Defining the Incidence, Pathology and Clinical Outcomes of Kidney Disease Related to Waldenström's Macroglobulinemia and IgM MGUS

Josephine M. Vos, MD[1,2*], *Robert R Manning*[1*], *Kirsten Meid, MPH*[1*], *Joshua Gustine, MPH*[1*], *Christopher J Patterson, MFA*[1*], *Philip Brodsky*[1*], *Sandra Kanan, NP, RN, MSN*[1*], *Marie José Kersten, MD, PhD*[3], *Steven P Treon, MD, PhD*[1,4], *and Jorge J Castillo, MD*[1,4]

[1]*Bing Center for WM, Dana Farber Cancer Institute, Boston, MA,* [2]*Internal Medicine/Hematology, St. Antonius Ziekenhuis, Nieuwegein, Netherlands,* [3]*Department of Hematology, Academic Medical Center, Amsterdam, Netherlands,* [4]*Division of Hematologic Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*

Key points

- Related kidney disease complicated WM/IgM MGUS in approximately 3% of cases in our cohort
- There was a wide range of kidney pathology associated with WM/IgM MGUS
- Renal function improved or remained stable in the majority of treated patients.
- Outcomes seem worse in patients with renal amyloidosis or light chain deposition disease.

Background & Methods

Background While kidney disease (KD) occurs in up to 40% of multiple myeloma (MM) patients, the incidence, pathology, and clinical correlations of KD in patients with Waldenström's Macroglobulinemia (WM) or IgM MGUS remain to be clarified.

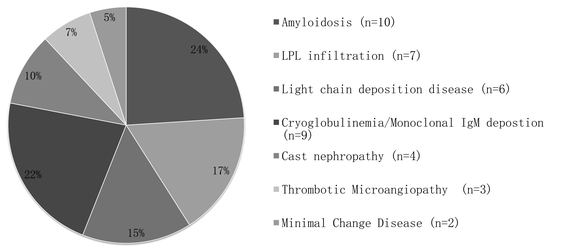
Methods Out of 1,738 patients with consensus criteria defined WM (N=1,655) or IgM MGUS (N=83) diagnosis who were evaluated at the Bing Center for WM from 2001-2015, we selected those individuals with at least one of the following abnormalities: serum creatinine ≥1.3; estimated GFR (eGFR) <60; or proteinuria. Patients with non-WM/IgM MGUS related KD were excluded.

Results - Crude incidence

Renal impairment and/or proteinuria were present in 259 patients. In 183 cases, this was unrelated to WM/IgM MGUS . We excluded 15 patients with urological carcinoma, and 4 patients with peri-renal diffuse large B-cell lymphoma (N=3) or lymphoplasmacytic lymphoma (N=1). Thus, a clinical diagnosis of WM/IgM MGUS associated KD was made in 57 (53 WM; 4 IGM MGUS) patients, of whom 41 had a confirmatory kidney biopsy. The crude incidence of WM/IgM MGUS-associated KD in this cohort was 3.3% (2.4% for renal biopsy confirmed cases). In biopsy confirmed cases, the median age was 66 (range 46-81 years), serum IgM was 2,053 (range 178-5,870 mg/dL), and eGFR was 30 (range 4-99 ml/min/1.73m^2). Nephrotic syndrome was present in 13 (31%) of these patients. Only four (10%) patients were anemic, while none had hypercalcemia. Renal pathology results in the 41 cases are shown in Figure 1. In 11 (27%) of these cases, additional multiple abnormalities were present in the renal biopsy. Kidney biopsy specimens demonstrating lymphomatous infiltration, IgM deposition, thrombotic microangiopathy, amyloidosis and light chain cast neprhopathy are shown in Figures 2-6.

Results- Kidney Pathology

Fig. 1: Kidney Biopsy Pathology



Kidney Biopsy Pathology

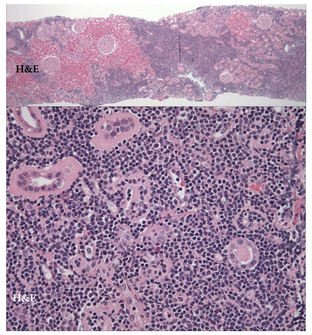


Fig.2:Infiltration of the kidney with lymphoplasmacytic lymphoma . The upper panel shows widespread infiltration of the cortex by lymphoid cells. The lower panel depicts this higher power. The majority of the cells are small lymphocytes; also few scattered plasma cells are present . The infiltrate was positive for CD20, IgM and kappa staining and contained clonal plasmacells. (not shown).

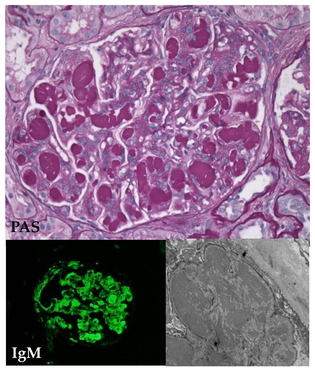


Fig. 3: Monoclonal immunoglobulin deposition/Cryoglobulinemia. Capillaries are occluded by large masses of PAS-positive proteinaceous material ("pseudothrombi"). The lower panel shows the reactivity for this material for the mu heavy chain and the electron microscopy appearance of the endoluminal depositis.. The depositis were reactive for kappa and not for lambda light chains (not shown).

Kidney Biopsy Pathology

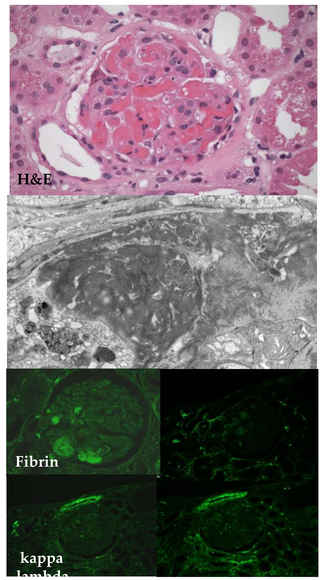


Fig 6.: Thrombotic Microangiopathy. The glomerulus depicted in the upper panel shows widespread microthrombi in the capillaries. The thrombi are intensely eosinophilic and PAS-negative (not illustrated). The middle panel shows the ultrastructural details of a cross-linked fibrin clot within a glomerular capillary. The four lower panels show immunofluorescence microscopy on paraffin sections after antigen retrieval with protease solution. The microthrombi in the glomeruli are reactive for fibrin but do not stain for the heavy chain of IgM. Lower panel: The reactivity for both kappa and lambda light chains is likewise negative.

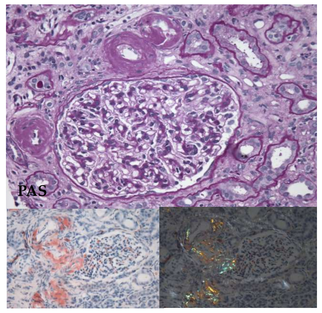


Fig. 4: AL Amyloidosis . The upper panel shows marked infiltration of small arteries by slightly PAS positive amorphous material. The middle panel shows the affinity of this material for Congo red and the characteristic "apple-green" birefringence under polarized light. The amyloid was strongly reactive for lambda but not for kappa light chains (not shown). There is virtually no involvement of the glomeruli.

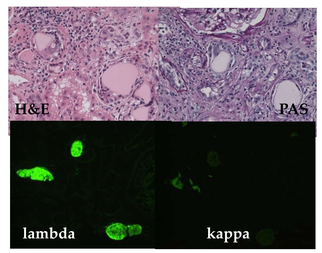


Fig. 5: Light Chain Cast Nephropathy. ("myeloma kidney"). The left upper panel shows eosinophilic casts surrounded by inflammatory cells. The casts are characteristically PAS-negative (right upper panel). The lower panels show the immuno-fluorescence microscopy; the casts are reactive exclusively for one of the light chains (lambda).

Kidney Biopsy: TMA

Interestingly, in 3 patients thrombotic microangiopathy was identified as the renal diagnosis. To our knowledge, no cases of TMA have previously been reported in association with WM. TMA has been reported in MM and CLL, although in most cases related to chemotherapy. However, the 3 WM patients presenting with TMA were all previously untreated. The pathophysiological process leading to TMA associated with WM is unknown. Several mechanisms could be suggested, including paraprotein- or tumor cell-related activation of the complement and/or coagulation cascades.

Results: Outcomes

The median follow-up was 17 months (range 1-162). A synchronous diagnosis of WM and KD was made in 17 patients (41%), while in the remaining 24 patients the median time to KD following the WM diagnosis was 29 months (range 5-88). KD was diagnosed mostly in untreated patients (N=29; 70%), while the remaining 12 patients had a median of 2 prior therapies. Thirty-six patients were treated after their kidney biopsy, regimens were as follows: proteasome-inhibitor based (N=19; 46%); alkylator based (N=11; 27%); nucleoside analogues (N=4; 10%); and rituximab monotherapy (N=2; 5%). Additional plasmapheresis was employed in 12 (31%) patients. WM treatment responses based on consensus criteria were as follows: CR (N=1; 3%), VGPR (N=4; 11%), PR (N=27; 75%), MR (N=1; 3%) progressive disease (N=1; 3%), or not evaluable (N=5; 14%). Renal outcomes for the 36 treated patients based on at least a 10 ml/min/1.73m2 change in eGFR were as follows: improved (N=14; 34%); stable (N=12; 29%); decreased (N=9; 22%) and unknown (N=1; 2%). Patients with either amyloid or light chain deposition (N=16) showed worse outcomes: 1 died of refractory nephrotic syndrome; 5 went on to dialysis. None of the patients with other renal pathology either died of renal complications or required dialysis.

Conclusion

KD complicates WM/IgM MGUS in approximately 3% of cases and shows a wide range of kidney pathology. Patients with amyloidosis or light chain deposition disease show worse outcomes, including the requirement for dialysis. Establishing the underlying WM related kidney pathology may help direct appropriate therapeutic interventions