

Monoclonal gammopathy in lupus nephritis

Sirs,

Monoclonal gammopathy of undetermined significance (MGUS) is an asymptomatic premalignant stage, defined by the presence of a serum M protein (concentration <30 g/L), <10% monoclonal plasma cells in the bone marrow, and the absence of the CRAB features (hypercalcaemia, renal failure, anaemia, bone lesions) (1). MGUS affects 3.2% of people over 50 years of age (2).

Lupus nephritis (LN) is a common and severe manifestation of systemic lupus erythematosus (SLE), which contributes to the development of end-stage renal disease and death (3).

MGUS seems to have higher prevalence in autoimmune conditions, but data in SLE are few (4) and absent in LN patients. The possible pathogenesis underlying this association, the specific features and outcome of MGUS in SLE remain unclear.

Among 207 biopsy-proven LN patients attending a nephrology clinic between 1971 and 2022, 13 (6.3%) developed MGUS (12 women, mean age at MGUS diagnosis of 49.11±10.15 years) (Table I). The prevalence of MGUS was higher and the age of LN patients was lowest than that reported in the general population (2). LN was active at diagnosis of MGUS in five patients and inactive in eight. MGUS developed earlier in LN course in 6 (median: 2.48 [1.15–4.07] years) and later in 7 patients (median: 27.00 [19.58–30.63] years). The most frequent serum M protein was IgG (69.2%), in accordance with what was reported in SLE patients (4, 5).

Each LN patient with MGUS was compared with two LN patients without MGUS matched by gender, age at LN diagnosis, and disease duration. There were more proliferative LN at baseline kidney biopsy in MGUS than in the non-MGUS group (92.3% vs. 65.4% respectively, $p=0.06$). This might be due to the higher severity of these histological forms that require more aggressive and prolonged immunosuppressive therapies. Lu *et al.* found that proteinuria was significantly more frequent in the MGUS SLE group than in the controls (6), suggesting that this may be due to higher SLE activity. Moreover, MGUS patients had an increased risk of developing infections (7). In our cohort, LN patients with MGUS had no increased risk of infection in comparison to controls. However, in two patients, we observed the emergence of MGUS during zoster infections occurring within a few weeks after a rituximab infusion. Hypogammaglobulinaemia is a known side effect of rituximab and there is a link between hypogammaglobulinaemia and infection risk after rituximab (8). Actually cases of MGUS associated hypogammaglobulinaemia in the absence of a defining primary immunodeficiency have been reported (9).

Table I. Clinical characteristics of the 13 patients with lupus nephritis and monoclonal gammopathy of undetermined significance.

General information		
Median (IQR) duration of LN (years)	13.74 (4.32, 31.06)	
Median (IQR) duration of LN at MGUS diagnosis (years)	7.83 (1.27, 27.13)	
Median (IQR) duration of follow up after MGUS diagnosis (years)	3.18 (1.21, 4.08)	
Age at LN diagnosis (years)	34.19 ± 13.26	
Age at MGUS diagnosis (years)	49.11 ± 10.15	
Gender (female/male)	12/1	
Histological class of LN podocytopathy/II/III/IV/V/VI (number of pts)	Podocytopathy: 1 Class III: 6 Class IV: 6	
Activity index	6.09 ± 4.39	
Chronicity index	2.55 ± 2.73	
Immunosuppressive therapy before MGUS diagnosis (number of pts)	Corticosteroids: 12, MMF: 11, CYC: 4, RTX: 2, AZA: 4, HCQ: 6, plasmapheresis: 1	
Immunosuppressive therapy at MGUS diagnosis (number of pts)	Corticosteroids: 12, MMF: 9, RTX: 2, AZA: 1, HCQ: 5	
Active LN at MGUS diagnosis (number of pts)	5	
Median (IQR) duration of activity (years)	0.12 (0.06, 0.71)	
Inactive LN at MGUS diagnosis (number of pts)	8	
Median (IQR) duration of inactivity (years)	12 (3.03, 28.06)	
Laboratory parameters at LN diagnosis		
Serum creatinine (mg/dL)	0.85 ± 0.33	
Proteinuria 24 hours (g/day)	.29 ± 2.11	
Albumin (g/dL)	2.95 ± 0.59	
AntidsDNA (number of positive pts)	12	
C3 (mg/dL)	63.99 ± 37.32	
C4 (mg/dL)	15.60 ± 12.05	
Laboratory parameters at MGUS diagnosis		
Serum creatinine (mg/dL)	1.05 ± 0.38	
Proteinuria 24 hours (g/day)	1.35 ± 2.10	
AntidsDNA (number of positive pts)	11	
ANA (number of positive pts)	12	
Albumin (g/dL)	3.82 ± 0.55	
C3 (mg/dL)	100.08 ± 32.64	
C4 (mg/dL)	18.85 ± 12.72	
Haemoglobin (g/dL)	12.47 ± 1.89	
Platelet count (/mm³)	280,000.46 ± 94,000.65	
Monoclonal type	Number of pts	Immune-quantitation (g/dL)
IgG kappa	6	0.30-2.30
IgG lambda	3	0.34-0.74
IgA lambda	1	0.89
IgM lambda	1	0.70
IgA kappa + IgG lambda	1	0.18
Unknown	1	Unknown
Bence Jones protein positive (number of pts)	3	

AZ: azathioprine; CYC: cyclophosphamide; HCQ: hydroxychloroquine; IQR: interquartile range; LN: lupus nephritis; MGUS: monoclonal gammopathy of undetermined significance; MMF: mycophenolate mofetil; Pts: patients; RTX: rituximab; SD: standard deviation. Unless specified, numbers refer to mean and ± standard deviation.

There were no differences regarding immunosuppressive therapy, except for a trend of less frequent use of antimalarials in the MGUS versus non-MGUS patients (46.2% vs. 73.1%, respectively, $p=0.09$). In line with a previous SLE cohort, no malignant evolution was observed in our cohort during 3.18 years after MGUS diagnosis and no worsening of renal function or SLE flare increase occurred (3). However, a longer follow-up is needed to completely exclude MGUS transformation. As a matter of fact, the progression of MGUS to lymphoproliferative disorders after kidney transplant was reported, within a follow-up time of 6–8.5 years (10). Our study limitations include the small sample size, the retrospective nature, and Caucasian ethnicity of all our patients.

In summary, this is the first study reporting the diagnosis of MGUS in a large cohort of biopsy-proven LN patients. Our results show that the prevalence of MGUS is higher in LN than in general people, especially in proliferative forms of LN. No progression to malignancy is documented. Hydroxychloroquine seems to protect from MGUS development. We hope this letter suggests a call to action for screening for MGUS in LN and its close surveillance during the follow-up.

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References

1. RAJKUMAR V, DIMOPOULS M, PALUMBO A *et al.*: International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol* 2014; 15(12): E538-48. [https://doi.org/10.1016/S1470-2045\(14\)70442-5](https://doi.org/10.1016/S1470-2045(14)70442-5)
2. ATKIN C, RICHTER A, SAPEY E: What is the significance of monoclonal gammopathy of undetermined significance? *J Clin Med* 2018; 18(5): 391-96. <https://doi.org/10.7861/clinmedicine.18-5-391>
3. GASPAROTTO M, GATTO M, BINDA V, DORIA A, MORONI G: Lupus nephritis: Clinical presentations a-d outcomes in the 21st century. *Rheumatology* (Oxford) 2020; 59(Suppl 5): 39-51. <https://doi.org/10.1093/rheumatology/keaa381>
4. ALI YM, UROWITZ MB, IBÁÑEZ D, GLADDMAN DD: Monoclonal gammopathy in systemic lupus erythematosus. *Lupus* 2007; 16(6): 426-9. <https://doi.org/10.1177/0961203307079045>
5. RUBIN L, UROWITZ MB, PRUZANSKI W: Systemic lupus erythematosus with paraproteinemia. *Arthritis Rheum* 1984; 27(6): 638-44. <https://doi.org/10.1002/art.1780270606>
6. LU C, YANGB C, YE J: Monoclonal gammopathy of undetermined significance increased the rate of infection in systemic lupus erythematosus. *Med Clin (Barc)* 2021; 156(11): 573-5. <https://doi.org/10.1016/j.medcli.2020.04.053>
7. TRIVIN C, TRAN A, MOULIN B *et al.*: Infectious complications of a rituximab-based immunosuppressive regimen in patients with glomerular disease. *Clin Kidney J* 2017; 10(4): 461-69. <https://doi.org/10.1093/ckj/sfw101>
8. VAN Vollenhoven RF, EMERY P, BINGHAM CO *et al.*: Longterm safety of patients receiving rituximab in rheumatoid arthritis clinical trials. *J Rheumatol* 2010 Mar;37(3):558-67. <https://doi.org/10.3899/jrheum.090856>
9. ZEMBLE RM, PATRICIA, TAKACH PA, LEVINSON AI: The relationship between hypogammaglobulinemia, monoclonal gammopathy of undetermined significance and humoral immunodeficiency: a case series. *J Clin Immunol* 2011; 31(5): 737-43. <https://doi.org/10.1007/s10875-011-9548-0>
10. ASLAM N, TRAUTMAN C, SHER T: Kidney transplantation and monoclonal gammopathy of undetermined significance. *Transplant Direct* 2021; 7: e723. <http://doi.org/10.1097/txd.0000000000001176>