Original article - Swiss J. Rad. Nucl. Med. (2024) 6: 11-15; DOI: 10.59667/sjoranm.v6i1.14

Multiple Myeloma - Extramedullary Manifestations

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Swiss Journal of Radiology and Nuclear Medicine - www.sjoranm.com - SJORANM GmbH - CH-3072 Ostermundigen bei Bern - Switzerland

Abstract

The second most common hematologic malignancy is the clonal proliferation of neoplastic plasma cells within the bone marrow. There is the presence of monoclonal immunoglobulins in the serum and/or urine. This results in anemia, myelosuppression, bone destruction, and clinical consequences of paraproteinemia on kidney function and other organ systems. The disease manifests through the acronym CRAB (hypercalcemia, renal impairment, anemia, and bone lesions). Less frequent manifestations of multiple myeloma are of extramedullary localizations. Myeloma cells can become independent of the bone marrow microenvironment, circulate freely in the blood, and infiltrate organs. This results in a high-risk state characterized by increased proliferation, evasion of apoptosis, and treatment resistance. It can affect any area of tissue. Most commonly it involves the pleura, lymph nodes, chest wall, liver, skin/soft tissue, lungs, CNS, genitourinary system, breast and pancreas. In patients with confirmed multiple myeloma, the diagnosis of extramedullary involvement is typically established by the presence of pathological soft tissue masses using radiological methods such as computed tomography (CT) scan, positron emission tomography/CT (PET/CT), magnetic resonance imaging (MRI), or ultrasound, along with biopsy or physical examination. The molecular mechanisms underlying the development of extramedullary multiple myeloma (EMM) have not been fully defined. Various cytogenetic abnormalities are observed, and some studies have generated genomic sequencing profiles that distinguish EMM from classic multiple myeloma. While plasma cell leukemia (PCL) and central nervous system (CNS) EMM indicate a poor prognosis, outcomes for other manifestations can be highly heterogeneous. Sensitive imaging modalities including PET/CT and MRI (Fig.1) are integral components of diagnosis and response assessment. Patients with extramedullary multiple myeloma (EMM) have a clear survival disadvantage.

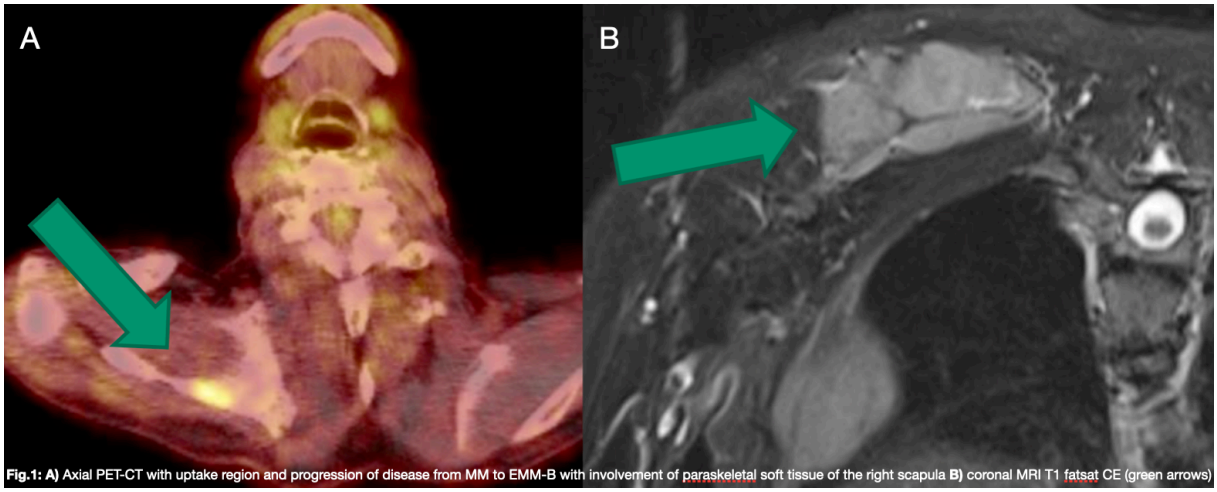

Fig.1: A) Axial PET-CT with uptake region and progression of disease from MM to EMM-B with involvement of paraskeletal soft tissue of the right scapula **B)** coronal MRI T1 fatsat CE (green arrows)

Keywords: *multiple myeloma, extramedullary manifestations, testicular blood barrier.*

[1]Corresponding author: Keivan Daneshvar - received: 02.03.2024 - published: 31.03.2024

Introduction

MM (Fig.4) is a malignant plasma cell dyscrasia and the second most common hematologic malignancy after (1) non-Hodgkin's lymphoma. While plasma cell proliferation generally occurs within the bone marrow, extramedullary involvement (defined as a soft tissue tumor arising

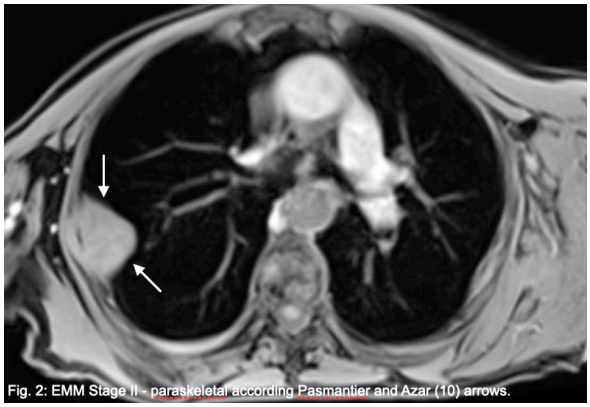

Fig. 2: EMM Stage II - paraskeletal according Pasmantier and Azar (10) arrows.

from a bony lesion or distant EMD outside of both marrow and bone) can also be (Fig. 2 & 3) observed. The reported incidence of EMD of

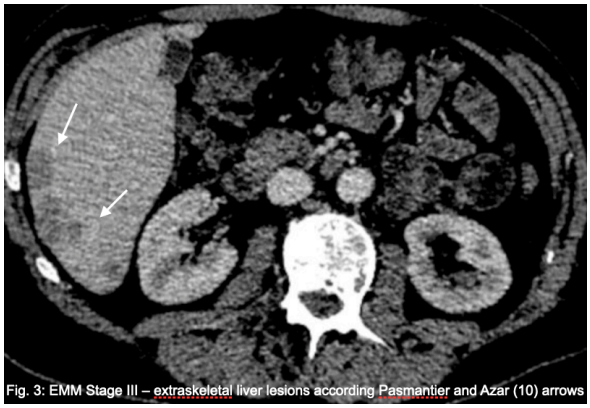

Fig. 3: EMM Stage III – extraskeletal liver lesions according Pasmantier and Azar (10) arrows

7% is increasing, likely due to more sensitive imaging technologies and the prolongation of survival in MM through the use of highly effective new medications as well as ASCT.

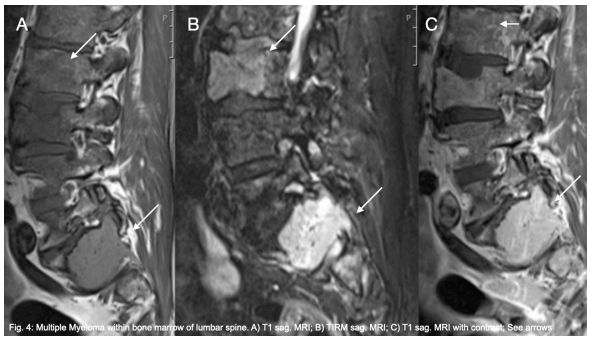

Fig. 4: Multiple Myeloma within bone marrow of lumbar spine. A) T1 sag. MRI; B) T1RM sag. MRI; C) T1 sag. MRI with contrast. See arrows

Autopsy reports show a higher than expected incidence, with 63.5% of cases described as extrabone-involved in one series. Extraosseous diseases (2) occur more frequently in younger, male patients; non-secretory/IgD/K light chain subtypes; advanced stage MM; extensive bone involvement; and (Tab. 1) plasma cell leukemia. The second most common affected sites include the aerodigestive tract, soft tissues, liver, spleen, (Fig. 4-11) lymph nodes, testes, kidneys, pleura, and peritoneum.

Diagnostic Imaging of EMM:

Traditionally, the diagnosis and treatment of MM have been triggered by clear end-organ damage. However, owing to recently introduced treatment options that can extend patient sur-

Extramedullary Multiple Myeloma (EMM)

- There is no uniform definition of EMM.
- A three stage anatomic classification was first proposed in 1969 by Pasmantier and Azar (10):
  - Stage I intraskeletal
  - Stage II paraskeletal (EMM-Bone)
  - Stage III extraskeletal with spread to distant sites (EMM-Soft-tissue)
- EMM-Bone cells are partially dependent on the bone marrow microenviron-ment and their morphology mimics marrow-localised cells. EMM-Soft-tissue cells on the other hand often exhibit immature, plasmablastic morphology.
- Some authors restrict the definition of EMM solely to soft tissue masses in extraskeletal locations.

Tab. 1: A three stage anatomic classification was first proposed in 1969 by Pasmantier and Azar (10).

vival and the increasing recognition of biomarkers that can be used to identify patients at high risk of progression to active disease, the diagnostic criteria have been revised. Bone diseases are among the (10) most prominent features of MM, and imaging plays an important role in diagnosis and follow-up, with each whole-body imaging modality having different indications in different disease situations. Skeletal radiography has been the standard imaging procedure (9) in recent decades but should no longer be used unless it is the only option. Whole-body low-dose CT is a reasonable and cost-effective initial imaging approach. Whole-body MRI is the most sensitive technique for detecting bone involve-ment and assessing painful complications. PET/CT is (Fig.5) the best tool for evaluating treatment response. The importance of radiologists has increased in this scenario. Therefore, it is essential for radiologists to be familiar with the updated diagnostic criteria for MM, the indications and limitations of each imaging option, and recommendations for follow-up in order to adequately support hematologists and improve the care of patients with MM.

Testicular involvement in the course of multiple myeloma is rare (3). The hematological malignant cells may remain in the testes even after chemotherapy (Fig. 12) because of the testicular blood barrier. Therefore, when reporting a

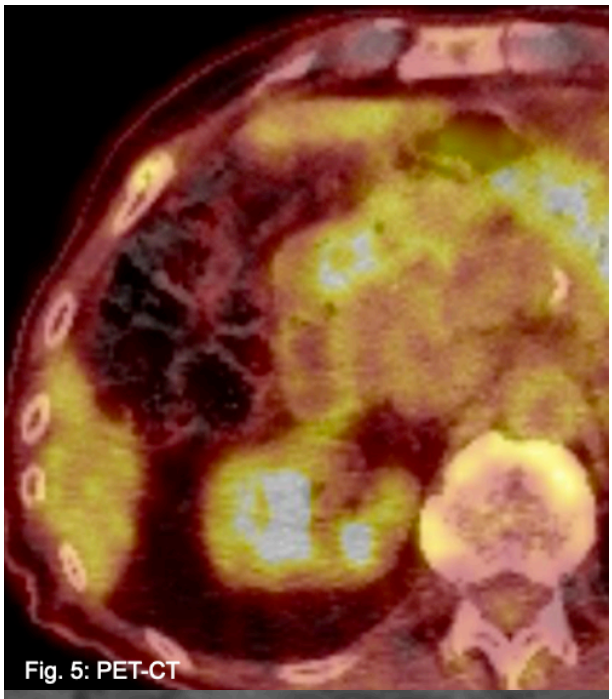
Fig. 5: PET-CT

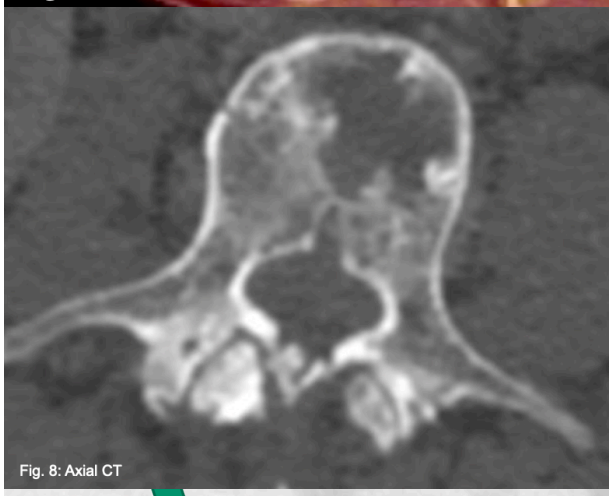
Fig. 8: Axial CT

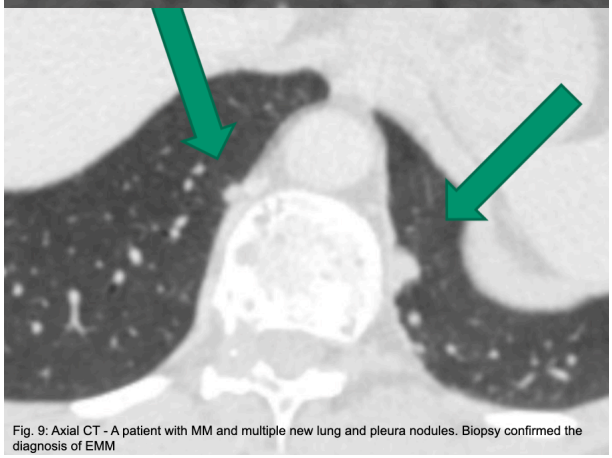
Fig. 9: Axial CT - A patient with MM and multiple new lung and pleura nodules. Biopsy confirmed the diagnosis of EMM

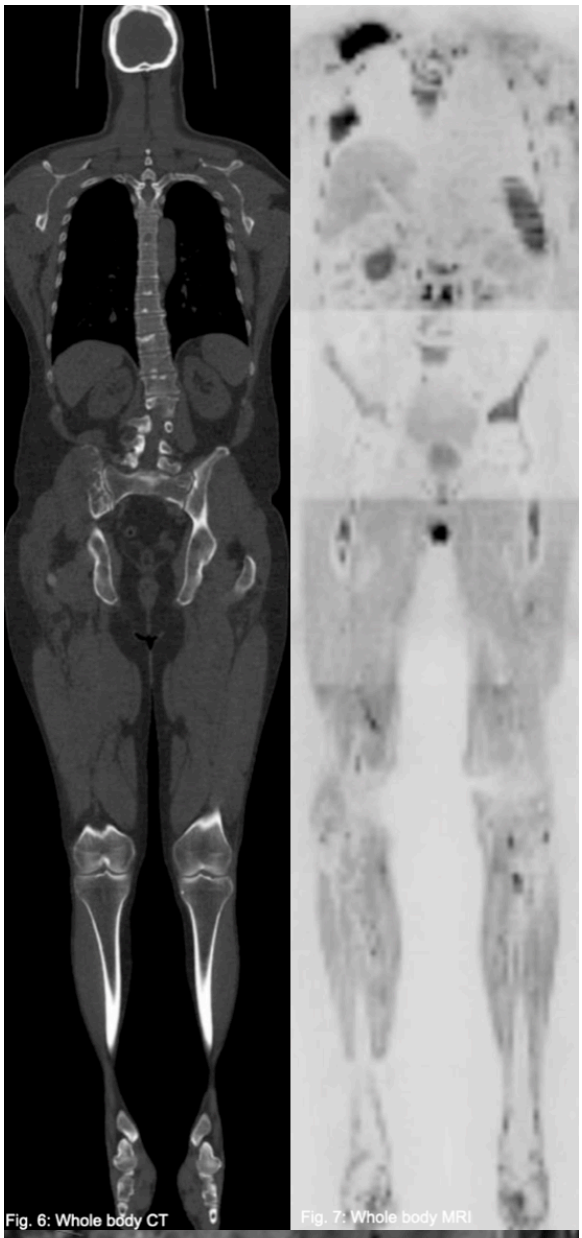
Fig. 6: Whole body CT

Fig. 7: Whole body MRI

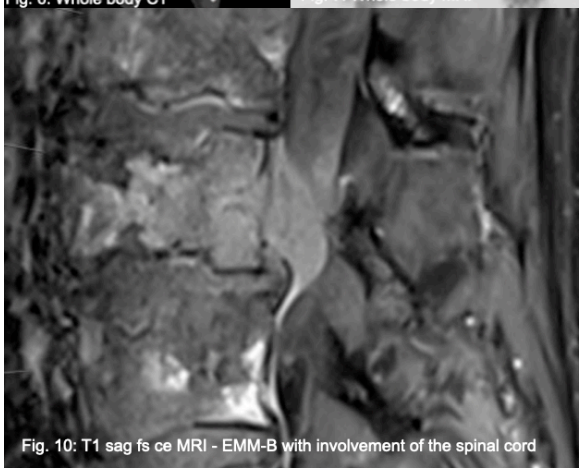
Fig. 10: T1 sag fs ce MRI - EMM-B with involvement of the spinal cord

whole-body CT or MRI, attention should be paid to nodular tumor components or hydrocele. The imaging method of choice for evaluating testicular involvement is ultrasonography.

The (4) greatest advantage of PET/CT lies in its contribution to post-therapeutic evaluation, enabling differentiation between metabolically active and inactive lesions. Performing a baseline scan can also be helpful to facilitate comparison of pre- and post-therapeutic imaging findings. PET/CT also provides prognostic

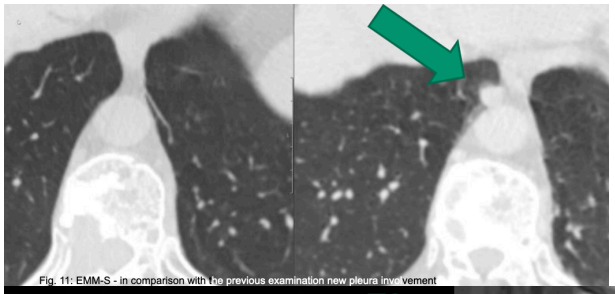

Fig. 11: EMM-S - in comparison with the previous examination new pleura involvement

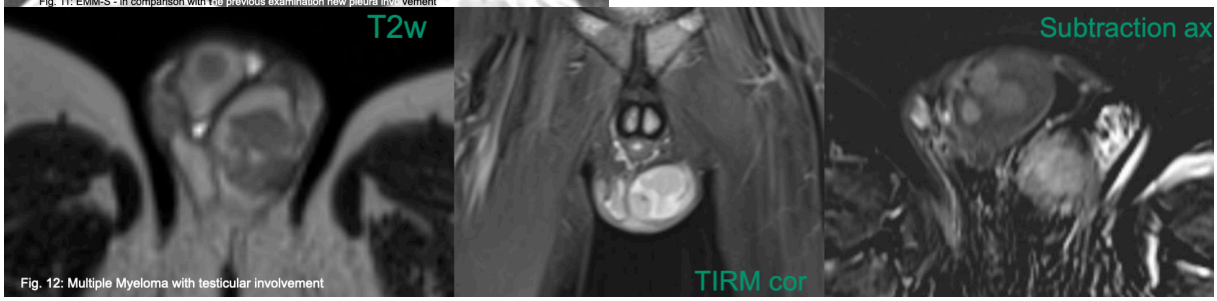

Fig. 12: Multiple Myeloma with testicular involvement

information about patients with MM. Generally, more than three focal lesions, extramedullary manifestations, and a maximum standardized uptake value (SUV) greater than 4.2 are associated with a poor prognosis.

Discussion:

Primary extramedullary myeloma (EMM) typically presents at the time of initial diagnosis, whereas secondary EMM occurs during disease relapse. Plasma cell leukemia (PCL) represents the most aggressive form of EMM. In some cases, patients may exhibit involvement of multiple extramedullary sites without concurrent bone marrow involvement. Diagnosis of EMM is established through the detection of soft tissue masses on imaging studies and/or biopsy confirmation (8).

Assessing the therapeutic response of MM using MRI involves identifying changes in the pattern of bone marrow involvement, such as transitioning from a seemingly normal or "salt-and-pepper" pattern to a diffuse or focal pattern, from a focal to diffuse pattern, or exhibiting an increase in the number and/or size of (7) bone lesions, indicative of radiological disease progression. Conversely, complete disappearance of lesions and transitioning from a diffuse pattern to seemingly normal bone marrow signify complete remission. Radiological recurrence occurs when lesions reappear in the bone marrow that had become apparently normal following treatment.

These classic MRI findings typically do not raise doubts during imaging assessment. However, when there is stability in the number and size of lesions and the pattern of bone marrow involvement, these findings should not be interpreted as indicating stable disease, as these lesions may be metabolically inactive.

Other signs of treatment response, which would be classified as partial radiological responses in other neoplasms, including high signal intensity around or within the nodule on T1-weighted MRI (i.e., fat repopulation), progressive disappearance of the lesion, absence or reduced enhancement on gadolinium-enhanced MRI, and transitioning from a focal or diffuse pattern to a "salt-and-pepper" pattern, may also constitute a complete radiological response, as these lesions could also be metabolically inactive.

Early after treatment, chemotherapy and radiation therapy induce cellular necrosis with edema and an intense inflammatory response, leading to lysis of cell membranes and an increase in extracellular water content, facilitating water molecule movement, resulting in increased signal intensity on ADC mapping, T2-weighted MRI, and DW imaging (i.e., T2 shine through). Subsequently, there is a phase of yellow bone marrow cell repopulation with an increase in signal intensity on T1-weighted MRI, a decrease in ADC, and a decrease in signal intensity on T2-weighted MRI. Several weeks after treatment, recovery of red bone marrow cells occurs, leading to a decrease in signal intensity on T1-weighted MRI.
Recent studies (5, 6) involving a small number of patients utilized DW imaging to evaluate MM treatment response, revealing that the increase in ADC, both qualitatively and quantitatively, is significant with a good response to treatment. Additionally, these findings demonstrate good reproducibility and agreement with laboratory response markers used in clinical practice. It was demonstrated that ADC values after induction therapy were significantly higher in deep responders than in non-deep responders, with percentage ADC increases of 46.96% and 78.0%, respectively, and specificities of 81.4% and 90.7%, respectively, (9) in discriminating deep response to induction therapy. Regarding the evaluation of treatment response using dynamic contrast-enhanced MRI, there is a sig-

nificant decrease in the vascularity of the bone marrow after effective therapy.
On CT scans and conventional film radiographs, modifications indicating treatment response often occur later or may not appear at all, even in patients who have achieved complete remission. Furthermore, due to the significant reduction in osteoblastic activity, many lesions fail to heal, potentially resulting in false-positive results. Consequently, these methods are not ideal for evaluating treatment response in patients with MM.

Conclusion:

Extramedullary myeloma (EMM) can manifest in various tissue sites. It predominantly affects the pleura, lymph nodes, chest wall, liver, skin/soft tissue, lungs, central nervous system (CNS), genitourinary system, breast, and pancreas. Testicular involvement in the context of multiple myeloma is an uncommon occurrence (Fig. 12). Hematological malignant cells may persist within the testes post-chemotherapy due to the presence of the testicular blood barrier. When interpreting whole-body CT or MRI scans, particular attention should be given to nodular tumor components or the presence of a hydrocele. Ultrasonography is the preferred (6, 7) imaging modality for evaluating testicular involvement.

Conflict of interest:

The authors declare that there were no conflicts of interest within the meaning of the recommendations of the International Committee of Medical Journal Editors when the article was written.

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