IGM MGUS AND ASYMPTOMATIC WALDENSTRÖM'S MACROGLOBULINEMIA: PROGNOSTIC FACTORS AND EVOLUTION

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IgM monoclonal components (MCs) without evidence of either overt Waldenström's macroglobulinemia (WM) or other malignant lymphoproliferative disease (MLD) are known as IgM asymptomatic monoclonal gammopathies (aMGs), and can be further distinguished into IgM MG of undetermined significance (MGUS) and smouldering WM (SWM). Since variable diagnostic criteria were previously used to separate IgM MGUS from SWM, a reliable distinction of asymptomatic populations with different transformation risk into active disease was lacking until recently. The two entities were definitively divided from the clinico-pathological point of view during the 2nd International Workshop on WM (September, 2002).1 Indeed, the unequivocal histopathological evidence of lymphoplasmacytic (LP) non Hodgkin's lymphoma (NHL) with an intertrabecular bone marrow (BM) infiltration pattern was recognized as the only parameter distinguishing SWM from IgM MGUS, characterized instead by the absence of BM infiltrates, or equivocal evidence of BM infiltrates without confirmatory phenotypic studies. In order to detect whether this definition allowed to identify two patient populations also differing in prognosis, a few studies have been performed so far. By evaluating retrospectively data from 207 IgM MGUS and 217 SWM defined according to the new criteria, Gobbi *et al.* demonstrated that IgM MGUS patients have a slight but significant overall survival (OS) advantage, and SWM patients have an equivalent mortality rate with respect to the general population.2 In another study, we found that OS did not differ significantly between 138 IgM MGUS and 34 SWM (p=0.76)(3). However, the event-free survival (EFS) at 5 and 10 years was 95% (95%CI, 87-98%) and 83% (95%CI, 71-90%), respectively, in IgM MGUS, and 77% (95%CI, 56-89%) and 42% (95%CI, 19- 64%), respectively, in SWM (p=0.0001). These data suggested BM evidence of LP-NHL to identify a subgroup of IgM aMGs with high probability of evolution to overt MLD, needing strict monitoring in view of an early treatment of their disease. As far as risk factors for evolution to overt MLD are concerned, the lack of unequivocal criteria for differentially diagnosing IgM MGUS from SWM as well as the evaluation of MGUS taken together irrespective of the MC isotype, make data before 2002 not homogeneous. In 1,014 MGUS patients,4 Cesana *et al.* found Ig A and IgM isotype, serum MC levels > 1.92 g/dL, detectable Bence Jones (BJ) proteinuria, the reduction of one or two serum polyclonal immunoglobulins (Ig), the erythrocyte sedimentation rate (ESR) and BM plasma cell (PC) or LP cell levels to be associated with an increased probability of evolution. At multivariate analysis, BM PC or LP infiltration, the presence of BJ proteinuria, polyclonal serum Ig reduction and ESR were independently associated with MGUS malignant transformation. On the basis of predictive variables, a prognostic index (PI) was determined allowing to identify four different risk groups. In other studies an independent prognostic value for evolution was confirmed for detectable BJ proteinuria, reduction of normal Ig and BM PC or LP cell levels, and was also found for

the serum paraprotein size.5 More recently, Rakjumar *et al.*6 tested the prognostic significance of an abnormal serum free light chain ratio in 1,384 MGUS patients, and showed this parameter to predict malignant transformation independently of the size and type of serum MC. Given a scoring system, IgM MGUS patients with a MC > 1.5 g% and an abnormal serum free light chain ratio would have a 58% 20-year-probability of evolution. Prognostic factors for SWM transformation to active disease were analyzed in few patients, in the contest of large WM series mostly requiring treatment at presentation.7 In 27 patients diagnosed as having SWM on the basis of IgM MC size greater than 3 g/dL, and/or BM LP infiltration 30% or greater, and/or a diffuse infiltration pattern on BM biopsy, high MC size and low haemoglobin (Hb) level were found to independently predict the risk of transformation. 8 Similarly, Alexanian *et al.* observed Hb levels < 11.5 g/dL, IgM MC greater than 3 g/dL and high β2-microglobulin levels to correlate with the risk of evolution.9 The finding of high MC levels as a prognostic factor in SWM disagreed with previous data,7 probably due to different patient selection criteria (in the majority of studies paraprotein levels greater than 5 g/dL had been chosen for SWM diagnosis). Given the assumption that the only parameter defining an overt WM is treatment requirement, the analysis of risk factors for evolution in IgM aMGs on a whole retains an important theoretical value, and allows to analyze large series of cases by evaluating also patients without BM findings. By analyzing 213 IgM aMGs during long-term follow-up, Kyle *et al.* found only the IgM MC size and the albumin level to independently predict evolution to MLD.10 After the 2nd International Workshop on WM, we analyzed 384 patients with IgM aMG defined according to the new criteria (i.e., those patients with any size of serum IgM MC, any degree of BM LP infiltration, any LP infiltration pattern except for the paratrabecular pattern on BM biopsy, no symptoms attributable to either IgM MC or tumour infiltration, and no evolution to overt WM or other MLD for at least 12 months from diagnosis).3 At univariate analysis MC level (p=0.0001), Hb level (p=0.0002), absolute lymphocyte counts (ALC) >4 ·109/L (p=0.0015), ESR level ≥40 mm/h (p=0.0035) and degree of BM LP-NHL infiltration (p<0.0001) were significantly associated with the evolution probability, while BJ proteinuria (p=0.067) and a diffuse BM infiltration pattern (p=0.081) were associated with a trend for increased transformation risk. Absolute neutrophil counts < 1.8·106/L, serum β2-microglobulin levels and reduced normal Ig levels were not associated with evolution probability. At multivariate analysis, IgM size (p=0.005) and lymphocytosis (p=0.0001) independently predicted malignant evolution, while Hb level was associated with a trend for a higher progression risk (p=0.076). Assuming a label (x) for each variable [x1=MC in mg/dL (log transformed), x2=Hb in g/dL, x3=1 if ALC >4·109/L, x3=0 if ALC 4·106/L, x4=1 if detectable BJ proteinuria and x4=0 if undetectable BJ proteinuria, and x5=ESR in mm/h], we calculated a PI (=1.2636x1-0.2684x2+2.4165x3-0.1190x4+0.4071x5) for each patient and identified 3 risk groups on the basis of PI distribution tertiles. The low-risk subgroup (1st tertile, PI ″8.97) had EFS rates at 5 and 10 years of 100% and 89% (95%CI, 60%-97%), respectively; the intermediate-risk subgroup (2nd tertile, 8.97 < PI ″ 10.06) had EFS rates at 5 and 10 years of 95% (95%CI, 85%-98%) and 83% (95%CI, 64%-93%), respectively; the high-risk group (3rd tertile, PI >10.06) had EFS rates at 5 and 10 years of 85% (95%CI, 72%-92%) and 44% (95%CI, 24%-63%), respectively. EFS of patients corresponding to the 3rd tertile significantly differed (p<0.0001) from that of patients corresponding to the first two tertiles pooled

together [EFS rates at 5 and 10 years of 97% (95%CI, 92%-99%) and 86% (95%CI, 72%-93%), respectively]. Whether previously found risk factors for evolution to symptomatic WM are confirmed for SWM patients, defined according to the Consensus Panel Recommendations of the 2nd International Workshop on WM, is still unknown. However, in our series 79.4% of SWM presented a PI by our prognostic model greater than 10.06 (3rd tertile),3 confirming that a large proportion of the population of IgM aMG at high risk of evolution is represented by patients with clear BM evidence of lymphoma. By evaluating IgM-MGUS apart, preliminary unpublished data from our series, re-defined retrospectively according to the new criteria,1 show that prognostic factors for evolution overlap not only those found in IgG/IgA MGUS, but also those found in IgM aMGs on a whole, suggesting that IgM MGUS could be considered as the first step of an indolent lymphoproliferative disease.

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