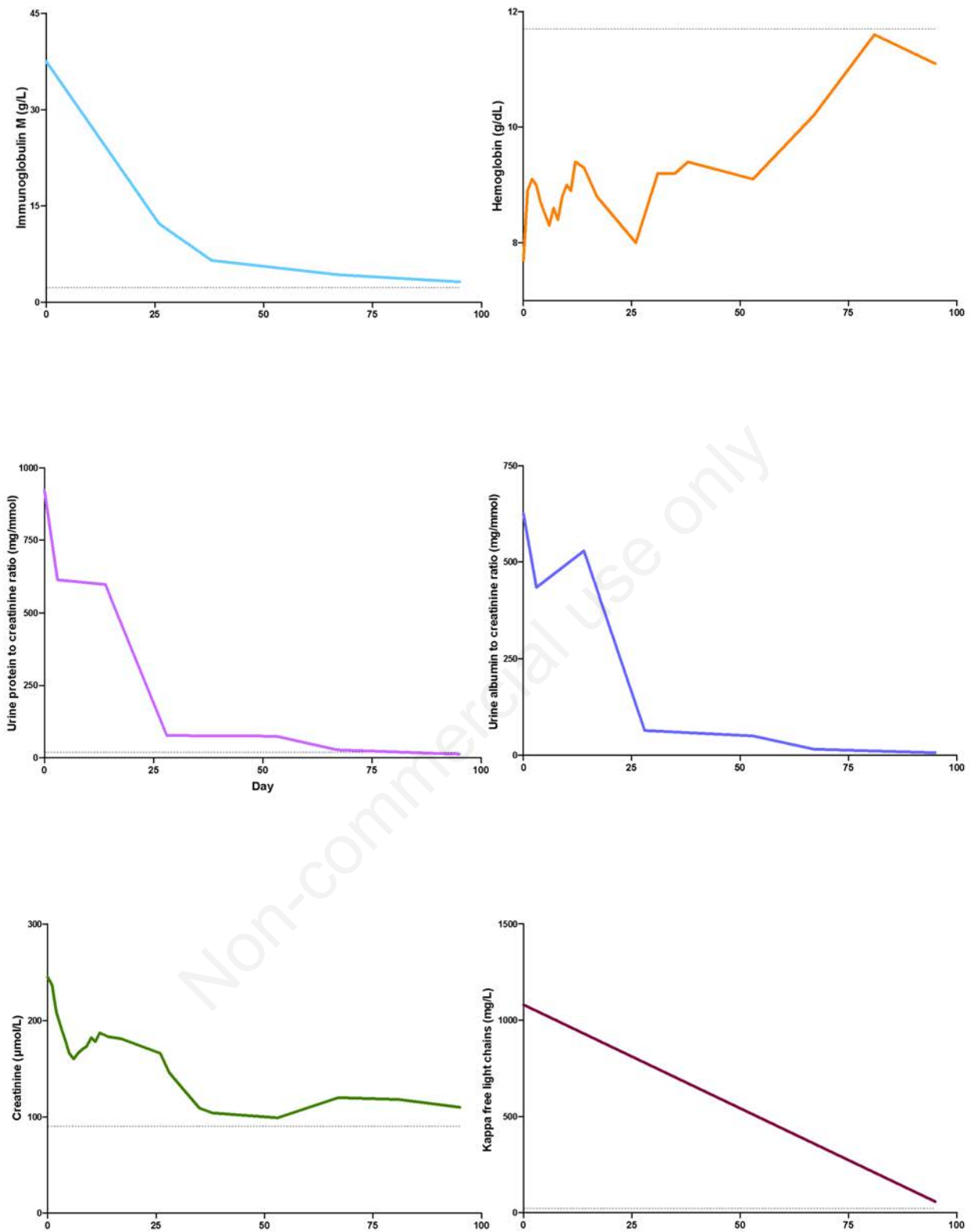


Figure 4. Development in laboratory test after start treating from WM. The figure illustrates the alteration in IgM, hemoglobin, urine albumin/creatinine, urine protein/creatinine, creatinine and kappa light chains after start treatment. Day 0 is stated as the day of diagnosis.

References

1. Mazzucchelli M, Frustaci AM, Deodato M, et al. Waldenstrom's Macroglobulinemia: An Update. *Mediterr J Hematol Infect Dis* 2018;10:e2018004.
2. Gertz MA. Waldenstrom macroglobulinemia: 2019 update on diagnosis, risk stratification, and management. *Am J Hematol* 2019;94:266-76.
3. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood* 2016;127:2375-90.
4. Heher EC, Rennke HG, Laubach JP, Richardson PG. Kidney disease and multiple myeloma. *Clin J Am Soc Nephrol* 2013;8:2007-17.
5. Higgins L, Nasr SH, Said SM, et al. Kidney Involvement of Patients with Waldenstrom Macroglobulinemia and Other IgM-Producing B Cell Lymphoproliferative Disorders. *Clin J Am Soc Nephrol* 2018;13:1037-46.
6. San Miguel JF, Vidrales MB, Ocio E, et al. Immunophenotypic analysis of Waldenstrom's macroglobulinemia. *Semin Oncol* 2003;30:187-95.
7. Treon SP, Xu L, Yang G, et al. MYD88 L265P somatic mutation in Waldenstrom's macroglobulinemia. *N Engl J Med* 2012;367:826-33.
8. Treon SP, Ioakimidis L, Soumerai JD, et al. Primary therapy of Waldenstrom macroglobulinemia with bortezomib, dexamethasone, and rituximab: WMCTG clinical trial 05-180. *J Clin Oncol* 2009;27:3830-5.
9. Vos JM, Gustine J, Rennke HG, et al. Renal disease related to Waldenstrom macroglobulinaemia: incidence, pathology and clinical outcomes. *Br J Haematol* 2016;175:623-30.
10. Uppal NN, Monga D, Vernace MA, et al. Kidney diseases associated with Waldenstrom macroglobulinemia. *Nephrol Dial Transplant* 2019;34:1644-52.
11. Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenstrom's macroglobulinemia. *N Engl J Med* 2015;372:1430-40.
12. Castillo JJ, Treon SP. Toward personalized treatment in Waldenstrom macroglobulinemia. *Hematology Am Soc Hematol Educ Program* 2017;2017:365-70.