

**W14: Natural history of IgM monoclonal gammopathy of undetermined significance and smoldering Waldenström macroglobulinemia**

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**Introduction:** Waldenström macroglobulinemia (WM) is a rare B-cell malignancy characterized by lymphoplasmacytic cell bone marrow infiltration secreting monoclonal IgM. As in multiple myeloma, WM is preceded by a monoclonal gammopathy of undetermined significance (MGUS) stage. It has recently been described that patients with IgM MGUS have a higher risk of progression in comparison to those with other MGUS isotypes. Even more, it's described that if the IgM MGUS is associated with adverse factors such as abnormal serum free light chains ratio and more than 15 g /L serum M-spike, the risk of progression at 20 years is as high as 55%.

**Methods:** In order to compare recently published results we retrospectively reviewed the medical records of 121 patients, 91 with IgM MGUS and 30 with smoldering WM (SWM) diagnosed in our institution between 2012 and 2017. In the absence of clinical manifestations, IgM MGUS was defined as the presence of less than 30 g/L of serum IgM monoclonal protein and less than 10% lymphoplasmacytic bone marrow infiltration. The diagnosis of SWM required the presence of any size IgM M spike associated with  $\geq 10\%$  lymphoplasmacytic bone marrow infiltration with no target organ involvement, constitutional symptoms, hyperviscosity, lymphadenopathies or peripheral neuropathy. Progression to WM was defined according to the 2014 International Consensus.

**Results:** Clinical and laboratory features of all 121 patients included in the study have been summarized in Table 1 (median age 70 years with female predominance in SWM). SWM group had a significantly higher median serum M spike than the MGUS group ( $p= 0.012$ ) as well as higher serum IgM levels (median 12.8 g/l vs. 6.1 g / L,  $p < 0.001$ ). We did not find differences in the  $\beta 2$ - microglobulin values between the two groups ( $p= 0.085$ ). IgG and IgA immunoparesis (low uninvolved immunoglobulin level) was more frequent in SWM but not reaching significant differences.

MYD88 L265P presence was determined in 40 patients, being positive in 95% of the SWM cases compared to 55% in the IgM MGUS group ( $p < 0.001$ ). Median time of follow up was of 18 months for living patients. The evolving pattern of the M-spike was significantly more frequent in the SWM group than in the MGUS one (17% vs. 3%,  $p=0.01$ ). This pattern was also concordant with the higher rate of progression to symptomatic disease in SWM (17% vs. 2%,  $p=0.015$ ). Thus, the risk of progression of SWM was 7 times greater than those with IgM MGUS (HR 7.1,  $p < 0.01$ ; 95% CI 1.68-30.02). There were no differences on survival between these two groups of patients.

**Conclusions:** In our series, the rate of progression to symptomatic WM of IgM MGUS was clearly inferior to the reported in other historical series and quite similar to those with IgG isotype (1% per year), being significantly higher for the patients with SWM. Evolving pattern is rare in MGUS but it was identified in 17% of patients with SWM. These findings suggest that bone marrow evaluation is crucial in the prognosis of asymptomatic IgM monoclonal gammopathies.

Table 1 Patient's characteristics (N = 121)

	IgM MGUS n = 91	SWM n = 30	p
Age (median)	71	68	0.327
Gender (M/F)	52/39	9/21	0.01
Serum M-spike (g/L) (median)	8.4	11.8	0.012
<b>β2-microglobulin (%)</b>			
< 2.5 mg/L	51.8	70	0.085
≥ 2.5 mg/L	48.2	30	
Albumin (g/L) (median)	42.9	41.3	0.017
Serum IgM (g/L) (median)	6.2	12.9	< 0.001
<b>Immunoparesis (%)</b>			
IgG < 6.8 g/l	16	26	0.23
IgA < 0.6 g/l	3.5	13.3	0.056
<b>Abnormal sFLC κ/λ ratio (%)</b>			
< 0.26 or > 1.65	38.8	50.0	0.286
<b>MYD88 L265P (%) *</b>	55.5	95.4	< 0.001
<b>Abnormal CT scan (%)**</b>	6.6	12.5	< 0.001
<b>Evolving M-spike pattern (%)</b>	3.3	16.6	0.011
<b>Progression rate to WM (%)</b>	2.2	17.3	0.015
<b>Mortality (%)</b>	7.6	6.6	0.853

MGUS: monoclonal gammopathy of undetermined significance; SWM: smoldering Waldenström macroglobulinemia; CT: Computed tomography. sFLC: serum free light chain

\*Data available in 18 MGUS and 22 SWM cases

\*\*CT scan was performed only in 15 MGUS and 16 SWM cases