2. Girschikofsky M, Arico M, Castillo D, et al. Management of adult patients with Langerhans cell histiocytosis: recommendations from an expert panel on behalf of Euro-Histio-Net. Orphanet J Rare Dis. 2013;8:72.
3. Berres ML, Merad M, Allen CE. Progress in understanding the pathogenesis of Langerhans cell histiocytosis: back to Histiocytosis X? Br J Haematol. 2015;169:3-13.
4. Badalian-Very G, Vergilio JA, Degar BA, et al. Recurrent BRAF mutations in Langerhans cell histiocytosis. Blood. 2010;116:1919-23.
5. Lampert F. Langerhans cell histiocytosis. Historical perspectives. Hematol Oncol Clin North Am.;12:213-9.
6. Gadner H, Grois N, Pötschger U, et al. Improved outcome in multisystem Langerhans cell histiocytosis is associated with therapy intensification. Blood. 2008; 111:2556-62.
7. Gadner H, Minkov M, Grois N, et al. Therapy prolongation improves outcome in multisystem Langerhans cell histiocytosis. Blood. 2013;121:5006-14.
8. Maia RC, de Rezende LM, Robaina M, Apa A, Klumb CE. Langerhans cell histiocytosis: Differences and similarities in long-term outcome of paediatric and adult patients at a single institutional centre. Hematology. 2015;20:83-92.
9. Cantu MA, Lupo PJ, Bilgi M, Hicks MJ, Allen CE, McClain KL. Optimal therapy for adults with Langerhans cell histiocytosis bone lesions. PLoS One. 2012;7:e43257.
10. Derenzini E, Fina MP, Stefoni V, et al. MACOP-B regimen in the treatment of adult Langerhans cell histiocytosis: experience on seven patients. Ann Oncol. 2010;21:1173-8.

SMOLDERING MYELOMA: WALKING THROUGH RISK FACTORS AND TENTATIVE CLASSIFICATION SYSTEMS

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The history of Smoldering Myeloma (SMM) started when Kyle and Greipp described six myeloma patients in whom the percentage of plasma cells in the bone marrow (BMPC) and level of M protein were higher than those seen in monoclonal gammapathy of uncertain significance (MGUS), but without lytic bone lesions, anemia, or hypercalcemia and maintained this status without any specific therapy for more than five years [1]. At the same time, Alexanian *et al.* described 20 patients with low tumor mass disease who were asymptomatic, with an hemoglobin level greater than 10 g/dL, and with not more than 3 lytic bone lesions or compression fractures or recurrent infection. These patients were defined as having an indolent MM [2]. Since then, the two terms of *smoldering* and *indolent* myeloma were variably used in an undefined manner until 2003 when the IMWG defined SMM as BMPC ≥10% and/or M protein level ≥30 g/L and lack of organ damage (CRAB—hypercalcemia, renal failure, anemia, and bone lesions) [3]. SMM accounts for about 15% of all the patients with newly diagnosed MM [4] and the risk of progression to symptomatic MM is higher compared to MGUS patients (10% per year *versus* 1% per year, respectively) [5, 6]. Although it is a well clinically defined entity, SMM is a biologically heterogeneous disease that includes patients with a premalignant condition, as MGUS, and patients who will develop clinical symptoms and end-organ damage within the first two years from diagnosis. Therefore, after the diagnosis of SMM, it is necessary to evaluate the risk of progression to symptomatic disease. Unfortunately, at this time, there is no single clinical or molecular feature that can reliably distinguish patients with SMM who have only premalignant plasma cells from those with a clonal malignant disease. However, several studies (the majority retrospective) described different parameters that can predict the risk of progression to symptomatic MM. *The Level and the Type of Serum M Protein Concentration*: the Mayo Clinic study underlined the relevance of size and type of the serum M-protein as a significant risk factor for progression in MM. The median time to progression (TTP) in patients with a component ≥4g/dL was 18 months *vs* 75 months in patients with a lower serum M protein; the median TTP was significantly shorter in patients with IgA *versus* IgG M-protein (27 *vs* 75 months, respectively, p=0.004). *Percentage of Bone Marrow Plasma Cells*: Kyle reported that the median TTP was 117, 26 and 21 months for patients with BMPC <20%, 20-50% and >50% respectively (P<0.001). On this basis, Kyle *et al.* divided patients with SMM into three prognostic groups by the percentage of BMPC and level of serum M protein. Group 1was defined by BMPC ≥10% and serum M protein ≥3 g/dL with a median TTP of 2 years. Group 2 included patients with BMPC ≥10% but serum M protein <3 g/dL, with a TTP of 8 years. Group 3: serum M protein ≥3 g/dL but BMPC <10% and a TTP of 19 years. Similarly, Kastritis *et al.* reported a median TTP of 19 months for patients with BMPC ≥10% and serum M protein ≥3 g/dL *vs* 73 months for patients with BMPC ≥10% but serum M protein <3 g/dL [7]. A recent study indicates that the risk of progression is extremely high (approximately 90% at 2 years) when the BMPC is ≥60%, and these patients are now considered as MM. It should be underlined that the amount of BMPC is evaluated on either the bone marrow aspirate or biopsy examination, and in case of discrepancies the higher of the two values should be used [8]. *Immunoparesis:* Kyle *et al.* reported that in SMM, immunoparesis (suppression of one or more uninvolved immunoglobulins) was a significant risk factor for progression. The median TTP was 159 months for patients without immunoparesis, 89 months in those with a reduction of only one isotype, and 32 months in patients with reduction in two isotypes of uninvolved immunoglobulins. The Spanish group reported similar findings, showing a not reached median of TTP in patients with normal immunoglobulins *versus* 31 months in those patients carrying one or more reduced uninvolved immunoglobulins [9]. *Immunophenotyping:* The same Spanish study [9] found that 60% of patients with SMM have an aberrant immunophenotype (defined by the absence of CD19 and/or CD45 expression, decreased expression of CD38, and overexpression of CD56) similar to MM, where >95% of PCs are aberrant and only <5% of the detected PCs are normal. The risk of progression in patients with aberrant phenotype was significantly higher compared to those who had a lower rate of aberrancy with a median TTP of 34 months *vs* not reached respectively. On these basis, Pèrez-Persona *et al.* defined a risk of progression to active MM at 5 years of 4%, 46%, and 72%, for patients with none, 1, or 2 risk factors respectively (aPCs/BMPC ≥95% and immunoparesis). *Serum-Free Light-Chain Ratio:* Dispenzieri and colleagues studied 273 patients with SMM and demonstrated that an involved/uninvolved free-lite chain (FLC) ratio of ≥8 was a significant risk factor for progression. Median TTP was 30 months in patients with an involved/uninvolved FLC ratio of ≥8 *vs* 110 months for patients with FLC ratio less than 8. The 2 years risk of progression was approximately 40% in patients with an involved/uninvolved FLC ratio of ≥8. Therefore, the FLC ratio was included in a risk-stratification model based on the following risk factors: BMPC ≥10%; serum M protein ≥3 g/dL; and FLC ratio >8. The 5-year progression rates were 25%, 51%, and 76%, in the presence of one, two, or three risk factors respectively [10]. When the involved/uninvolved FLC ratio rises to ≥100, the median TTP is only 15 months, and the 2 year risk of progression approaches 80%. Therefore, this can be considered as a biomarker of early progression and such patients are now considered as MM [11]. *Circulating Peripheral Blood Plasma Cells (PBPC).* Bianchi *et al.* have shown that patients with high circulating PBPC have a higher risk to progress to active disease within 2 years compared with patients without high circulating PC (71 *versus* 25%, respectively, P=0.001). However, the detection of circulating PC is still not standardized and difficult to reproduce [12]. *Genetic Abnormalities* Neben *et al.* described the impact of chromosomal aberrations in patients with SMM and found that the presence of del (17p13), t(4;14), +1q21 and hyperdiploidy predicted shorter TTP [13]. The same conclusion was reached by Rajkumar *et al.*, who reported that a median TTP was not reached in patients without detectable abnormalities (low-risk), while patients with t(4;14) and/or del(17p) were defined as high risk SMM with a significantly shorter median TTP (24 months) compared with patients with trisomies (intermediate-risk), or other cytogenetic abnormalities including t(11;14) (standard-risk) [14]. Based on a cohort of 331 patients with MGUS and SMM, Dhodapkar and colleagues identified a gene expression profiling (GEP70-gene signature) signature as an independent predictor of the risk of progression to MM [15]. Very recently, a study conducted at the University of Arkansas has identified four genes that can predict high risk of progression from smoldering to symptomatic MM [16]. *Imaging:* Bone disease detectable by magnetic resonance imaging (MRI) are able to predict TTP. Moulopoulos *et al.* first demonstrated that in patients with asymptomatic myeloma TTP was 16 months for patients with abnormal MRI *versus* 43 months for those with normal MRI. In addition, median TTP was shorter in patients with focal lesions (6 months) compared with those who had diffuse (16 months) or variegated pattern (22 months) [17]. Kastritis *et al.* confirmed that an abnormal marrow signal of MRI of the spine in a patient with SMM is associated with a significant factor for progression to symptomatic myeloma (median 15 months). Similar findings have been found in the Dhodapkar's study. In a recent study of 149 patients with SMM, using whole-body MRI, Hillengass and al. detected focal lesions in 28% of patients and they found that 15% of patients had more than one focal lesion on wb-MRI imaging.