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Editorial
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The Existing Gap in Addressing Extramedullary Disease in Multiple Myeloma

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Editorial

Extramedullary Multiple Myeloma Disease (EMD) refers to the dissemination and proliferation of malignant plasma cells in tissues other than the bone marrow [1,2]. EMD frequently manifests in soft tissues, the skin, and the liver. But it's essential to point out that any other part of the body is susceptible and can be affected, including the central nervous system [3]. However, there has been a lack of consistency in the literature on the description of EMD. The term has often been used to describe soft tissue masses that arise from bone lesions and expand in close proximity [4]. Therefore, the primary concern at present is the lack of a clear and precise definition of EMD, which complicates both our understanding of biology and the management of EMD itself.

EMD can be detected either at the time of diagnosis or as the disease progresses. In both disease settings, around 30% of patients develop EMD. However, this figure may be an underestimate since around two-thirds of the individuals evaluated in an autopsy series had evidence of plasma cell infiltration at various sites outside the marrow [5]. There has been a rise in the occurrence of EMD, which can be attributed to an improvement in overall survival rates and/or advancements in myeloma imaging techniques [6,7]. A recent study conducted on patients with triple-class exposed relapsed or refractory MM who were treated with innovative immunotherapies revealed rates of about 50%. This indicates that the real size of EMD remains mostly unknown [8].

Furthermore, EMD is a significant prognostic factor linked to inferior survival outcomes. The overall survival was less than 18 months (7-16 months) in patients with secondary EMD and this continues to be poor even for patients who received BCMA-directed CAR-T cells [9].

Managing extramedullary disease can be quite challenging, especially in patients who have already undergone extensive treatment. Finding the right combination of treatments to reduce the impact of this disease is crucial.

So far, intensive chemotherapy-based treatments, including PACE (cisplatin, doxorubicin, cyclophosphamide, and etoposide), have yielded favorable results for certain patients. However, the overall survival rate and prognosis continue to be dismal. In palliative care, radiotherapy has been utilized. Large prospective trials are required to advance the development of treatment strategies for EMD [10].

Pathogenetically, EMD may result from the hematogenous dissemination and growth of myeloma clones that get independence from the bone marrow microenvironment.

This hypothesis may have a dose of truth. However, it is still unclear what truly triggers extramedullary disease. Nearly all patients with myeloma relapse and develop resistance to treatment. The genomic makeup of the malignant clones largely determines who, when, and how someone relapses [11].

Still, the duration and intensity of therapy have been connected to secondary EMD because they can cause selective pressure, clonal evolution, and/or DNA damage during therapy. More than two prior lines of therapy and the utilization of autologous hematopoietic stem cell transplantation are two recognized risk factors [12]. Additionally, high-risk cytogenetics such as t(4;14), t(14;16), del(17p), and gain(1q), as well as a characteristic gene expression profile at diagnosis, namely the EMD-like phenotype, are molecular drivers of extramedullary evolution [13,14].

Understanding the transitions of plasma cells from bone marrow to extramedullary sites is essential for preventing and treating EMD. The development of such a disease can be accelerated through adhesion molecules and signaling pathway modifications. Myeloma cells detached from the

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supportive bone marrow milieu due to low expression of chemokine receptors, adhesion molecules, and integrins, which reduced their adherence to stromal cells and the extracellular matrix [1].

High expression of heparanase and upregulation of CXCR4 by growth factors and hypoxia facilitate plasma cells to migrate to different areas [15,16].

Activation of signaling pathways, such as the NF-kappa B and RAS/MAPK pathways, promotes growth and survival even in the absence of bone marrow stroma support and contributes to the aggressive nature of EMD [17,18].

Managing patients with EMD has significant challenges for several reasons, including a lack of data on effective treatments and differentiating between extramedullary disease subtypes [19].

It's important to have a clear definition of the different types of EMD when reporting and interpreting study results. Is it extraosseous or paraskeletal EMD? This differentiation will be crucial regarding at least response and impact on survival, since patients with extraosseous myeloma typically have a median survival of about 1.3 years from disease onset [20].

Similarly, this concept also applies to the rare cases of EMD that involve the Central Nervous System (CNS). Bone lesions in the cranial vault, skull base, or paranasal sinuses frequently cause extramedullary masses in the CNS. This type of involvement is linked to a longer overall survival rate than primary leptomeningeal involvement [21]. Patients with CNS disease have a diminished response to the various treatment options available. While there is emerging data suggesting that some novel therapies, such as pomalidomide or Selinexor, may be able to cross the blood-brain barrier, there is still a lack of substantial studies to support this [22].

To prevent the spread of myeloma to extramedullary sites, it is important to target the surrounding microenvironment in addition to plasma cells. Given the ongoing difficulties presented with the management of EMD, it may be important for these lesions to be biopsied [11]. This will allow for thorough genetic profiling, enabling the identification of potential therapeutic vulnerabilities. This approach has the potential to facilitate the development of targeted and effective treatment strategies for this aggressive type of myeloma. By examining the genetic makeup of EMD, new treatment options can be identified that may enhance patient outcomes, especially in situations where conventional therapies have proven ineffective. By investing in such research efforts, we can make meaningful progress towards the understanding and treatment of EMD.

Moreover, the biology of extramedullary myeloma might exhibit variations based on the specific site of involvement, since each tissue has a distinct microenvironment.

Finally, it is crucial to acknowledge that myeloma has the potential to recur even during a decade-long period of remission. This implies that potential therapeutic interventions aimed at eradicating this malignancy necessitate consideration of the diverse cellular composition inside the tumor as well as their dormant state.

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