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HEMATOLOGICAL NEOPLASMS AND SPINE INVOLVEMENT FROM DIAGNOSIS TO TREATMENT: A LITERATURE REVIEW

NEOPLASIAS HEMATOLÓGICAS E O ENVOLVIMENTO DA COLUNA VERTEBRAL DO DIAGNÓSTICO AO TRATAMENTO: UMA REVISÃO DE LITERATURA

NEOPLASIAS HEMATOLÓGICAS Y COMPROMISO DE LA COLUMNA VERTEBRAL DEL DIAGNÓSTICO AL TRATAMIENTO: UNA REVISIÓN DE LA LITERATURA

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ABSTRACT

Hematologic malignancies are diseases that originate in the lymphohematopoietic system and are typically found in the blood, bone marrow, lymph nodes, and secondary lymphoid organs. However, certain conditions such as multiple myeloma, frequently involve the skeleton, with the spine being the most common site of bone disease. In a smaller proportion of cases, including lymphomas, acute leukemias, and myeloproliferative disorders, tumor-infiltrating cells invade spinal tissues, making histopathologic evaluation essential for establishing the diagnosis and guiding targeted therapy. When pain and neurological symptoms are present, advanced imaging modalities play a pivotal role in elucidating the pathophysiologic mechanisms of spinal involvement and informing the appropriate supportive management. Such care often requires a multidisciplinary team. In this review, we summarize current practice recommendations on the diagnostic work-up, differential diagnosis, imaging approaches, and evidence of management strategies for neoplasms affecting the spine, with practical case examples. ***Level of Evidence V; Narrative Review.***

Keywords: Spine; Hematologic Malignancies; Bone Tumors; Multiple Myeloma; Spinal Cord Compression.

RESUMO

Neoplasias hematológicas são doenças que se originam no sistema linfo-hematopoiético e são tipicamente encontradas no sangue, na medula óssea, nos linfonodos e órgãos linfoides secundários. No entanto, o mieloma múltiplo frequentemente envolve o esqueleto, sendo a coluna vertebral o local mais comum de acometimento ósseo. Apesar de com menor frequência, em linfomas, leucemias agudas e doenças mieloproliferativas, células tumorais também podem invadir os tecidos da coluna, sendo uma avaliação histopatológica essencial para determinar o diagnóstico e a terapia específica. Na presença de acometimento da coluna vertebral associado a dor e sintomas neurológicos, diferentes técnicas avançadas de imagem desempenham um papel fundamental na elucidação dos mecanismos fisiopatológicos do acometimento vertebral e na definição do manejo de suporte adequado. Esse cuidado frequentemente requer uma equipe multidisciplinar. Nesta revisão, são apresentadas as atuais recomendações práticas sobre investigação diagnóstica, diagnóstico diferencial, abordagens de imagem e estratégias de manejo baseadas em evidências para neoplasias que afetam a coluna, com casos clínicos. ***Nível de Evidência V; Revisão Narrativa.***

Descritores: *Coluna; Malignidades Hematológicas; Tumores Ósseos; Mieloma Múltiplo; Compressão da Medula Espinal.*

RESUMEN

Las neoplasias hematológicas son enfermedades que se originan en el sistema linfohematopoyético y se encuentran típicamente en la sangre, la médula ósea, los ganglios linfáticos y los órganos linfoides secundarios. Sin embargo, ciertas condiciones como el mieloma múltiple afectan con frecuencia el esqueleto, siendo la columna vertebral el sitio más común de compromiso óseo. En una proporción menor de casos, que incluyen linfomas, leucemias agudas y trastornos mieloproliferativos, las células tumorales infiltrantes invaden los tejidos de la columna, lo que hace que la evaluación histopatológica sea esencial para establecer el diagnóstico y orientar la terapia dirigida. Cuando hay dolor y síntomas neurológicos, las modalidades avanzadas de imagen se desempeñan un papel crucial en la elucidación de los mecanismos fisiopatológicos del compromiso vertebral y en la determinación del manejo de soporte adecuado. Este cuidado a menudo requiere un equipo multidisciplinario. En esta revisión, resumimos las recomendaciones actuales sobre el abordaje diagnóstico, el diagnóstico diferencial, las técnicas de imagen y las estrategias de manejo para las neoplasias que afectan la columna vertebral basadas en evidencia, con ejemplos prácticos de casos clínicos. ***Nivel de Evidencia V; Revisión Narrativa.***

Descriptores: *Columna; Neoplasias Malignas Hematológicas; Tumores Óseos; Mieloma Múltiple; Compresión de la Médula Espinal.*

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INTRODUCTION

Hematologic neoplasms, such as multiple myeloma, lymphomas, leukemias, and myeloproliferative diseases, may affect the spinal column through various mechanisms, posing a diagnostic and therapeutic challenge for the specialist. Bone malignancies are more frequently secondary to metastatic solid tumors—such as those of the lung, breast, prostate, kidney, and thyroid—which together account for approximately 80% of bone metastases, with the spine being the most affected site.[1] In the setting of hematologic neoplasms, plasma cell neoplasms are the most prevalent when there is vertebral involvement, while lymphomas, leukemias, and other causes are less frequent. In general, these lesions involve the epidural space, affecting the bone or adjacent soft tissue, and differ from lesions that involve nerves and meninges, as the latter are typically intradural.[2] Initial clinical manifestations may mimic other more prevalent conditions, hindering early diagnosis. The most common symptoms include mechanical axial pain, radicular pain, pathological fractures, and, in more severe cases, spinal cord compression syndrome (SCCS), which may require urgent surgical intervention to preserve neurological function.[1,2] Due to these symptoms, patients with hematologic neoplasms involving the spinal column frequently first seek out a spine specialist,[1] and diagnostic delay, in addition to morbidity from neurological injury, can lead to progression of the neoplastic process.[2] Imaging methods, such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography-computed tomography (PET-CT), aid both in diagnostic assessment and therapeutic planning.[2,3] However, despite advances in these techniques, the differential diagnosis between vertebral lesions of hematologic origin and other etiologies remains challenging, considering the difficulty of establishing a diagnosis based solely on clinical presentation and radiological findings. In most cases, surgical intervention and histopathological analysis are required.[2] The treatment of these lesions typically necessitates a multimodal approach combining surgery, radiotherapy, and chemotherapy, aiming not only at treating the local complication but also the underlying disease.[1] The objective of the present article is a comprehensive review of the main hematologic diseases that may affect the spinal column, with emphasis on their epidemiological, clinical, radiological, and therapeutical characteristics, taking multiple myeloma spine disease as a model of different approaches and recommendations in the management, thereby supporting clinical and surgical decisions in such conditions.

Hematologic neoplasms affecting the spine

A- Multiple Myeloma

Multiple Myeloma is a hematologic malignancy, with the global incidence rate of 7.0/100,00 person-years and is characterized by clonal plasma-cell bone marrow infiltration and the secretion of a monoclonal protein in serum and /or urine.[4] Bone lesions (BL) are the most common defining event of symptomatic Myeloma and will affect 90% of patients during the disease. Kyle et al, reported in 1027 newly diagnosed MM patients, the frequencies of initial clinical manifestations and the OD was present in 79%, followed by Anemia 62%, Renal insufficiency 19% and Hypercalcemia 13%.[5] Also, a humoral immunodeficiency with low levels of uninvolved immunoglobulins known as immunoparesis are frequent, and consequently infections are common seen during the course of the disease.[5,6] For the diagnosis of the symptomatic disease, patients must fullfill the International Myeloma Working Group Criteria (IMWG). The work-up for the diagnosis needs the detection of the monoclonal component both by the techniques of electrophoresis and immunofixation in (blood/urine) and free light chains (Freelite) in serum together with histopathological demonstration of tissue infiltration by malignant plasma-cells by bone marrow biopsy or aspirate examination. Alternatively, a soft tissue plasmacytoma biopsy, can confirm the diagnosis. Also, patients should present at least one of the defining events of the disease such as: hypercalcemia. renal insufficiency: anemia and bone lesions known by the acronym CRAB criteria.[6]

Pure osteolytic bone lesions are a pathognomonic finding, and were originally described in plain radiographs, which show "punched-out" resorptive lesions, including the "raindrop" appearance of the skull.[7] In long bones, lesions can take distinct aspects, ranging from simple to multiple lesions, or extend with infiltration of the bone cortical invading the periosteum, which can form tumors in soft tissues and with the rupture of the compact bone generating pathological fractures.[8] In histopathological studies, it has been shown that these lesions represent a nodular replacement of bone marrow tissue by plasma cells, with complete destruction of the bone at this site.[7] In addition to the alterations described, 10% of the patients present only diffuse osteopenia and osteoporosis as an expression of bone involvement.[8]

Ai -Multiple Myeloma and Spine

Even though both the axial and appendicular skeletons are commonly involved, the spine is the most frequent bone site injured. In a case series, the distribution of affected bone showed: vertebrae (49% of patients), ribs (33%), skull (35%), pelvis (34%), humeri (22%), femurs (13%) and mandible (10%), being uncommon in distal bones.[9] At diagnosis, a common scenario for patients is to present fractures and multiple vertebral collapses resulting in acute pain that evolves to chronic pain due to nerve root compression and generating functional disability and worsening of quality of life. As a result of vertebral fractures and ribs, patients commonly can reduce height and become with limited thoracic expansion, making them more susceptible to respiratory infections. In addition, spinal cord compression syndrome may be the first manifestation of MM in 12% of patients and may appear in up to 20% of cases during the disease course.[10] When is present characterizes a medical emergency that must be recognized immediately, by an imaging method such as MRI scan according with the different pathologic spine mechanisms to avoid persistent neurologic deficit.[11] (Figures 1, 2, 3)

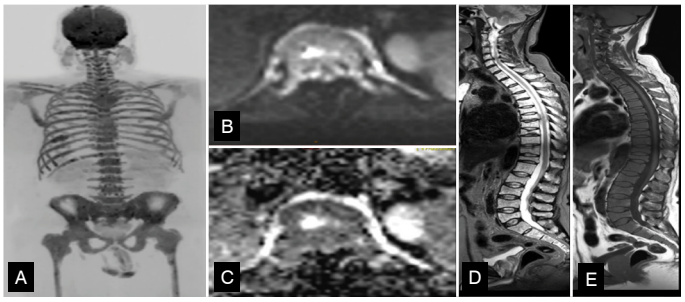

Figure 1. Multiple Myeloma. A) 3D diffusion, (B) Axial diffusion, (C) Axial ADC, (D) Sagittal STIR and (E) Sagittal T1. A 60-year-old male with Multiple Myeloma presenting diffuse infiltration with hypointensity on T1 and hyperintensity on STIR throughout the axial skeleton. There is a collapse of multiple vertebral bodies, more evident on D7, which results in compression of the dural sac and the dorsal medulla.

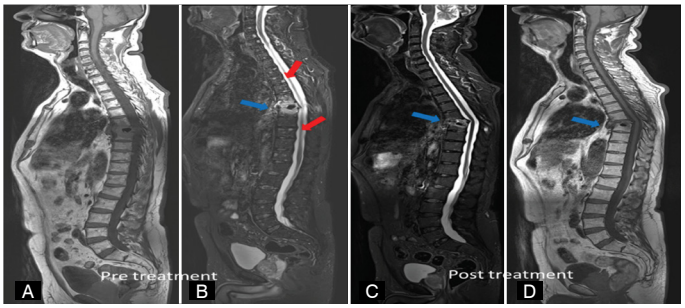

Figure 2. Multiple myeloma pre-treatment (A) Sagittal T1, (B) Sagittal STIR. After treatment (C) Sagittal STIR, (D) Sagittal T1. A 72-year-old male with multiple bone lesions in T1 and STIR (red arrows) presents an infiltrative lesion in D7 and D8 (blue arrow), with hyperintensity in (B) and hypointensity in (A), with partial collapse of D7, compressing the dural sac and spinal cord. After treatment, there was complete collapse of D7 and increased spinal cord compression at this level. There was improvement of bone lesions in (C) and (D), with post-therapeutic changes with hyperintensity.

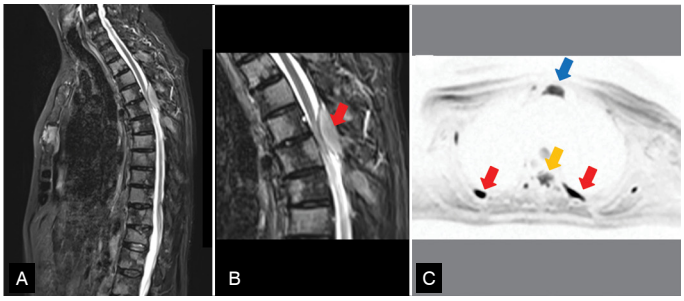

Figure 3. Multiple Myeloma. (A and B) Sagittal STIR, (C) Axial DWI images. A 67-year-old male with multiple viable bone lesions distributed across multiple dorsal vertebral bodies, posterior arches, and sternum, noting a soft tissue tumor component (red arrow in B) originating from the posterior arch of D4, which extends into the spinal canal and compresses the dorsal spinal cord. (C) Multiple bone lesions in ribs (red arrows), sternum (blue arrow), and in posterior epidural space (yellow arrow).

Aii - Imaging Techniques in Multiple Myeloma

Various imaging techniques are used for diagnosis, staging, and monitoring treatment response. These include X-rays, Whole body CT scan with low dose radiation (WBLDCT), PET/CT FDG-18 scan and Magnetic resonance modalities. Importantly, bone scan scintigraphy is not indicated in MM due to lower sensibility than X-ray to detect osteolytic lesions and may play a role in other scenarios such as osteoblastic lesions from bone metastasis due to solid tumors. Otherwise, bone density measurement for osteoporosis is helpful to see response to bisphosphonates, for some patients with limited or only the first stage of osseous disease, can be helpful due to its high sensitivity and specificity, however it cannot distinguish between disease versus aged related osteoporosis.[11]

PET/CT scans are valuable for assessing metabolic activity and response to therapy. Outside the bone marrow, PET–CT can help identify hypermetabolic skeletal areas in 15–20% of patients with negative bone marrow measurable residual disease (MRD) examination and is considered one of the best methods currently available for post therapy imaging evaluation.[12] In turn, MRI is particularly useful for visualizing bone marrow involvement and soft tissue masses. A meta-analysis found that DWI MRI is significantly more sensitive than PET–CT in depicting abnormal areas in the bone marrow of patients with MM.[13] Recently in the EMN 2025 guidelines recommended both techniques as mandatory for diagnosis and post-therapy monitoring of MM.[14] The rational use of imaging techniques depends on the clinical context and can provide a comprehensive assessment of the specific type of spine pathological involvement and best guide appropriate modality of intervention. (Table 1)

Aiii- Multiple Myeloma treatment

Specific treatment and initial supportive care should me the initial goal of treatment. The therapeutic landscape of multiple myeloma (MM) has evolved significantly in recent years, particularly with the integration of novel agents such as proteasome inhibitors (e.g., bortezomib, Carfilzomib) and immunomodulatory drugs (e.g., Thalidomide, Lenalidomide) and anti-CD38 antibodies (e.g. Daratumumab, Isatuximab) into autologous hematopoietic stem cell transplantation (auto-HSCT) in the up-front of treatment. Moreover, relapsed patients can receive modern personalized immunotherapy such as belantamab mafodotin, an antibody drug conjugate targeting plasma-cells by BCMA. At this same target and in others, the t-cell redirecting therapies such as bi-specific antibodies (e.g,:Teclistamab, Elranatamb, Talquetamab) and with CAR-T cells. These advancements have led to a substantial increase in overall survival.[14]

AiV- Multiple Myeloma Adjuvant treatment

Bisphosphonates (BP), pyrophosphate analogues with high bone affinity, are the only pharmacological agents currently recommended for the treatment and prevention of MM-related bone disease (osteolytic disease, OD) and remain the standard of care. Pamidronate and zoledronic acid are the most commonly used BP, alternatively for patients with renal failure Denosumab is recommended.[15-17] Generally safe, these drugs significantly decrease the risk of skeletal-related events such as pathologic fractures, spinal

Table 1. Advantages and Limitations of Different Imaging Techniques.

Imaging Technique	Advantages	Limitations
Whole-body X-ray (WBXR)	- Low cost - Widely available - Historically validated	- Poor sensitivity; detects damage only at advanced stages - Long acquisition time - Discomfort due to repositioning and multiple films - Cannot assess bone marrow involvement - Cannot differentiate malignant vs. benign fractures - Inaccurate for pelvis and spine visualization - Inadequate to assess treatment response - Observer-dependent
Whole-body Low-Dose CT (WBLDCT)	- Higher sensitivity and specificity for lytic lesions - Provides 3D anatomical detail - Useful for CT-guided biopsy/surgery/radiotherapy - Can visualize extramedullary disease and bone marrow involvement - Faster acquisition time - More comfortable for patients - Less expensive than MRI/PET	- Prognostic value of lesion count not clearly defined - Higher radiation dose and cost than WBXR
PET/CT	- Functional imaging modality - Evaluates disease activity pre-/post-treatment - Superior for assessing CR and MRD - Detects extramedullary disease - Provides prognostic insights - Novel radioisotopes may improve relevance	- High cost - Limited accessibility - Risk of false positives (infection/inflammation) - Lack of standardization - Lower spatial resolution
MRI	- No ionizing radiation - Superior for soft tissue and spinal cord compression detection - Detects both diffuse and focal marrow infiltration - Identifies extramedullary disease - Number of focal lesions has prognostic value - 3D anatomical detail information for CT-guided biopsy, surgery, and radiotherapy planning	- Expensive - Long scan time; may cause claustrophobia - Contraindicated with metal implants or severe renal insufficiency (if contrast used)

Adapted from reference [11]: WBXR:whole-body x-ray; WBLDCT: whole-body low-dose CT; EMD: extramedullary disease; CR, complete response; MRD, minimal residual disease.

cord compression and hypercalcemia evidenced in different clinical trials. The use of high doses can led to some adverse events such as renal toxicity and osteonecrosis of the jaw especially in patients under dental invasive intervention.[16] Optimal duration and dosing of BP therapy have been proposed in recent guidelines.[14] (Table 2)

Table 2. Management of Bone Disease in Multiple Myeloma and Level of Evidence.

Intervention	Indication/Context	Level [Grade]
Antiresorptive therapy	All patients with MM and osteolytic lesions at diagnosis; alongside disease-directed therapy.	I [A]
Denosumab	Patients with severe renal impairment where bisphosphonates are contraindicated; monitor for hypocalcemia.	III [C]
Zoledronic acid (monthly)	Patients with suboptimal response (PR or less), for at least 4 years.	I [A]
Zoledronic acid (12–48 months)	Patients in CR or vgPR; reinitiate at relapse.	III [B]
Denosumab (continuous)	Administer every 4 weeks. Upon discontinuation, give a single dose of zoledronic acid 6–9 months later to prevent rebound.	III [B]
Calcium + Vitamin D	Mandatory with bisphosphonates or denosumab to avoid hypocalcemia.	I [A]
Low-dose radiotherapy (≤30 Gy)	Palliative treatment for pain, impending pathological fractures, or spinal cord compression.	II [A]
Balloon kyphoplasty	Symptomatic vertebral compression fractures with refractory pain.	II [B]
Surgical intervention	Long-bone fractures, spinal cord compression, vertebral instability.	II [A]

PR: partial response; CR: Complete response; VGPR: Very good partial response. Table adapted from reference [14].

AV- Multiple Myeloma and Vertebral Augmentation Procedures

Complex interactions between myeloma cells and the vertebral bone marrow microenvironment lead to bone loss and destruction, causing a disturbance in the natural skeletal architecture and predisposing patients to vertebral compression fractures (VCFs). The most common site of VCFs in MM is the thoracic spine, followed by the lumbar and cervical spines. VCFs are known to occur at the onset of diagnosis in 34% to 64% of patients.[18] Current non-operative interventions to treat VCFs include oral and parenteral opioidca analgesics (NSAIDs are not recommended), steroids, bisphosphonates, spinal braces, and radiotherapy. While traditional non-operative management may improve pain control, it does not stabilize the VCF or minimize the progressive kyphotic deformity, which can only be achieved by vertebral augmentation procedures (VAPs), including percutaneous vertebroplasty (PVP) and percutaneous kyphoplasty (PKP).[18,19] In 2019 the IMWG published the recommendations for VAPs in MM. Absolute indications were: i) persistent, significant pain from a fractured vertebral body, ii) persistent, significant symptoms that had not resolved with normal conservative measures after 4 weeks of treatment affecting daily activities, iii) significant pain associated with a significant change in disability in conjunction with a new event, iv) acute-disease patient whose procedures were delayed for medical reasons, v) Selective chronic fractures.[19] Some of the contraindications to performing VAPs identified in the literature include severe coagulopathy, >75% vertebral body collapse, the presence of epidural disease, posterior vertebral body wall fractures, spinal cord compression, and radiculopathy. One of the most common complications of VAPs is cement leakage outside the confines of the vertebral body into adjacent dural, vascular, or soft tissue spaces or may embolize via the vertebral veins.[20] Multiple studies revealed higher cement leakage rates among PVP (30%-75%) compared to PKP (8%-33%).[21]

Avi- Radiotherapy in Multiple Myeloma

Solitary plasmacytomas (PCs) are radioresponsive tumors with RT alone achieving excellent long-term local control (79% to 91%).[22] Nevertheless, in patients with systemic disease the indications for RT are restricted to specific situations.[23] In 2018 the IMWG recommended for patients: i) with a soft tissue mass or PC that had not resolved with systemic therapy or who could not receive systemic therapy; ii) for PCs associated with severe pain or for PC location precluding use of VAPs (e.g., tumor impacting posterior part of the vertebral body close to spinal cord and nerves). Moreover, iii) its use in palliative approach for poor performance status patients RT alone has also been shown to be a very effective palliative treatment for patients with spinal cord compression.[19] A recent study of 238 myeloma patients showed excellent response rates (97%), local control (93% at 1 year and 82% at 2 years), and functional outcomes (64% of non ambulatory patients regained the ability to walk) in patients treated with RT alone.[24] Moreover, RT has been shown to provide pain relief with reduction of analgesic drug use, ameliorate neurologic symptoms, promote recalcification of bone, and improve both motor function and quality of life in patients with MM. The American Society for Radiation Oncology guidelines suggest schemes of a single 8 Gy fraction, 20 Gy in 5 fractions, 24 Gy in 6 fractions, or 30 Gy in 10 fractions, which showed adequate pain relief from painful bone metastasis.[25]

AVii- Surgical intervention in Multiple Myeloma

Bone involvement, often associated with tumor extension into surrounding soft tissues, commonly manifests as bone pain, pathologic fractures, and neurologic compromise such as spinal cord compression, nerve root compression, and cranial nerve deficits.[26] The most typical symptoms of these conditions include pain (local and radicular), weakness, paresthesia, and loss of bladder or bowel control. Currently, surgery considered in the following cases: i) to fix pathological fractures of the long bones; ii) to prevent and restore axial skeleton in cases of unstable spinal fractures; and iii) for spinal cord compression with bone fragments within the spinal canal.[14,27]

Patients with compression fractures or impending fractures of weight-bearing bones should first undergo surgical stabilization prior to RT. For pain due to vertebral body collapse in the absence of spinal cord compression, when soft tissue disease is not apparent, vertebroplasty can be beneficial. A surgical evaluation is often recommended for cases of rapidly evolving symptomatic spinal cord compression, as prompt intervention may improve the chances of immediate and sustained neurologic recovery.[28] (Figure 4)

AViii- Work-up and management of patients with spinal myeloma disease

Briefly, any patient known to have MM who presents with back pain should undergo a careful assessment to determine the severity of pain and any accompanying neurological findings. In most cases, epidural tumors are treated very effectively by steroids/chemotherapy and radiotherapy, obviating the need for surgical decompression. MRI should confirm this, specifically on T1-weighted and short-T1 inversion recovery sequences, to rule out any spinal cord compression and facet joint-related pain.[26] A CT scan must be performed for Spinal Instability Neoplastic Score (SINS) classification to determine spinal instability and posterior vertebral wall defects. VAPs are also considered in patients with non-healing chronic fractures with a fracture cleft on imaging, and in patients with persistent symptoms from VCFs initially treated with conservative measures for 8-12 weeks,

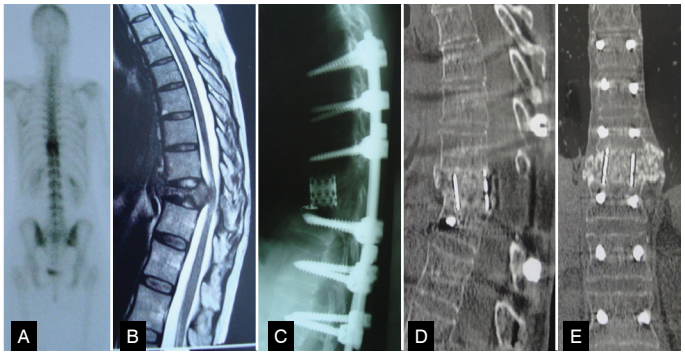

Figure 4. Clinical case 1: Female 47 Years-old patient with multiple myeloma presents with severe back pain, spine instability, spine cord compression and acute paraparesis. Underwent preoperative embolization tumor resection, spinal cord decompression and spinal reconstruction with a Harms cage by costotransversectomy approach and posterior spine fusion.: A- Bone Scintigraphy showing increased uptake in the thoracic spine. B- MRI in sagittal plane demonstrating vertebral collapse greater than 50% with spinal canal stenosis. C- Radiograph in lateral view after tumor resection with alignment restoration after anterior and posterior instrumentation. D and E- Postoperative CT scan in sagittal and coronal views showing spinal stability with complete bone fusion inside the cage with wide space available for spine cord.

such as external supportive devices, including thoracolumbar spinal orthosis and thermoplastic braces.[28] In most cases, epidural tumors are treated very effectively by steroids/chemotherapy and radiotherapy, obviating the need for surgical decompression Therefore, surgical intervention is reserved for those with significant spinal instability, for example, where there has been significant destruction to all three bony columns of the spine (determined by the SINS classification and in concert with the spinal surgeon).[29] (Figure 5)

B-Non-Hodgkin Lymphomas

Non-Hodgkin lymphomas (NHL) constitute a heterogeneous group of hematologic neoplasms originating from B cells, T cells, or NK cells, either mature or immature. The precise diagnosis of these lymphomas depends on histopathological evaluation and immunohistochemical analysis. Mature B-cell neoplasms account for more than 90% of lymphomas and are responsible for approximately 4% of all new cancer cases. The most common types of NHL include diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma, which together represent more than 60% of registered cases.[30] (Figure 6)

The age of onset varies, with a predominance among patients in their sixth and seventh decades of life and most types show a slightly higher prevalence in males.[3,30,31]

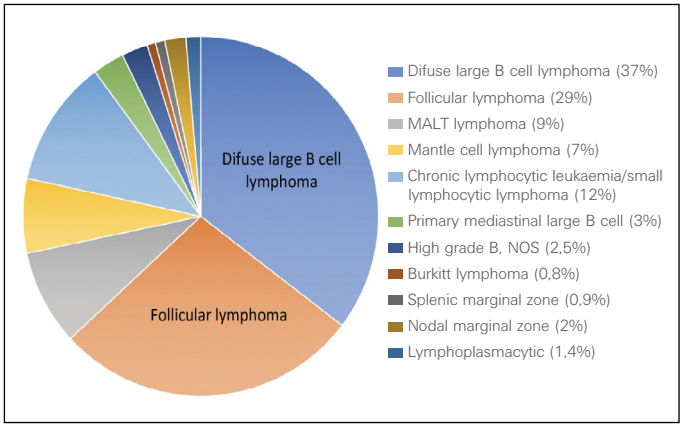

Figure 6. Epidemiological distribution of B-cell lymphoma subtypes in the adult population. Source: WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues (Swerdlow SH, et al; 2017).

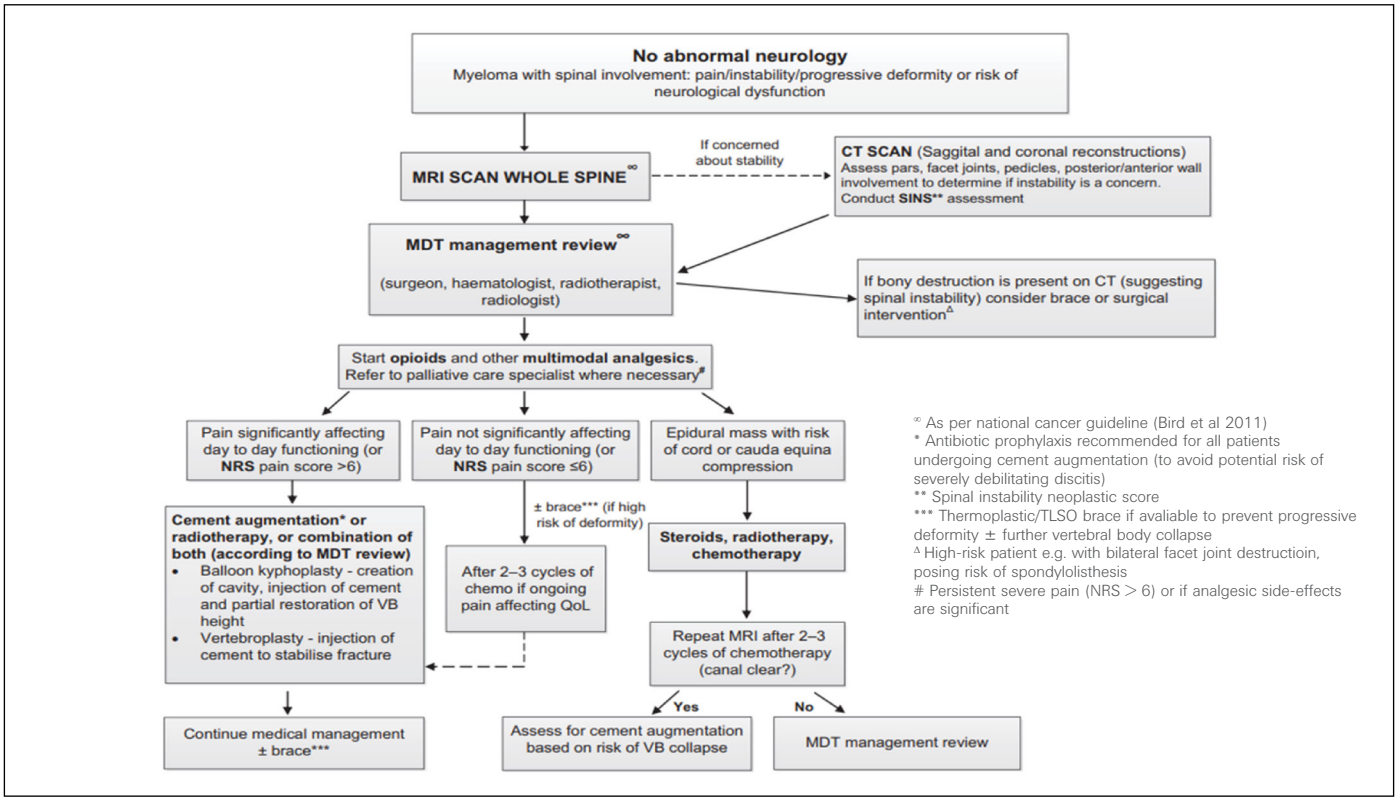

Figure 5. Proposed algorithm for the management of patients with known history of myeloma presenting with persistent back or radicular pain/ weakness with no abnormal neurology. CT, computerized tomography; MRI, magnetic resonance imaging; MDT, multidisciplinary team; SINS, spinal instability neoplastic score; NRS, numerical rating scale; VB, vertebral body; TLSO, thoracolumbosacral orthosis; QoL, quality of life. From ref [13] Uk Spinal Myeloma Working Group.

Extranodal involvement occurs in 24 to 48% of cases, generally indicating more advanced disease. One of the extranodal sites of involvement is the spinal column, which may affect the bony portion or the epidural or intradural spaces.[3] DLBCL is the subtype most frequently found in spinal involvement, whether primary or secondary.[31-33] Primary bone lymphoma is rare, occurring in less than 5% of extranodal lymphomas and in less than 1% of NHL, being more common in long bones than in the spine.[31,33] Spinal involvement may be an incidental finding on imaging exams or may present as oligosymptomatic or even as a medical emergency. Bone pain is the most common initial symptom, generally manifesting months before diagnosis.[1,31] Other symptoms include signs of radiculopathy or myelopathy, and even SCCS with neurological symptoms, whether due to an epidural mass, epidural invasion in advanced-stage NHL, or pathological fracture, which constitutes a medical emergency.[34] Although B symptoms, such as fever, night sweats, and weight loss, may be present, these are not pathognomonic for lymphoma and may hinder differential diagnosis with infectious conditions, especially tuberculous spondylitis.[3] There is no single radiological pattern for bone involvement by NHL; the most common radiologic presentation is lytic lesions, described in approximately 70% of cases, likely due to increased release of factors that stimulate osteoclasts. Other forms of presentation include cortical lesions, mixed sclerotic-lytic lesions, periosteal reaction, and soft tissue involvement. When the bone is affected by osteoblastic or sclerotic lesions, a differential diagnosis includes Hodgkin lymphoma, although its extranodal involvement is even rarer than that of NHL.[3,31] Epidural involvement of the spinal column represents 0.9 to 6.5% of extranodal involvement in NHL and 9% of all epidural tumors.[1] The most commonly affected site is the thoracic spine, followed by the lumbar and cervical regions.[1,3,33] One hypothesis for its higher occurrence in the thoracic spine, besides its greater length, is the richer local vascularization, suggesting that the origin of the mass arises from lymphoid tissue associated with the local venous system.[3] Plain radiography offers limited value in evaluating this condition, with MRI being the gold-standard method for assessing both the spinal canal and the epidural space, and which may be replaced by CT or myelography in patients with contraindications. Another essential test in the evaluation of patients suspected of lymphoma is PET-CT, used for disease staging.[3] However, it should be noted that accurate diagnosis depends on biopsy of the lesion, given the current limitations of imaging methods, which are inadequate for establishing the diagnosis independently (Figure 7).[35] Lymphomas generally show high sensitivity to chemotherapy, corticosteroids, and radiotherapy, with surgical interventions being reserved for biopsies, unstable fractures or SCCS[3]. In the latter case, treatment may also include emergency radiotherapy combined with chemotherapy, which is associated with favorable outcomes.[32] The intradural space lymphoma, involving both the spinal cord and cauda equina, is usually secondary to tumor dissemination rather than primary involvement; in the latter case, it is considered primary central nervous system lymphoma. The cerebrospinal fluid (CSF) and imaging findings are nonspecific and overlap with inflammatory conditions. Radiologically, it may present as an expansile lesion with abnormal enhancement in the spinal cord on MRI, showing isointense signal on T1-weighted (T1-W) images and hyperintense signal on T2-weighted (T2-W) images compared to the spinal cord. The CSF analysis typically reveals elevated protein, reduced glucose concentrations and increased leukocyte count with cytology demonstrating an estimated sensitivity of approximately 30%.[3]

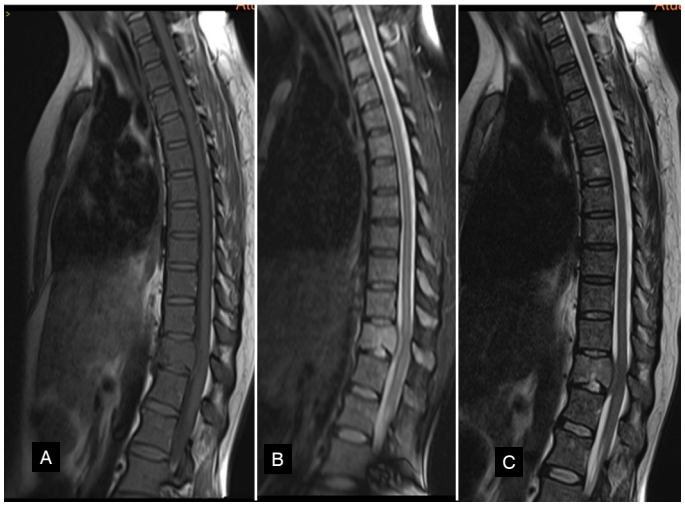

Figure 7. Non-Hodgkin's lymphoma A) Sagittal T1, (B) Sagittal STIR, and (C) Sagittal T2. A 45-year-old woman presenting diffuse infiltration with hypointensity on T1 images, and hyperintensity on STIR and T2 images in the dorsal vertebral bodies, pedicles and posterior arches, highlighting partial collapse of D10, with a soft tissue component extending posteriorly and protrusion of the posterior wall causing compression on the spinal cord.

C-Acute Leukemias

Acute leukemias are hematologic neoplasms characterized by clonal proliferation of hematopoietic precursors, with a blockade of cellular differentiation. They may originate from myeloid precursors, resulting in acute myeloid leukemia (AML), or from lymphoid precursors, resulting in acute lymphoblastic leukemia (ALL), which may involve B or T lineages. The accumulation of blasts in the bone marrow leads to suppression of normal hematopoiesis and the development of cytopenias.[30,36,37] Both are heterogeneous diseases, classified based on cytogenetic and molecular characteristics.[38,39] In AML, the median age at diagnosis is 68 years, whereas ALL predominantly affects children between 1 and 4 years of age, with about 60% of cases occurring before the age of 20. A second, less pronounced incidence peak is observed in individuals over 60 years of age.[36] Clinical manifestations may range from asymptomatic cytopenias or nonspecific constitutional symptoms such as fatigue, fever, and weight loss, to signs associated with cytopenias, such as symptomatic anemia, bleeding, and recurrent infections. Tumor lysis syndrome may also be present. In laboratory tests, anemia and thrombocytopenia are commonly observed, and the white blood cell count may vary widely—being normal, decreased, or increased—and may even exceed 100,000/μL.[36,37] Diagnosis is established based on blast morphology, immunophenotyping by flow cytometry, cytogenetic analysis, and molecular evaluation. For AML, ≥20% myeloid blasts in the bone marrow or peripheral blood are required for diagnosis, except in cases with defining cytogenetic alterations in AML, such as t(8;21)(q22;q22.1)/RUNX1-RUNX1T1, inv(16)(p13.1;q22)/CBFB-MYH11, and t(15;17)(q22;q12)/PML-RARA, where the diagnosis can be made regardless of blast percentage.[30,38] In immunophenotyping, markers associated with the myeloid lineage include CD33, CD13, and myeloperoxidase (MPO), as well as CD34, CD117, and HLA-DR as progenitor cell markers. In ALL, markers vary depending on the lineage: CD19, CD22, CD79a, and PAX5 are most commonly found in B lymphocyte cases, and TdT, CD3, and CD7 in T lymphocyte cases.[10] Central nervous system (CNS) infiltration is considered rare and often asymptomatic.[14] In ALL, CNS assessment by lumbar puncture at the time of diagnosis is mandatory, both for disease detection and to initiate prophylaxis with intrathecal chemotherapy. Although the incidence of CNS involvement reported in clinical studies is less than 10%, it is believed that this number is underestimated, as patients with CNS involvement may have been excluded from these studies. In patients not receiving intrathecal prophylaxis, the risk of CNS relapse may reach 30–40%.[36] Neurological manifestations, such as radiculopathies and signs of SCCS, are rare but possible in cases with CNS infiltration.[40] Another form of spinal involvement by acute leukemia is observed in AML: myeloid sarcoma (MS), also known as chloroma. It is a tumor composed of myeloid blasts outside the bone marrow, which may occur with or without a prior AML diagnosis. About 25% of cases occur in patients with no previous diagnosis of myeloid neoplasm.[30] Among patients with AML, the

incidence of MS ranges from 1.1% to 9.1%.[1] The most frequently affected sites include lymph nodes, skin, gastrointestinal tract, CNS, ovaries, testes, and soft tissues.[30,36] However, spinal involvement is also described and may result in SCCS, which requires early intervention.[1] Differential diagnosis with other epidural tumors, such as lymphomas, may be challenging. Immunohistochemistry assists in this process, with positivity for markers such as CD45, CD43, CD117, CD68, lysozyme, CD34, and MPO.[1] The treatment of myeloid sarcoma is based on systemic chemotherapy. Radiotherapy may be used as adjuvant therapy for local control, especially in symptomatic cases or in cases with residual disease following chemotherapy.[36]

D-Extramedullary Hematopoiesis

Extramedullary hematopoiesis (EMH) is defined as the production of blood cells outside the bone marrow and generally occurs in response to conditions that lead to chronic anemia or chronic ineffective hematopoiesis.[41-43] Its most common etiology is thalassemia, with other causes, such as myeloproliferative syndromes—including polycythemia vera and myelofibrosis—being rarer.[41,44] In general, EMH occurs in locations associated with fetal hematopoiesis, most commonly in the spleen and liver, but it may also be observed in other organs, including lymph nodes, thymus, kidneys, adrenal glands, and the mediastinum.[41-44] Vertebral manifestation of EMH is rare, accounting for approximately 10 to 15% of all cases.[41,43] Although there is no definitive proof, one of the proposed hypotheses for its occurrence in the spinal column is that the dura mater has hematopoietic potential during fetal development, and that EMH could originate from remnants of this tissue.[44] Among cases of EMH involving the spinal column, up to 80% may be asymptomatic and incidentally detected through imaging studies. When symptomatic, it may cause anything from localized pain or mild radiculopathy to SCCS. [41-43] The thoracic and lumbar regions are most frequently affected, with a predominance in the thoracic region. This predilection for the thoracic spine may be explained by local anatomical characteristics, such as the smaller caliber of the subarachnoid space and spinal canal, as well as reduced segmental mobility, which favors symptom development even with small-volume lesions.[43] Diagnosis is usually made via MRI, as it allows detailed evaluation of both lesion features and their extent. Active lesions are highly vascularized, generally multifocal or bilateral, and appear as well-demarcated masses, iso- or hypointense on T1-W images and T2-W images, with little or no gadolinium enhancement.[43] Areas of fat or iron deposition may be present in inactive lesions, appearing as hyperintensity or hypointensity on T1-W images and T2-W images, respectively.[42,43] Biopsy remains the gold standard for diagnosis but is reserved for cases with atypical imaging, MRI contraindication, or suspected malignancy, due to the risk of bleeding and the invasive nature of the procedure.[43] Treatment varies depending on the clinical presentation, and there is no well-defined consensus due to the rarity of this condition.[41,43] In asymptomatic patients, management is conservative and focused on treating the underlying hematologic disease, including regular transfusional support when indicated, as a strategy to inhibit EMH.[41-43] Pharmacological agents such as hydroxyurea can also reduce ineffective erythropoiesis and, consequently, the need for EMH.[41,43,44] In cases with SCCS, treatment may include corticosteroids, radiotherapy, decompressive surgery (laminectomy), or a combination of these methods.[43,44] Surgical intervention must be carefully evaluated, as EMH masses are highly vascularized, increasing the risk of intraoperative bleeding, hemodynamic instability and worsening of postoperative anemia due to the removal of a compensatory hematopoietic site.[41,43] Additionally, complete resection of these lesions is not always possible due to their infiltrative nature and multifocal presentation, and recurrence may occur.[43,44] Another possible complication is related to multilevel laminectomy, which may result in postoperative kyphosis.[43] Therefore, surgical indication is generally reserved for cases of severe neurological deterioration or those with acute, progressive, or refractory presentation to conservative treatment.[43]

CONCLUSION

Spine involvement is common in multiple myeloma and most patients experience bone lytic disease at diagnosis and throughout the course of the illness. For MM, the treatment modality must always combine specific disease treatment with measures guided by the kind of spine pathophysiologic mechanism involved. Strategies and guidelines with level of evidence for supportive treatment are summarized in this review. Other hematologic malignancies, in lower proportion, also may affect the spine primarily or secondarily. Lymphomas, acute leukemias and myeloproliferative diseases, each one with a specific profile and management. The common initial work-up for all these diseases should first focus on biopsy of suspected lesion for histopathologic diagnosis, with an appropriate imaging expert. In a way to guarantee a fast diagnosis and best primary and therapeutic adjuvant modality to treat the spine and improve neurologic symptoms and pain. Key strategies for primary care physicians to improve early detection and ensure appropriate referrals to specialized treatment centers are crucial to avoid disability. A multidisciplinary care approach, involving hematologists, radiologists, intervention-radiology, orthopedic and neurosurgeons, radiotherapy specialists, pain specialists, and rehabilitation teams, is essential for optimal patient outcomes. Together, these coordinated efforts contribute to preserving quality of life and functional independence in patients with MM.

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