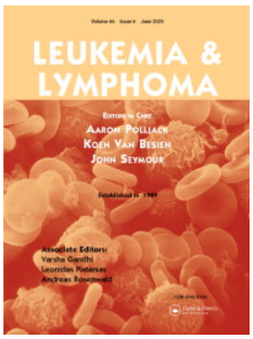

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REVIEW ARTICLE

Not just amyloidosis: the spectrum of Waldenstrom's macroglobulinemia-associated renal disease

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ABSTRACT

Renal involvement in Waldenström's macroglobulinemia (WM) is a rare but clinically significant complication that is often underrecognized and inadequately described in the scientific literature. When kidney damage occurs, it negatively impacts both patient prognosis and renal outcomes, highlighting the importance of early recognition and targeted therapy. While B-cell directed treatment is crucial, therapeutic strategies remain non-standardized, and much of the existing literature predates the widespread use of Bruton's tyrosine kinase (BTK) inhibitors. In this manuscript, we present a case of WM-associated heavy and light chain deposition disease successfully treated with the second-generation BTK inhibitor zanubrutinib, emphasizing the potential role of novel targeted agents in this setting. Additionally, we provide a brief review of renal complications associated with WM and discuss some therapeutic considerations. However, the available data are heterogeneous and insufficient to draw definitive conclusions regarding the relationship between clinical outcomes and specific treatment strategies.

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Introduction

Renal complications in Waldenström's Macroglobulinemia (WM) and IgM monoclonal gammopathies are less common compared with kidney involvement in multiple myeloma. WM is a rare disease, accounting for only 1%–2% of hematologic neoplasms, and renal injury is uncommon. This is likely due to the typically low levels of Bence Jones proteinuria, a modest burden of free light chains (FLC), and a low incidence of hypercalcemia [1]. The existing literature on WM-related renal disease consists primarily of case reports, with larger retrospective cohorts emerging only in the last decade [2–5]. The true incidence of this complication remains unknown. A case series from the Dana Farber Cancer Institute reported renal infiltration in 8% of 43 WM patients with extramedullary disease; however, cases of renal damage secondary to IgM paraprotein deposition were not included [6]. A subsequent retrospective analysis by Vos et al. at the same institution, examined 1,391 cases of WM and analyzed 44 patients with biopsy-proven renal disease, estimating a cumulative incidence of 5.1% over 15 years [4].

However, this likely underestimates the true incidence, as renal biopsy is essential for diagnosis yet not routinely performed in WM patients with renal impairment.

In a smaller, recently published Italian case series, Danesin et al. report biopsy-proven renal involvement in 3.3% of cohort cases with WM treated between 1990 and 2023 [7].

Renal damage in WM and other IgM-secreting lymphoproliferative disorders can be the result of direct infiltration of the interstitium by neoplastic lymphoid cells or be related to the deposition of a entire or truncated monoclonal immunoglobulin (MIg). In the latter case, the pattern of deposition is influenced more by the physicochemical properties of the variable regions of the pathogenic heavy and/or light chains, than by their serum concentration. Depending

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on their molecular characteristics (charge, hydrophobicity, glycosilation), MIg may deposit as organized substructures (e.g. fibrils, microtubules and crystals), or as amorphous aggregates.

The extent of renal injury is modulated by the inflammatory response elicited in glomerular structures [4,8]. MIg deposition can lead to glomerular, tubulointerstitial, and/or vascular damage through complement activation and formation of the membrane attack complex. This results in cellular damage, release of pro-inflammatory mediators, and recruitment of effector cells including mast cells, monocytes, macrophages, and neutrophils. Their activation is followed by the release of interleukins that cause cellular injury, and stimulate cellular proliferation and/or remodeling of the extracellular matrix.

Additionally, nephrotoxicity may arise from an immune-mediated disorder not related to the deposition of circulating MIg or lymphocytic infiltration but induced by the autoimmune activity of MIg or by the overproduction of specific patterns of cytokines secreted by lymphocyte clone or by dysregulated T cells [8,9].

The most common clinical presentations include nephrotic syndrome (NS) and nephritic syndrome characterized by microhematuria, mild proteinuria, and variable degrees of renal dysfunction.

Acute kidney injury (AKI) is less frequent in WM than in multiple myeloma and it's generally due to tumor infiltration [3], while cast nephropathy is rarely reported. Sporadic cases of rapidly progressive glomerulonephritis have been documented [10,11].

Other rare manifestations have also been described, like proximal tubular damage leading to acquired Fanconi syndrome (non-diabetic glycosuria, uricosuria, phosphaturia, and generalized aminoaciduria).

Clinical case

In February 2018 a 72-year-old man was referred for hematological evaluation due to the incidental finding of an serum immunoglobulin M k-restricted (IgMk) monoclonal paraprotein (IgM 1010 mg/dl), and a diagnosis of lymphoplasmacytic lymphoma was made on bone marrow biopsy.

Molecular testing for *MYD88* L265P and *CXCR4* mutations was not performed, as it was not available at our institution at that time. The patient was asymptomatic, his serum creatinine was 0.9 mg/dL, urinalysis was normal, and Bence Jones proteinuria was negative. He was managed with an observational approach.

In May 2020 he presented with progressive fatigue, anemia without iron or vitamin deficiency, increased IgMk (IgM 3200 mg/dl) and abdominal lymphadenopathy of 6 cm. First-line therapy with rituximab-bendamustine was started. Of the 4 planned cycles, 3 were carried out due to recurrent infusion reactions to rituximab, as the patient had achieved a partial remission and was clinically asymptomatic.

Over the subsequent two years, regular monitoring (every 4 months) was performed, revealing slow but gradual increase in serum paraprotein. In October 2022, the patient presented with progressive fatigue affecting his activities. Hemoglobin was 11.7 gr/dL, serum IgM level was 2400 mg/dL, Bence Jones was 559 mg/24 h, FLC kappa was 581 mg/L (6.7–22.4 mg/L), FLC lambda was 17.1 mg/L (8.3–27 mg/L), with a kappa/lambda ratio of 33.97 (0.31–1.56), proteinuria was 1.75 gr/24 h, creatinine was 0.9 mg/dl. No signs of nephritic syndrome (hypertension, microhematuria or deterioration of renal function) were present. Ultrasonography of the abdomen and superficial lymph node stations did not reveal any abnormalities. Serum antinuclear antibodies and cryoglobulins were negative, as were serology for hepatitis B and C and HIV, and no circulating immune complexes were detected. C3 was 83 mg/dL (90–180), C4 was 16 mg/dL [10–40]. The patient underwent a nephrology consultation that recommended a renal biopsy, but it was initially delayed due to his refusal. The biopsy was ultimately performed in May 2023. Bone marrow reevaluation and biopsy were not repeated due to patient refusal.

The kidney biopsy showed by light microscopy 12% global glomerulosclerosis (3 of 24 glomeruli) and focal increase of mesangial matrix; the tubulo-interstitial compartment showed 30% interstitial fibrosis and tubular atrophy. Examination under polarized light of thick Congo Red stained sections resulted negative for amyloid.

Immunofluorescence on frozen tissue showed IgM and kappa light chain granular deposits in glomerular mesangium and capillary walls, in tubular epithelium and lumen and in arterioles.

Electron microscopy showed partially structured electron-dense material compatible with immunoglobulin in capillary lumens and in subendothelial space, with glomerular basement membrane splitting and signs of podocyte injury.

Therefore, a diagnosis of Waldenstrom-associated nephropathy characterized by light and heavy chain deposition disease (LHCDD) was made (Figure 1).

Kidney diseases associated with Waldenstrom macroglobulinemia

Kidney involvement in WM and IgM-related monoclonal gammopathies is relatively rare but shows a diverse range of clinical and pathological presentations. Unlike

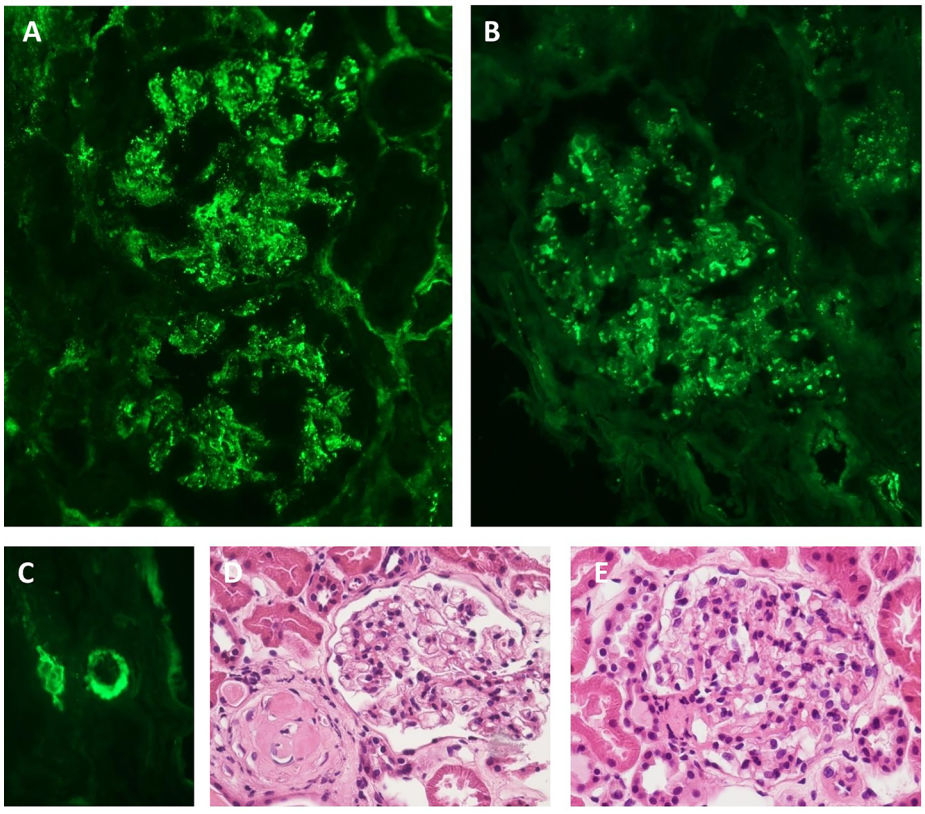

Figure 1. A, B and C: Immunofluorescence on frozen kidney tissue showing diffuse glomerular granular deposition of IgM (a), glomerular and tubular deposition of kappa light chain (B), vascular deposition of IgM (C). D and E: Hematoxylin eosin staining on paraffin sections showing global glomerulosclerosis (D) and focal increase of mesangial matrix (D and E). (A, B, C, D, E magnification 20x).

multiple myeloma, where tubular injury predominates, WM-associated renal disease often involves the glomeruli.

In a recent review and case series, 4 categories of renal damage are recognized: light chain (AL) amyloidosis-related, non-amyloid-related glomerulonephritis (GN), tubulointerstitial disease and non-paraprotein mediated process [1,3–5], summarized in Table 1.

Different patterns of renal damage may coexist within the same patient.

Table 1. Spectrum of renal disease in Waldenstrom macroglobulinemia.

Amyloidosis
Light chain (AL) amyloidosis
Heavy chain (AH) amyloidosis
Light and heavy chain (AHL) amyloidosis
Glomerular non-amyloidotic diseases
Organized deposits
Cryoglobulinemic glomerulonephritis
Immunotactoid glomerulopathy
Unorganized deposits
Proliferative GN with monoclonal immunoglobulin deposits (PGNMID)
Monoclonal immunoglobulin deposition disease (MIDD)
Light chain deposition disease (LCDD)
Heavy chain deposition disease (HCDD)
Light and heavy chain deposition disease (LHCDD)
Tubulointerstitial diseases
Lymphomatous infiltration
Cast nephropathy
Light-chain proximal tubulopathy
Non paraprotein mediated diseases
Minimal change disease (MCD)
Focal segmental glomerulosclerosis (FSGS)
Membranous glomerulonephritis
Thrombotic microangiopathy (TMA)

Amyloidosis related disease

Different studies have identified AL amyloidosis as the most frequent renal lesion in WM.

Chauvet et al. conducted a retrospective study on 35 patients with biopsy-proven renal disease associated with monoclonal IgM-secreting B-cell lymphoproliferative disorders, most of them with WM, and 11 (31%) showed AL amyloidosis [3]. Vos et al. reported amyloidosis in 25% of cases of WM-associated renal disease and described three different pattern of amyloid deposition: light chain (AL) amyloidosis, heavy chain (AH) amyloidosis, and combined heavy and light chain (ALH) amyloidosis [4]. A retrospective study from the Mayo Clinic evaluated 57 patients with WM and other IgM-secreting B-cell lymphoproliferative disorders who underwent renal biopsies; 47 (82%) patients were identified with monoclonal gammopathy-related renal lesions of which 33% had amyloidosis with Ig light chain being the most numerous subtype [5].

AL amyloidosis is characterized by deposition in glomeruli, blood vessels, mesangium and interstitium of amorphous material, positive at Congo red staining, producing an apple-green birefringence under a polarized light and consisting of randomly arranged fibrils with diameters of 7–12 nm [12,13]. Monoclonal λ light chain is the most common immunoglobulin involved. The main clinical picture is proteinuria and NS, possibly associated with decreased kidney function, and frequent multiple organ involvement.

Non amyloid glomerular diseases

This group includes a wide variety of pathologies, characterized on immunofluorescence by the presence of IgM-stained deposits, with kappa or lambda light chain restriction, involving the mesangium and the glomerular capillary walls; the deposits may be seen as intraluminal pseudothrombi. Arterioles and arteries may also show monoclonal IgM staining. Kappa light chain restriction in these deposits is more common than lambda light chain restriction [1,5]. Electron microscopy usually shows large subendothelial deposits unorganized or organized in structures which may have fibrillary and microtubular features [12,13].

Cryoglobulinemic glomerulonephritis (CGN) is the most common glomerular disease after amyloidosis in the case series [1]: Higgins et al. diagnosed it in 20% (12/57) of cases studied and 60% of non-amyloid glomerulopathies [5]; Chauvet et al. found it in 14% (5/35) of cases [3]. Numerous case reports have also been published [14–18].

Histologically, CGN is characterized by the presence of intracapillary 'pseudothrombi' that in immunofluorescence stain positive for monoclonal IgM (kappa or lambda restricted) and negative for fibrin; monoclonal IgM staining also involves the mesangium, and the walls of glomerular capillaries. Electron microscopy often reveals organized deposits with microtubular structure, characterized by hollow centers and large diameters (17–52 nm), although unorganized or fibrillar deposits have also been described. This histopathologic entity can exhibit various pattern of damage on light microscopy with membranoproliferative glomerulonephritis (MPGN) being the most common, but mesangio- or extracapillary (crescentic) glomerulonephritis have also been described. Endocapillary hypercellularity with frequent monocytes and neutrophils is often present.

The clinical picture includes nephritic syndrome, chronically decreased kidney function, NS, and rapidly progressive GN. Low serum complement component C4 levels are commonly detected and serum cryoglobulins are often present, although they may be negative [5,18]. Cases with both type I and type II cryoglobulinemia have been described [19,20].

Extrarenal manifestations of cryoglobulinemia, involving the skin, nervous system, and joints are often present.

Other non-cryoglobulinemic glomerulopathies associated with unorganized monoclonal Ig deposits have been reported and include a wide spectrum of proliferative and non-proliferative GN.

MPGN with monoclonal IgM deposits is the main pattern of injury reported [3,21], but in literature we can find other histopathologic entities variously named as intracapillary monoclonal deposits disease, proliferative GN with monoclonal Ig deposits, monoclonal Ig-associated membranous nephropathy [22], mesangial proliferative GN [3,5].

Chauvet et al. consider these aspects consistent with proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) IgM variant. This entity belongs to the group of glomerulopathies with unorganized monoclonal-Ig deposits and was originally described with monoclonal IgG deposits, often in patients without serum monoclonal paraprotein. The MIg deposits are amorphous and are localized, to the mesangium, subendothelial space and occasionally in the subepithelial space [23]. MIg deposition triggers complement activation, leading to glomerular capillary wall injury, followed by proliferative and reparative changes. This pathological process is supported by the frequent co-localization of C3 with the MIg in the mesangium and along capillary walls. Cases without hypercellularity may represent an early stage of the same pathogenic process, preceding the development of glomerular hypercellularity [3].

PGNMID is characterized by the presence of granular deposits in an exclusively glomerular localization with prevalent kappa clonality. The pathology is typically limited to the kidney. The main clinical manifestation is proteinuria even with NS; hematuria, sometimes macroscopic, is found in 80% of cases. Two thirds of patients have renal insufficiency. Renal prognosis is poor, with progression to end-stage renal disease in 25% of patients within 30 months, and frequent early recurrence on the renal allograft [24].

Monoclonal immunoglobulin deposition disease (MIDD) is also found in glomerular lesions with unorganized deposits. Primarily described in multiple myeloma, has been sporadically reported in WM [25–27]. In the Dana Farber series 4/35 cases (9%) are diagnosed [4], while Higgins and Chauvet reported only one case [3,5]. It is characterized by pseudolinear, Congo red-negative deposition of monoclonal immunoglobulin along glomerular, and often tubular, and

occasional arterial wall basement membranes, tipically associated with nodular glomerulosclerosis. According to the composition of the deposits, MIDD can be subcategorized as light chain deposition disease (LCDD), heavy chain deposition disease (HCDD), or light and heavy chain deposition disease (LHCDD). While PGNMID involves only intact immunoglobulins confined to the glomeruli, deposits in heavy- chain MIDD or light and heavy chain MIDD, typically lack the first constant domain of the immunoglobulin. Kappa light chains are involved in approximately two-third of cases.

In MIDD renal involvement is prominent, but extrarenal lesions (cardiac, hepatic, neurologic) may also be associated and require adequate investigation, including measurements of serum cardiac biomarkers (NT-ProBNP, troponine), echocardiography, alkaline phosphatase. The typical presentation is hypertension, microhematuria, and proteinuria; nephrotic syndrome affects half of the patients. If untreated, the clinical course is one of inexorably progressive chronic kidney disease, leading to the need for renal replacement therapy [28,29].

Finally immunotactoid glomerulopathy (ITG) has been rarely described in patients with WM [5]. It is characterized by the presence of Congo red-negative organized glomerular deposits that stain for Ig and complement by immunofluorescence. The glomerular deposits are uniformly composed of large diameter microtubules (17–52 nm), typically arranged in parallel arrays, with predominantly subepithelial and subendothelial localization [30]. ITG is usually a renal-limited disease and the main pattern of injury is MPGN. Clinical manifestations include proteinuria (often nephrotic), hematuria, hypertension, and varying degrees of renal insufficiency. In approximately 30% of cases, ITG has been associated with underlying lymphoproliferative disorders.

Tubulointerstitial diseases

Tubulointerstitial diseases are the most common renal pathological finding in patients presenting with AKI [3]. Patterns of tubulointerstitial kidney injury include diffuse infiltration by lymphoplasmacytic lymphocytes and light chain precipitation manifesting as cast nephropathy or light chain proximal tubulopathy, with acquired Fanconi Syndrome (FS).

The most common tubulointerstial disease found in WM is diffuse interstitial infiltration by abnormal B lymphocytes wich can be seen alone or with other lesions [1–5,31,32]. Higgins et al. reported tubulointerstitial disease in 14% of patients in their large series, with lymphoma infiltration being the most common etiology [5]. In the series described by Chauvet lymphoplasmocytic infiltration was found in 51% of patients.

When severe, tumor parenchymal infiltration (even in the absence of IgM deposits or light chain casts) can cause AKI due to elevated interstitial pressure caused by the invading lymphocytes, resulting in tubular obstruction, compression of peritubular capillaries with increased postglomerular vascular resistance, and without much destruction of renal parenchymal elements (e.g. tubular apoptosis/necrosis). In fact, AKI often resolves rapidly with therapy, suggesting a readily reversible mechanism [33].

Cast nephropathy is the second most frequent tubulointerstitial lesion. It is less common in WM than in myeloma due to the low frequency of Bence Jones significant proteinuria and the lower level of FLC in WM. Few cases have been described in the literature [34–37] and often have elevated FLC [3,4,34], consistent with the fact that casts result from coaggregation of light chains and uromodulin in the distal nephron. Light chain cast nephropathy is reported in 4/44 (9%) patients by Vos et al. and 3/55 patients by Higgins [4,5]; Chauvet et al. reported 8/35 (17%) patients with poor response to therapy, with 3/6 patients reaching end stage renal disease with a median of 13 months [3].

Light-chain proximal tubulopathy has also been rarely described in WM patients and often manifests as acquired FS [3,4,38,39]. It is caused by the accumulation, in the lysosomal compartment of proximal renal tubular cells, of pathogenic light chains (most often k) in the form of organized crystals, that cannot undergo complete proteolysis [38]; this leads to cellular dysfunction with urinary leakage of phosphate, uric acid, glucose, amino acids, determining hypophosphatemia, hypouricemia and osteomalacia. Decreased renal function may be mild and slowly progressive over years, but kidney failure is also possible. Its course can be indolent and relatively benign and if the lymphoproliferative disorder also has an indolent course, the risks and benefits of chemotherapy should be carefully weighed [38].

Non paraprotein mediated diseases

Non-monoclonal gammopathy-related renal pathologies described in the literature include minimal change disease (MCD) [4,5,40–42], secondary focal segmental glomerulosclerosis [43], acute tubular necrosis, membranous GN and thrombotic microangiopathy [4,5]. The cases are rare and it could be a coincidental association with WM, but the temporal correspondence and the absence of other concomitant risk factors for the kidney disease (such as active infection, other

cancers or use of medications) suggest that there may be a link, presumably on a paraneoplastic basis. Furthermore they have been described in association with other lymphoproliferative syndromes.

MCD is characterized by diffuse effacement of the visceral epithelial cell foot processes resulting in NS; commonly associated with Hodgkin lymphoma, it appears to occur very rarely in patients with WM in absence of concomitant risk factors. It is thought to be mediated by a soluble permeability factor that determines podocyte injury, probably secreted by deregulated T cells or directly released by B cells [9,44].

Similarly, cases of membranous nephropathy without IgM deposits have been described [4] and a paraneoplastic significance has been suggested.

Isolated renal thrombotic microangiopathy (TMA), is characterized by the presence of intracapillary 'true' thrombi which staining for fibrin and negative for monoclonal IgM, in absence of signs of systemic microangiopathic hemolytic anemia and thrombocytopenia, and it is reported in 3/44 (7%) patients by Vos et al. and in one patient by Higgins et al. [4,5,44]. In one patient TMA relapse occurred at the same time with the recurrence of WM [4]. Its causal relationship with WM is controversial, but a study from the Mayo Clinic shows an unexpectedly high prevalence of monoclonal gammopathy in patients with TMA, suggesting a possible pathogenetic mechanism [45].

Clinical case (continued)

While awaiting the result of the kidney biopsy, the clinical picture evolved toward a full-blown nephrotic syndrome. In July 2023 total proteinuria had increased to 3.6 gr/24h, serum albumin had decreased to 3 gr/dl and the patient presented modest sloping edema; serum creatinine was 0.71 mg/dL and an estimated glomerular filtration rate (eGFR) of 115 mL/min/1.73m^2. Urinalysis showed no other alterations. Hemoglobin declined to 10.7 g/dL without nutritional deficiencies, but IgM remained stable at 2766 mg/dL and lymphoadenopathies and splenomegaly were absent.

The patient had no extrarenal manifestations of LHCDD: NT-ProBNP was 54 pg/mL and alkaline phosphatase was 96 U/L. The echocardiogram was normal.

Due to the presence of IgMk-associated organ damage, specific therapy for WM with zanubrutinib was initiated in August 2023 with rapid hematologic and renal response.

Table 2 shows the blood and urinary chemistry parameters before and after the start of therapy.

After one month of therapy a hematologic partial remission (PR) was achieved, reaching a very good partial response (VGPR) after 4.5 months, as per standard response criteria [46].

Given the absence of validated response criteria for light and heavy chain deposition disease (LHCDD), renal response was assessed using the established criteria for renal AL amyloidosis [47]. After the first month of therapy with zanubrutinib a renal response was achieved, with reduction of proteinuria > 50%, and a progressive improvement over subsequent months.

After two months of therapy the patient reported significant improvement in fatigue and resumption of daily activities. To date, there have been no side effects associated with zanubrutinib therapy.

Therapeutic considerations

WM is an indolent and currently non-eradicable lymphoma in which treatment is reserved for patients with symptomatic disease or evidence of organ damage due to lymphomatous infiltration or monoclonal IgM. The presence of renal involvement in WM significantly influences the prognosis and represents an indication for specific therapy targeting the underlying B-cell clone. In the case series analyzed by Vos et al. the median overall survival was significantly shorter in patients with biopsy-proven WM-related nephropathy than remaining cohort (11.5 years vs. 16 years), and better overall survival was observed in patients with stable or improved renal function after treatment [4]. Similarly, Chauvet et al. reported poor overall and renal survival in their cohort: 23% of patients died

Table 2. Changes in blood chemistry and urinary parameters before and after treatment with zanubrutinb.

	07/24/23	09/20/23	10/18/23	01/10/24	05/03/24	10/11/24
Hemoglobin (g/dl)	10.7	11.4	13.4	13.7	13.7	14
Creatinine (mg/dl)	0.84	1.06	1.06	0.99	0.99	1.04
Total Proteinuria (g/24h)	3.63	1.14	0.59	0.17	0.13	0.11
Albumin (g/dl)	3	2.9	3.7	3.9	4.1	4.2
BJ mg/24h	608	129	67	traces	traces	negative
IgM mg/dl (40–230)	2766	1262	327	166	135	170
FLCk (mg/L)	1110	404	206	117	91	60
FLC lambda (mg/L)	26.7	22.9	13.2	9.7	8.4	8.5
dFLC	1083.3	381.1	192.8	107.3	82.6	51.5

BJ: Bence Jones; IgM Immunoglobulin M; FLC: free light chain.

within a median of 11 months from diagnosis, and 6 out of 35 progressed to end-stage renal disease. Notably, there was also a correspondence between the hematologic response and the renal response, as renal response occurred in all 7 patients who achieved a complete or very good hematologic response to therapy [3]. Similar results are reported in the study by Javauge et al. who retrospectively analyzed 52 patients with lymphomatous renal infiltration 21 of whom had a diagnosis of WM [44]. Patients with renal response had significantly higher survival, suggesting that improvement of renal function is an important clinical outcome, and hematologic response was a major determinant of renal response. In this study the presence of MIg-related lesions (in patients with lymphomas other than diffuse large B-cell) was associated with a worse renal response compared to cases with lymphomatous infiltration alone [44].

There are two major concepts in WM therapy, which are fixed duration rituximab-based regimens or BTK inhibitors until disease progression, both effective and well tolerated. Rituximab can be combined with chemotherapy e.g. dexamethasone-cyclophosphamide and bendamustine or with bortezomib.

Currently, the optimal therapeutic strategy for WM-associated renal disease remains undefined due to the limited and heterogeneous nature of available data, which derive primarily from case reports or retrospective case series with non-uniform therapies; this data often predate the use of BTK inhibitors, except for rare case reports [16,48,49]. Most of the published cases are treated with rituximab-based regimens. Rituximab-bendamustine or rituximab-cyclophosphamide-desametasone results in a good renal response rate with low toxicity [18,19,50,51], as well as rituximab-bortezomib-dexamethasone [7,17].

The choice of treatment should be based on both the expected hematologic response, which should be as profound as possible (CR or VGPR), and the characteristics of the nephropathy, which may require an urgent renal response. The patient's symptoms and comorbidities must also be considered.

In the clinical case presented, we treated the patient with a BTK inhibitor considering the high efficacy of this class in WM, especially in the earliest lines of therapy. In addition, the patient had experienced repeated infusion reactions to rituximab and had no cardiac involvement.

The main limitation is the lack of genetic data on MYD88 and CXCR4 mutational status. In the era of BTK inhibitors a genomic-based algorithm for symptomatic patients has been developed by Treon et al. [52,53].

WM is characterized by two highly recurrent mutations: *MYD88* L265P, found in approximately 95–97% of cases, and *CXCR4* mutations, present in about 40%. Differences in treatment outcomes have been reported depending on the mutational status: patients with wild-type MYD88 show a poor response to ibrutinib, with no major response observed in the pivotal study by Treon et al. [54]. Also CXCR4 non-sense mutations adversely impact depth and duration of response to ibrutinib, effect partially overcome by the addition of rituximab [55], but they do not seem to affect PFS on alkylator-based or proteasome inhibitor-based regimens.

The genomic profile of our patient was unknown and we started therapy with zanubrutinb due to the best safety profile, to comparable efficacy to ibrutinib in MYD88 mutated patients, and its greater efficacy in MYD88WT and CXCR4 mutated patients, according to the data from the ASPEN trial [56].

At present the role of FLC determination in the assessment of WM is unclear and the relationship between the burden of the FLC and renal disease has not been established due to lack of literature data. Elevated levels of FLC are sometimes observed (like in our case), but can also be normal in some patients [18]. Chauvet et al. found that among 17 patients tested for free light chains, all had abnormal FLC ratio except for 3 patients with AL amyloidosis and the value is particularly high in cast nephropathy [3]. Higgins et al. found abnormal serum FLC in 74% of patients, suggesting that FLC monitoring may can provide information about your risk of kidney disease [5].

Specific criteria for response to therapy in MIDD are not established and studies published to date have used the hematologic response criteria developed for AL amyloidosis, based on the difference between the involved and the uninvolved FLC (dFLC) [29], but an IgM paraprotein is present in less than 10% of cases in these studies. In our case, the level of FLC and dFLC remain high despite a good renal response, which seems to correlate better with the hematologic response criteria established by the IWWM [46].

In literature, it's reported that a renal response can be achieved even in the absence of a complete hematologic response [3,17]. We can speculate that a reduction of the monoclonal component below a certain pathogenic threshold may be sufficient to mitigate renal inflammation and damage, at least in some Mig deposition diseases. However, this hypothesis cannot be extended to AL amyloidosis, where a rapid and profound hematologic response (CR and VGPR) is associated with a significantly reduced risk of death, as

prompt reduction of the toxic light chain, precursors to amyloid deposits, is essential [57].

The reviewed studies suggest that patients with WM should have their renal function monitored during follow-up, including an inexpensive urinalysis and proteinuria, and possibly complement and cryoglobulin [1]. Kidney disease may be due to other common comorbidities (e.g. hypertension, diabetes), especially in patients >60 years of age, and renal biopsy is unique tool for a correct diagnosis and need to be considered. Clinicians must balance the risks associated with underdiagnosis of a potentially treatable conditions against those of complications from the biopsy procedure [13]; it is indicated in patients with unexplained kidney disease, age <50 years, but also in those with known risk factors for chronic kidney disease but an atypical clinical course [13].

In addition to establishing the diagnosis, renal biopsy can provide prognostic information e.g. the percentage of sclerotic glomeruli and the presence MIg-related renal lesions are associated with poor renal outcome [44]. Also, histology can guide the treatment plan: in AL amyloidosis ibrutinib appears to produce unsatisfactory light chain control and poor tolerability, and autologous BMT is recommended in eligible patients [58]. Newer BTK inhibitors, such as zanubrutinib, with better tolerability, deserve further investigation, but this category may not be the most effective in AL amyloidosis [59], while it may provide an excellent response in other IgM deposition diseases.

The spectrum of renal disease in WM is very broad and the rarity of these entities makes targeted studies difficult; further research is warranted to determine the efficacy of available treatment options, and this would require a multi-institutional effort to collect data from uniformly treated patients.

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Statement of consent

The patient's consent to publication was acquired.

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