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### On Waldenström's macroglobulinemia and IgM related disorders

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# Chapter 3

Renal disease related to  
Waldenström macroglobulinemia:  
incidence, pathology and  
clinical outcomes

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**ABSTRACT**

The incidence and prognostic impact of nephropathy related to Waldenström macroglobulinemia (WM) is currently unknown. We performed a retrospective study to assess biopsy-confirmed WM-related nephropathy in a cohort of 1,391 WM patients seen at a single academic institution. We identified 44 cases, the estimated cumulative incidence was 5.1% at 15 years. There was a wide variation in kidney pathology, some directly related to the WM: amyloidosis (n=11, 25%), monoclonal-IgM deposition disease/cryoglobulinemia (n=10, 23%), lymphoplasmacytic lymphoma infiltration (n=8, 18%), light-chain deposition disease (n=4, 9%), light-chain cast nephropathy (n=4, 9%), and some likely related to the WM: thrombotic microangiopathy (TMA) (n=3, 7%), minimal change disease (n=2, 5%), membranous nephropathy (n=1, 2%) and crystal-storing tubulopathy (n=1, 2%). The median OS in patients with biopsy-confirmed WM-related nephropathy was 11.5 years, shorter than for the rest of the cohort (16 years,  $p=0.03$ ). Survival was better in patients with stable or improved renal function after treatment ( $p=0.05$ ). Based on these findings, monitoring for renal disease in WM patients should be considered and a kidney biopsy pursued in those presenting with otherwise unexplained renal failure and/or nephrotic syndrome.

## INTRODUCTION

Waldenström macroglobulinemia (WM) is a B-cell lymphoproliferative disorder characterized by bone marrow (BM) infiltration by a lymphoplasmacytic lymphoma (LPL) and a serum immunoglobulin M (IgM) paraprotein (Swerdlow *et al*, 2008; Owen *et al*, 2003). Lymphadenopathy and/or hepatosplenomegaly occur in up to 20% of patients at initial presentation, whereas LPL infiltration in other organs is considered rare (<5%) (Banwait *et al*, 2015).

In multiple myeloma (MM), renal insufficiency occurs in up to 40% of patients and is associated with adverse outcomes (Dimopoulos *et al*, 2010). While WM-related nephropathy is an established indication for initiation of therapy (Dimopoulos *et al*, 2014), only approximately 80 biopsy-confirmed cases have been published. These were mostly single case reports or retrospective case series without a comparison group of WM patients without renal complications (Chauvet *et al*, 2015; Audard *et al*, 2008; Salviani *et al*, 2014; Harel *et al*, 2015; Gnemmi *et al*, 2012). Hence, data delineating the incidence, characteristics and prognostic implications of WM-related renal disease are currently unavailable.

We performed a retrospective cohort study on 1,391 individual WM cases seen at a single academic institution, and report the cumulative incidence, kidney pathologies and outcome for 44 biopsy-confirmed cases of WM-related nephropathy.

## METHODS

### Study population

The study was approved by the Institutional Review Board of the Dana-Farber Cancer Institute (DFCI) and was conducted in accordance with the principles of the Declaration of Helsinki. Between January 1999 and September 2015, 1,391 patients with a confirmed diagnosis of WM were seen at the Bing Center for WM. To identify cases, medical files were manually reviewed for WM patients with an estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m<sup>2</sup> or with the presence of any amount of proteinuria at any time point. We then selected those patients that had a kidney biopsy confirming the diagnosis of WM-related nephropathy. The indication for kidney biopsy was at the discretion of the treating physician. Baseline demographic and clinical characteristics were recorded at the time of the kidney biopsy. WM diagnosis was made according to the consensus panel recommendations from the Second International Workshop on WM (Owen *et al*, 2003). Bone marrow involvement was reported as the percentage infiltration of intertrabecular space by LPL. WM response to treatment was determined using the criteria established at the Sixth International Workshop on WM (Owen *et al*,

2013). The eGFR was calculated using the CKD-EPI equation (Levey *et al*, 2009). Nephrotic syndrome was defined as the combination of  $\geq 3$  g/24 hours proteinuria, serum albumin  $\leq 3$  g/dL and the presence of peripheral edema. Renal response after treatment was defined as “better” when achieving a  $\geq 25\%$  rise in eGFR, “worse” when there was  $\geq 25\%$  decline in eGFR or initiation of renal replacement therapy (RRT), and “stable” in all other cases. Renal response for patients with nephrotic syndrome was reported using the International Society of Amyloidosis criteria (Gertz *et al*, 2005).

### Renal pathology

For in-house cases ( $n=30$ ), kidney biopsies underwent standard processing at the Brigham and Women’s Hospital (BWH), including light microscopy, immunofluorescence and/or immunohistochemistry and electron microscopy. The reagents were purchased from Dako North America, Inc., Carpinteria. For light microscopy, specimens were stained with hematoxylin-eosin, periodic acid Schiff, Masson trichrome, and Jones’ methenamine silver. Congo red was used when amyloid was suspected. For immunofluorescence microscopy, specific antibodies were used for the heavy chains of IgG, IgM, and IgA, for C3, C1q, and kappa and lambda light chains. Electron microscopy was performed on epoxy-embedded tissue, post-fixed in osmium tetroxide and stained on the section with uranyl acetate and lead citrate. Additional immunohistochemistry stains for hematological markers such as CD20, CD3, CD5, CD23, and CD138, combined with Ig-heavy chains and kappa/lambda light chains, were performed when LPL infiltration was suspected. For the purpose of this paper, all available kidney biopsies ( $n=30$ ) were re-evaluated at the BWH by a kidney pathologist (HR). In cases in which the original biopsy material was unavailable for review, the local pathology report was used for data collection ( $n=14$ ).

### Statistical analysis

Patient characteristics were summarized using non-parametric descriptive statistics. Overall survival (OS) was defined as time from WM diagnosis to death or last follow-up. Survival curves were calculated using the Kaplan-Meier method (Kaplan & Meier, 1958), and comparisons were made using the log-rank test (Mantel, 1966). Univariate OS models were fitted using the Cox proportional-hazard regression method (Cox, 1972). All p-values were 2-sided and considered statistically significant if  $<0.05$ . All statistical calculations and graphics were performed with STATA version 13.1 (StataCorp, College Station, TX).

## RESULTS

Among the 1,391 WM patients in our cohort, 265 patients had an eGFR <60 ml/min or proteinuria at some timepoint. Many were known with chronic hypertensive or diabetic nephropathy (n=106). In 66 patients there was an intercurrent medical condition or the cause of the renal dysfunction was unknown. In 19 patients there was a kidney neoplasm such as renal cell or bladder carcinoma. In 21 patients there was a clinical suspicion of WM related nephropathy but this was not confirmed by kidney biopsy. A total of 52 patients in the cohort had a kidney biopsy performed. In 8 cases this showed a condition unrelated to WM: non-specific chronic changes (n=5), lupus nephritis (n=1), IgA nephropathy (n=1), drug induced nephritis (n=1). In 44 patients, the kidney biopsy confirmed a nephropathy that was considered to be related to the WM. The baseline characteristics for those cases are summarized in **Table 1**.

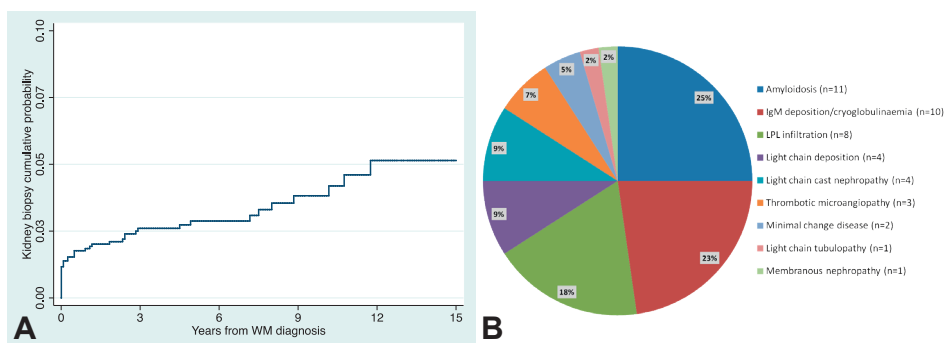
The estimated cumulative incidence of confirmed WM-related kidney disease at 5, 10 and 15 years was 2.9%, 3.8% and 5.1%, respectively (**Figure 1A**). WM and renal disease were diagnosed simultaneously in 24 (54%) cases. The median time of WM diagnosis to kidney biopsy was 3 months (range 0-188). Amyloidosis, Monoclonal IgM Deposition Disease (MIDD)/cryoglobulinemia and LPL infiltration were the most common renal pathologies. The distribution of the pathologies identified by renal biopsy is shown in **Figure 1B**. Kidney biopsy specimens for all major diagnostic groups are illustrated in **Figure 2**. Specific disease characteristics and outcomes per diagnostic group are summarized in **Table 2 and 3**.

### Renal pathology directly related to the WM

Amyloidosis was diagnosed in 11 (25%) patients. In the 3 patients without nephrotic syndrome, amyloid deposition was limited to intraparenchymal vessels only without involvement of the glomeruli (**Figure 2**). Three types of amyloid were reported: AL-amyloidosis (n=9), immunoglobulin heavy chain (AH)-amyloidosis (n=1), and heavy and light chain (ALH)-amyloidosis (n=1). MIDD/cryoglobulinemia was diagnosed in 10 (23%) patients, a serum cryoglobulin was found in 3 (30%) cases. Light chain deposition disease (LCDD) was diagnosed in 4 (9%) patients. Serum free light chain (FLC) levels (kappa restricted) were available for three patients: 1360, 1450 and 2157 mg/L. Light chain cast nephropathy (myeloma kidney) was diagnosed in 4 (9%) patients. Serum FLC levels (kappa restricted) were available for two patients: 41400 and 2165 mg/L. Finally, one (2%) patient was diagnosed with crystal-storing tubulopathy with kappa light chain staining within the proximal tubules. This is the pathological finding that is typically seen in acquired Fanconi syndrome. However, in this patient the only sign of tubular dysfunction was a subnephrotic range of proteinuria and he had no electrolyte or acid-base abnormalities.

**Table 1.** Clinical characteristics and kidney biopsy findings for 44 patients with biopsy confirmed WM related nephropathy

Characteristic	Number (%) or Median [range]
<b>Clinical data at biopsy</b>	
Age, years	66 [46-81]
Male sex	28 (64)
Hemoglobin, g/dL	11.6 [8.3-15.5]
Bone marrow infiltration (%)	25 [3-95]
Beta 2 microglobulin, mg/L	5 [2.1-25]
Albumin, g/dL	3.4 [1.3-4.3]
Calcium, mg/dL	9.1 [8.4-10.1]
eGFR, mL/min/1.73 m <sup>2</sup>	35 [4-99]
History of hypertension	11 (25)
History of diabetes	3 (7)
Presenting with Nephrotic Syndrome	15 (34)
eGFR, mL/min/1.73 m <sup>2</sup>	57 [15-99]
24-hour urine protein, g	8.1 [3.7-15.2]
Presenting with Renal Insufficiency	29 (66)
eGFR, mL/min/1.73 m <sup>2</sup>	29 [4-81]
24-hour urine protein, g	1.2 [0.06-4.1]
Previously untreated for WM	32 (73)
Prior lines of therapy in previously treated group	2 [1-4]
<b>Immunohematologic data</b>	
Serum IgM level, mg/dL	1920 [178-7458]
Serum monoclonal Ig	
IgM κ	29 (66)
IgM λ	15 (34)
Serum free light chains	
κ, mg/L	577 [23.6-414,000]
λ, mg/L	163 [15.1-808]
Abnormal κ/λ ratio	32 (94)
<b>Kidney biopsy</b>	
Glomeruli count	24 [4-68]
Electron microscopy used	39 (89)
Year of kidney biopsy	
<2000	4 (9)
2000-2005	9 (20)
2006-2010	15 (34)
>2010	16 (36)



**Figure 1:** Cumulative incidence of biopsy-confirmed renal complications in this cohort of Waldenström macroglobulinemia (WM) patients (A) and distribution of WM-associated renal pathologies as demonstrated by kidney biopsy (B).

**Table 2.** Hematological, renal and nephrotic syndrome responses after treatment in patients with biopsy confirmed WM-associated nephropathy

Type of Response	Patients (percentage)
Hematological response	28 (64)
Complete remission	1 (4)
Very good partial	3 (11)
Partial	16 (57)
Minor	5 (18)
Stable disease	2 (7)
Progressive disease	1 (4)
Renal response	32 (73)
Better	13 (41)
Stable	13 (41)
Worse	6 (19)
Nephrotic syndrome response	10 (67)
Complete	1 (10)
Partial	4 (40)
None	5 (50)

### Renal pathology likely to be related to the WM

Isolated renal thrombotic microangiopathy (TMA) was diagnosed in 3 (7%) patients. Signs of systemic thrombotic angiopathy, such as schizocytes in the peripheral blood smear, were absent in all 3 cases. ADAMTS13 levels were not tested in any of the patients at the time of kidney biopsy. None of these patients had a previous history of thrombotic events. One patient had a previous history of antinuclear antibody-negative SLE. She presented with acute renal failure, cold autoimmune hemolytic anemia and cold agglutinins. In addition, she tested positive for beta-2 glycoprotein 1 antibodies.

**Table 3.** Clinical characteristics and outcomes based on kidney pathology in patients with WM related nephropathy

Renal pathology	N (%)	Time from WM diagnosis to kidney biopsy	BM involvement	Nephrotic syndrome (%)	Kappa (%)/lambda (%)	Median OS	Need for RRT (%)
Amyloidosis	11 (25)	22 months	25%	8 (73)	4 (36)/7 (64)	11.5 years	2 (18)
IgM/cryoglobulin deposition	10 (23)	0 months	10%	4 (40)	8 (80)/2 (20)	10 years	1 (10)*
Lymphoma infiltration	8 (18)	22 months	60%	0 (0)		16 years	1 (13)
Light chain deposition	4 (9)	0 months	43%	1 (25)	4 (100)/0 (0)	9.4 years	2 (50)
Light chain cast nephropathy	4 (9)	6 months	35%	0 (0)	4 (100)/0 (0)	8.3 years	1 (25)
Thrombotic microangiopathy	3 (7)	0 months	15%	0 (0)		Not reached	0

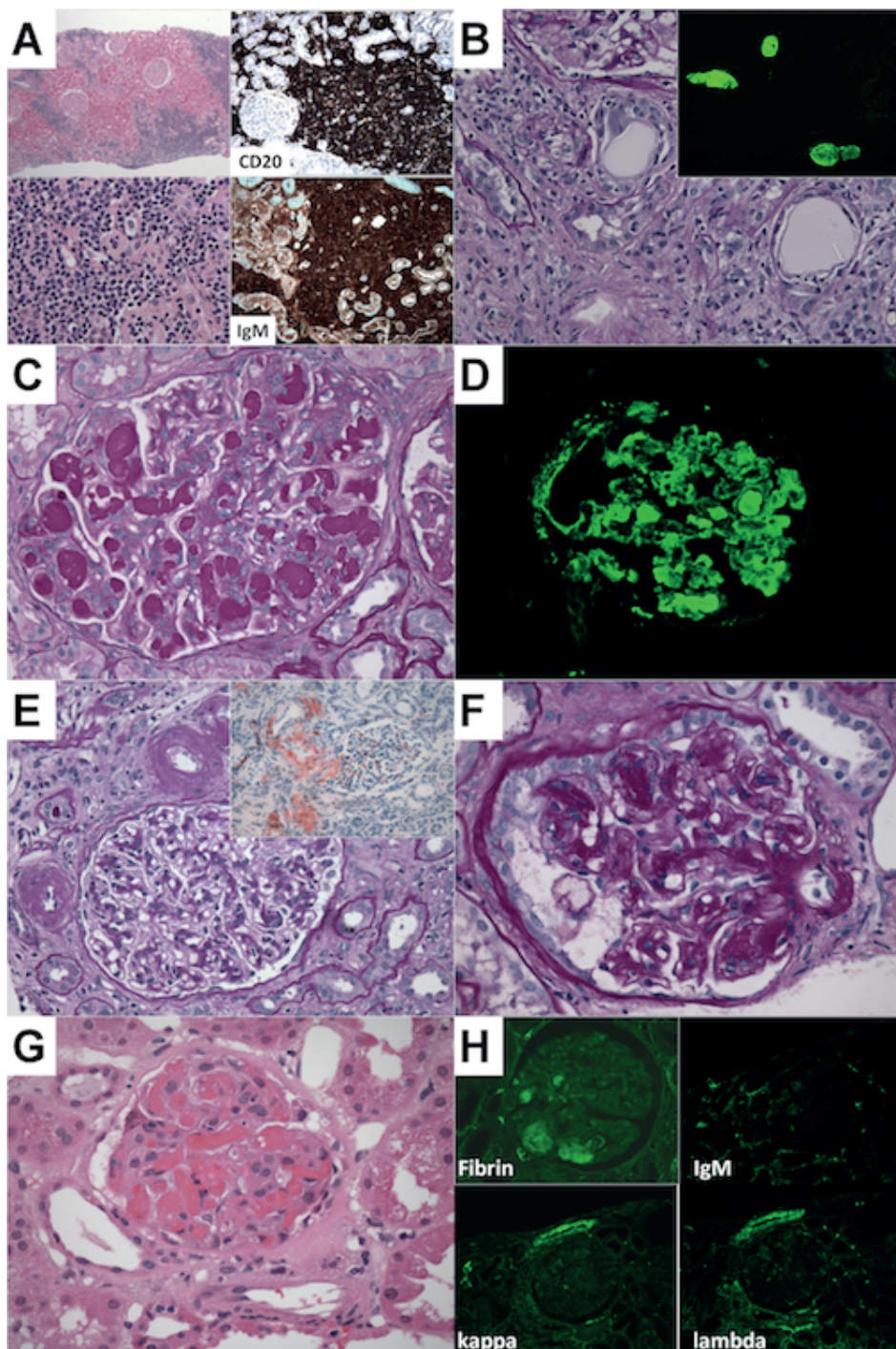
N: number; BM: bone marrow; OS: overall survival; RRT: renal replacement therapy

\*amyloid was diagnosed in both bone marrow and fat pad biopsy within one year after initial diagnosis; also in retrospective the kidney biopsy was negative for amyloid.

**Figure 2:** Kidney biopsy findings in Waldenstrom macroglobulinaemia-related renal disease. →

- (A) Infiltration of the kidney by lymphoplasmacytic lymphoma (LPL). The upper left panel shows widespread infiltration of the cortex by lymphoid cells. The lower left panel depicts the details of the infiltrating cells at higher power. The majority of the cells are small lymphocytes; there are also few scattered plasma cells present. The infiltrating lymphoid cells are CD20 and IgM positive (upper and lower right panels, respectively).
- (B) Light chain cast nephropathy ('myeloma kidney'). The large panel shows casts surrounded by inflammatory cells, including some multinucleated giant cells. The casts are characteristically periodic acid Schiff (PAS)-negative because the light chains are not glycosylated. The inset panel illustrates the immunofluorescence microscopy findings; the casts are reactive exclusively for one of the light chains (kappa).
- (C, D) Glomerular monoclonal IgM deposition disease (MIDD). Most capillaries are occluded by large masses of PAS-positive proteinaceous material ('pseudothrombi') (C). This material is reactive for the mu heavy chain (D). The deposits were reactive for kappa and not for lambda light chains. The serum monoclonal IgM/kappa demonstrated cryoglobulin characteristics (cryoglobulinaemia type I).
- (E) AL amyloidosis in the kidney. The main panel shows marked infiltration of small arteries by amorphous, slightly PAS positive material. The inset panel shows the affinity of this material for Congo red. Note, there is virtually no involvement of the glomeruli in this case.
- (F) Light chain deposition disease. The glomerulus depicted in this panel shows a nodular pattern of injury.
- (G, H) Thrombotic microangiopathy. The glomerulus depicted in (G) shows widespread microthrombi in the capillaries (H) shows that the microthrombi in the glomeruli are reactive for fibrin but do not stain for the heavy chain of IgM, the reactivity for both kappa and lambda light chains is likewise negative.

Original magnification: x15-x250



Two (5%) patients were diagnosed with minimal change disease. Both presented with nephrotic syndrome. Concomitant risk factors for MCD, such as active infection, other cancer, or use of medications associated with MCD, were not present in any of these patients at the time of the kidney biopsy. One (2%) patient presenting with nephrotic syndrome was diagnosed with membranous nephropathy stage I. Other associated risk factors such as active infection, drug use or autoimmune disease were not present.

One or more additional pathological findings were identified in 23 (52%) kidney biopsies; acute tubular injury (n=11), LPL infiltration (n=3) advanced chronic changes (n=3), thin glomerular basement membrane (n=2), podocyte foot process effacement (n=2), early diabetic changes (n=2), interstitial nephritis (n=1) and hyaline casts (n=1).

### Treatment after diagnosis of kidney disease and outcomes

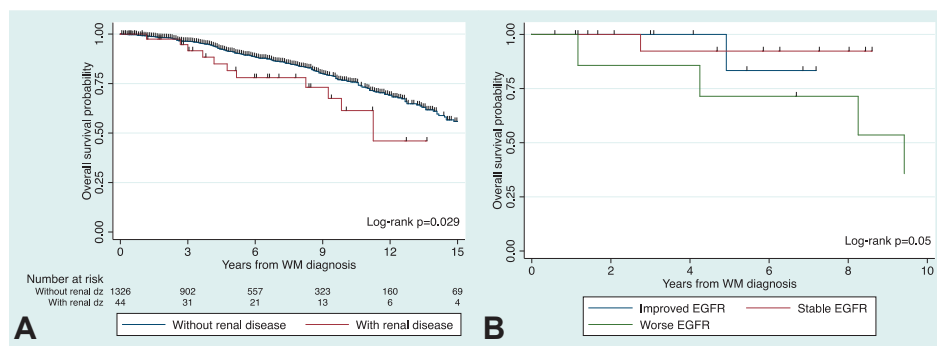
WM-related renal disease was the indication for treatment in 25 of 28 (89%) treated patients. In addition, two patients developed renal complications while on therapy for WM. However, this was not considered causally related to therapy: one patient was on ibrutinib and had a kidney biopsy that showed LPL infiltration. Ibrutinib was discontinued due to progressive disease and concurrent diagnosis of metastasized salivary gland carcinoma. The other patient was treated with the oral proteasome inhibitor oprozomib and developed renal amyloidosis; oprozomib was discontinued.

WM, renal, and nephrotic syndrome responses at 6 months post-treatment were evaluable for 28, 32, and 10 patients, respectively. The remaining patients were not evaluable for a response due to: missing data (n=4), diagnosis too recent for adequate follow-up (n=4), death within 6 months of diagnosis (n=4), or not having received WM treatment (n=4). The treatment regimens of the 28 evaluable patients include: proteasome inhibitor + rituximab (n=16; 50%), alkylator + rituximab (n=8; 25%), nucleoside analogue + rituximab (n=2; 6%), bendamustine (n=1; 4%), and single-agent rituximab (n=1; 4%). The response rates 6 months post-treatment are summarized in **Table 2**.

### Overall survival

After a median follow-up time of 36.5 months, there were 14 deaths (32% of patients). Causes of death were as follows: renal complications (n=5), second primary malignancy (n=2), transformation to large cell lymphoma (n=1), pneumonia/progression of WM (n=1), progression of amyloidosis (n=1), coronary dissection (n=1), and unknown cause (n=3). A total of 7 patients (16%) went on to RRT. The median OS in patients with biopsy-confirmed WM-related nephropathy was 11.5 years, significantly shorter than the median OS for the rest of the cohort (n=1,326) which was 16 years (log-rank p=0.03; **Figure 3**). The OS in patients with WM related nephropathy differed significantly by the renal response that was achieved after therapy (p=0.05; **Figure 3**); better OS was observed in

patients with stable or improved renal function after treatment. The OS did not significantly differ based on the specific renal diagnosis (log-rank  $p=0.5$ ).



**Figure 3.** Overall survival curves for patients with and without biopsy-proven WM-related nephropathy (A), and by renal outcome following therapy (B). EGFR, estimated glomerular filtration rate.

## DISCUSSION

To our knowledge, this is the largest series of biopsy proven WM-related nephropathy and the first study based on a large cohort of WM patients. In this cohort we found a cumulative incidence of WM-related nephropathy of 5.1% at 15 years from WM diagnosis. The wide variety of WM-related renal pathology included pathological processes associated with the LPL tumor cells, IgM paraprotein and light chains. This confirms at a larger scale what was previously published (Chauvet *et al*, 2015; Audard *et al*, 2008; Salviani *et al*, 2014), including AL-amyloidosis, MIDD and LPL infiltration as the most prevalent conditions. However, TMA has not been previously described as a complication of WM. WM related nephropathy seemed to have an adverse impact on survival, specifically in those patients with a decline in renal function after WM treatment.

Some causes of renal disease, such as AL-amyloidosis or light chain deposition, are directly linked to the aberrant proteins produced by the WM clone (IgM and light chains). Other renal pathologies such as TMA, membranous glomerulopathy and MCD have a less clear relation with the WM tumor clone. However, these have all been described in the context of various types of lymphoproliferative conditions including WM, multiple myeloma (MM), chronic lymphocytic leukemia (CLL), Hodgkin and non-Hodgkin lymphoma (Strati *et al*, 2015; Da'as *et al*, 2001; Kofman *et al*, 2014; Lodhi *et al*, 2015; Leeaphorn *et al*, 2014). Since these patients had no other concomitant risk factor for the renal condition besides WM, and there was a temporal relationship between the WM and renal diagnosis, we consider it likely that the renal pathology was related to WM. However, in such cases, careful consideration and crosstalk between hematologist,

nephrologist and pathologist should be pursued to establish a potential causal relation and treatment indication.

Our data highlight the differences between renal disease in WM and MM. Contrary to the 30-40% incidence of renal complications in MM (Dimopoulos *et al*, 2010), the cumulative incidence of 5% we found for WM is much lower. Whereas the vast majority of renal disease in MM is considered to be due to cast nephropathy (Dimopoulos *et al*. 2010), the kidney pathologies we found related to WM were highly variable. These differences in incidence and pathology may be attributed to several distinct disease characteristics. While hypercalcemia and elevated serum FLC levels are known contributors to renal failure in MM, none of the patients with WM related nephropathy was found to have an elevated calcium level. Median sFLC levels however, were 339 mg/L in the 34 patients with WM-related nephropathy that had serum FLC levels measured. This is high compared to the levels typically reported in WM (50-100 mg/L), and in fact more characteristic of the higher levels typically found in MM patients (>300 mg/L)(Leleu *et al*, 2008; Itzykson *et al*, 2008; van Rhee *et al*, 2007; Snozek *et al*, 2008). However, since we did not have serum FLC levels available for the entire cohort, we could not establish a particular value predictive of renal disease. Finally, the physicochemical properties of the various paraproteins and the specific immunological activity of the tumor clones might lead to a different pattern of renal injury. There is a paucity of data on the incidence of renal complications in other B-cell malignancies. Data from a recent retrospective cohort of patients with CLL showed a crude incidence of biopsy-confirmed CLL-associated renal disease estimated at 0.9% (Strati *et al*, 2015). This lower incidence relative to what we found in WM may be attributed to the typical absence of paraproteinemia and/or elevated serum FLC levels in patients with CLL.

WM patients with biopsy-confirmed related nephropathy had a shorter survival compared to patients without renal complications. Survival was also found to be comparatively inferior in patients with a worse renal function post-therapy, although this is based on a small number of patients with a variety of renal pathology (**Figure 3**). This is consistent with the data in MM, where patients who achieve reversal of renal insufficiency are known to have improved outcomes, although still inferior to patients with normal renal function at diagnosis (Gonsalves *et al*, 2015).

We propose TMA as a renal condition related to WM. A remarkable biopsy-confirmed diagnosis of renal TMA (meaning without signs of systemic microangiopathic hemolysis) was identified in 3 of 44 cases. This entity should be distinguished from the classical “pseudo-thrombi” associated with cryoglobulinemia or MIDD. Pseudo-thrombi are composed of large intracapillary aggregates of monoclonal IgM that stain negative for fibrin, while TMA is characterized by the presence of true fibrin and platelet thrombi that are negative for IgM (**Figure 3**). Renal TMA has been reported in MM and CLL, although mostly in relation to chemotherapy (Lodhi *et al*, 2015; Strati *et al*, 2015). This was not

the case in the 3 WM related cases of TMA in our cohort: in 2 patients, TMA was the presenting symptom of the WM diagnosis, while the third patient had not received chemotherapy for over 2 years. In this last patient, TMA relapses occurred two times, and were related in time to relapse of the WM. TMA was limited to the kidney in all cases, without systemic signs of thrombotic thrombocytopenic purpura. The pathophysiology of isolated renal TMA associated with WM is unknown, however, there are several possible mechanisms. WM patients are known to have an elevated risk of venous thrombosis (Hultcrantz *et al*, 2014). Known complications of WM include hyperviscosity and elevated von Willebrand factor (Treon, 2015; Hivert *et al*, 2012). Additionally, the paraprotein may act as an antiphospholipid antibody, interactions of the paraprotein or tumor cell with the local renal microvasculature or the complement system could all contribute to a prothrombotic state. Given the much higher perfusion rate of the glomerular microcirculation compared to any other territory in the body, the glomerular circulation is exposed to higher shear stress under normal physiological circumstances, and hence the kidney is particularly vulnerable to endothelial damage.

In the elderly population of WM patients, the differential diagnosis of renal failure also includes WM-unrelated renal conditions. This is illustrated by the many patients in our cohort with a chronic renal condition and those cases where a kidney biopsy revealed a process unrelated to WM. Attributing the renal failure to WM is clinically relevant since this represents a potential indication to initiate therapy (Dimopoulos *et al*. 2014). Indeed, renal complications were the indication for WM therapy in the majority (87%) of treated patients in our study. In addition, the diagnosis of specific renal pathologies by kidney biopsy (such as AL-amyloidosis or LCDD), will impact clinical management and treatment choices (Treon, 2015; Sayed *et al*, 2015). Therefore, a kidney biopsy is an important tool in the evaluation of WM patients with otherwise unexplained renal insufficiency and/or nephrotic syndrome, and should be pursued accordingly.

Many of our study's limitations are due to the fact that renal disease related to WM is a rare complication of a rare disease (Wang *et al*, 2012). While a retrospective cohort study is probably a desirable design in this setting, some patients may be lost to follow-up or have missing data. Because the clinical diagnosis of WM related renal disease may be missed and kidney biopsies may not always be performed, our data might represent an underestimation of the incidence of renal complications in WM. In addition, there was a heterogeneous pattern of treatment strategies in our cohort, reflecting the lack of a standard of care for treatment of WM and the evolution of treatment options since 1999. Our data therefore did not allow for an assessment between clinical outcomes and specific treatment strategies. As such, treatment recommendations cannot be formulated based on our study. Finally, our study is based on a selected patient population at a tertiary referral center, which may affect generalizability: compared to the patients comprising the SEER database, our cohort of WM patients without renal complications

exhibited longer OS (Castillo *et al*, 2015). This difference may be related to a selection bias with regard to younger age and better performance status, inherent in patients seen and treated at a tertiary referral center. Consistent with the concept of monoclonal gammopathy of renal significance (MGRS) (Fermand *et al*, 2013), many of these renal conditions might also occur in the context of (IgM) MGUS, however our cohort contained insufficient data on IgM MGUS patients to comment on this.

In summary, we reported on the incidence, unique pathological spectrum and prognostic impact of WM-related nephropathy, including TMA as a new finding. Our study suggests that monitoring for renal complications should be considered in the surveillance of WM patients. Kidney biopsy should be pursued in those patients presenting with otherwise unexplained renal insufficiency or nephrotic syndrome. Patients with a decline in renal function after treatment had worse outcomes, which may suggest that early detection of kidney disease and measures to preserve renal function are of importance in the management of patients with WM-related nephropathy.

Author contributions: JMV, MJK, MM, JJC, SPT designed the research project. JMV, JG, RM, ZH, HR, TD, KM collected the data. JMV, JG, JJC, HR, SPT carried out the project and analyzed the data. All the authors helped drafting or revising the manuscript. All the authors approved the final manuscript.

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