# Extramedullary involvement in multiple myeloma

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Multiple myeloma (MM) is characterized by a proliferation of malignant plasma cells with strong dependence on the bone marrow (BM) microenvironment. In fact, MM is considered the prototype of cancer in which the malignant cells interact with the microenvironment.[1,2] It has recently been shown that virtually all cases of MM are preceded by a monoclonal gammopathy of undetermined significance (MGUS), an asymptomatic condition exclusively confined to the bone marrow.[3,4] When MGUS evolves to MM, both the proportion of bone marrow plasma cells (BMPCs) and the size of the M-protein, increase. However, the disease typically remains confined to the BM and the skeleton. Clinical manifestations are related to tissue and/or organ impairment, resulting in the so-called CRAB acronym: elevated serum calcium, renal function impairment, anemia and/or bone involvement.[5] Although a number of patients with MM develop extramedullary soft-tissue plasmacytomas, that can constitute the most prominent clinical feature,[2,6,7] it is surprising that so little data on the incidence and biology of extramedullary disease (EMD) is available.

The mechanisms of extramedullary spread in MM are poorly understood. Potential mechanisms are decreased expression of adhesion molecules, particularly VLA-4 and CD-44, as well as a loss of CD56, which can facilitate disease dissemination by impairing the adherence of myeloma cells to the BM endothelium, downregulation of P-selectin, low expression of chemokine receptors, such as CCR1, CCR2, or downregulation of CXCR4 and its ligand SDF-1alpha, that are critically linked to the BM homing of myeloma cells.[1,2] Finally, downregulation of tetraspanins expression or increased angiogenesis have also been considered as possible mechanisms in the extramedullary dissemination in MM.[1,2]

Soft-tissue plasmacytomas in MM can have two different origins: 1) direct extension from skeletal tumors when they disrupt the cortical bone; or 2) hematogeneous metastatic spread.[2] However, only observational data are available on EMD in MM and no control studies have been published. The reported incidence of EMD in newly diagnosed MM ranges from 7% to 18%.[6-9] In addition, 6% to 20% of patients develop EMD later in the course of the disease.[8,9] Interestingly, in one of the studies, up to 45% of patients with extramedullary involvement at diagnosis developed EMD at the time of relapse.[6] It has been suggested that patients undergoing allogeneic transplantation, particularly those receiving dose-reduced intensity conditioning, have a higher incidence of EMD at relapse.[2] However, we must consider that allogeneic transplantation is usually offered to very high-risk patients, while autologous transplantation (ASCT) is an upfront standard of care for all younger patients with MM. Consequently, the real incidence of EMD after allogeneic *versus* ASCT should be studied in comparable groups of patients. It has also been suggested that extramedullary relapse is more frequent in patients exposed to novel agents.[10] However, Varettoni *et al.*[6] showed that previous exposure to bortezomid, thalidomide or lenalidomide was not associated to a higher risk of extramedullary relapse.

As far as the development of EMD is concerned, local growth of soft-tissue masses arising from skeletal lesions is the most frequent mechanism, while the second most common is the hematogenous spread which can involve any tissue or organ, the most frequent being skin, liver, kidney or central nervous system.[2] Interestingly, plasmacytomas can be triggered by invasive surgical procedures performed during the course of the disease.[2,11] Therefore, they can arise from laparothomy scars or catheter insertions, and can precede systemic relapses.[2] Several imaging techniques can help to assess EMD in MM and a consensus statement has been published by the International Myeloma Working Group.[12] Positron emission tomography (PET)/computed tomography (CT) imaging may be very useful and a PET/CT should be performed in all patients in whom extramedullary involvement is suspected.

Plasma cells from EMD usually have a more immature morphology, particularly in the metastatic spread.[2] There is very limited information on the biology of plasma cells at the extramedullary sites, especially in comparison with the characteristics of the malignant BMPCs. In a recent ASCT series from Spain, 18% of patients had extramedullary involvement and the proportion of patients with high-risk cytogenetics was similar in patients with and without extramedullary involvement (24% *vs.* 21%, respectively).[13] Thus, the genetic abnormalities of BM myeloma cells determined by *in situ* hybridization studies are not associated with extramedullary spread.

Two studies[6,7] found that the presence of EMD at diagnosis was associated with a significantly shorter survival in patients treated with conventional chemotherapy. However, in both studies, patients who received ASCT had a similar outcome, irrespective of the presence or absence of extramedullary involvement, indicating that high-dose therapy can overcome the negative impact of EMD. In contrast, in a recent ASCT trial from PETHEMA, there were no significant differences in progression-free survival (PFS) among patients with and without extramedullary plasmacytomas, but the overall survival (OS) was significantly shorter in patients with extramedullary disease. We and others have reported the lack of efficacy of thalidomide on EMP, the dissociation between medullary and extramedullary response, as well as progression of EMD despite good medullary and serological response while undergoing thalidomide treatment.[14,15] The efficacy of bortezomib on EMD in MM has also been reported.[16] There are no convincing reports on the possible efficacy of lenalidomide in treating extramedullary disease in MM.

In this issue of Haematologica, Usmani *et al.*[17] report their experience on extramedullary disease involvement in a large series of 1,965 patients with MM treated at the Myeloma Institute for Research and Therapy at the University of Arkansas, USA. These patients had baseline PET scans to document EMD both at diagnosis and at the time of disease progression. The authors defined EMD as the presence of soft-tissue masses resulting from hematogenous spread and apparently did not include the presence of soft-tissue masses arising from bone lesions. The frequency of EMD at diagnosis was

3.4% (66 of 1,965) and around 5% at the time of relapse or progression. The most frequent location at diagnosis was skin while at progression the most striking feature was liver involvement. The presence of EMD was associated with a significantly shorter progression-free survival and overall survival. However, most interestingly, the authors performed molecular/GEP studies on bone marrow plasma cells and extramedullary disease was associated with high-risk features including both the 70-gene and 80-gene risk models, MF molecular subgroup, representing *MAF* and/or *MAFB* gene overexpression, and PR molecular subgroup, representing high proliferative disease. The cumulative incidence of EMD was significantly increased in patients who had GEP-defined high-risk at baseline and baseline cytogenetic abnormalities. Finally, centrosome amplification was associated with higher incidence of EM involvement. The authors conclude that EMD is more prevalent in genomically defined high-risk multiple myeloma and that GEP studies may help to identify EMD-unique genes that might be amenable to the development of targeted agents.

All of this shows that many important questions on extramedullary involvement in MM remain unanswered. Is it: more frequent in the era of novel agents? Is there a different pattern of extramedullary involvement in patients treated with novel agents? Is it more frequent after allogeneic as opposed to autologous transplantation? Would patients with extramedullary disease be more efficiently treated with lymphoma-like *versus* typical 'myeloma' regimens? Some key questions for future research are: i) could genomic studies identify MM with extramedullary potential? ii) what are the mechanisms involved in the hematogenous myeloma spread? iii) do these mechanisms differ from those involved in local extension from bone marrow? and iv) which are the mechanisms of myeloma cell growth and cell survival at extramedullary sites?

Once the extramedullary disease is already established, crucial issues are the molecular genetic status of the malignant clone, including gene expression profiling and epigenetics, and particularly drug sensitivity and resistance. Experimental models have been developed from cells obtained from plasmacytomas of patients with MM who also develop extramedullary disease, and each tumor reproduces the patient pattern of drug sensitivity and resistance.[18-20] These experimental models can provide a unique opportunity for physiopathological and molecular studies, as well as for new drug development that can improve the poor outcome of our patients with multiple myeloma and extramedullary involvement.

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