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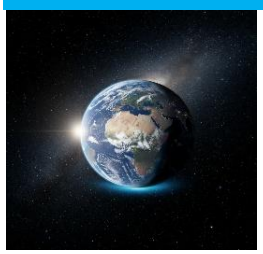

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Pain and Pathological Fractures as Primary Causes of Mobility Impairment in Multiple Myeloma

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Abstract

Background: Multiple myeloma (MM) is a malignant plasma cell disorder frequently complicated by skeletal involvement, affecting up to 80% of patients. Osteolytic lesions, pathological fractures, spinal instability, and chronic pain lead to functional impairment, neurological complications, and reduced quality of life. Bone disease in MM results from an imbalance between bone resorption and formation caused by dysregulation of the RANK/RANKL/OPG pathway.

Aim: To review current literature on bone disease in multiple myeloma with emphasis on functional impairment, rehabilitation, and the role of orthopedic equipment in patient care.

Material and methods: A narrative review was conducted using PubMed, Scopus, Google Scholar, and Polish medical databases. Articles published in English or Polish concerning adult MM patients with skeletal complications were included and analyzed qualitatively.
Results: The literature shows that bone pain and pathological fractures, particularly in the spine, pelvis, ribs, and long bones, are major causes of disability and limited mobility. Pharmacological treatment, radiotherapy, and minimally invasive procedures such as vertebroplasty and kyphoplasty reduce pain and improve stability. Rehabilitation improves muscle strength, balance, and mobility. Orthopedic devices, including spinal orthoses, walkers, and crutches, increase safety and support daily activities.
Conclusion: Skeletal complications remain a significant source of disability in patients with multiple myeloma. A multidisciplinary approach combining pharmacological treatment, interventional procedures, rehabilitation, and orthopedic support is essential to improve functional capacity and quality of life.

Keywords: multiple myeloma; bone disease; osteolytic lesions; rehabilitation; physical therapy; pathological fractures

1. Introduction

Multiple myeloma (MM) is a malignancy of the immune system characterized by the monoclonal proliferation of plasma cells, which represent the final stage of B-cell maturation and differentiation. In this context, plasma cells act as the tumor equivalent, producing structurally abnormal monoclonal immunoglobulins. As a result, the disease manifests with a wide range of symptoms, including bone lesions, anemia, renal impairment, hypercalcemia, hyperviscosity syndrome, and recurrent bacterial or viral infections [1,4].

MM accounts for approximately 10% of all hematological malignancies. Men are affected more frequently than women. The median age at diagnosis is 65 years, with fewer than 3% of patients presenting under the age of 40. Patients older than 65 years represent 35% of cases [6,11].

MM arises from a premalignant asymptomatic condition known as monoclonal gammopathy of undetermined significance (MGUS). MGUS is defined by the presence of less than 10% clonal bone marrow plasma cells, serum M-protein <30 g/L, and the absence of end-organ damage, which may include hypercalcemia, renal insufficiency, anemia, or bone disease-related osteolytic lesions (CRAB criteria) [7].

Bone pain is often the predominant symptom in patients with multiple myeloma, presenting as the first clinical sign in approximately 70% of cases. The accumulation of myeloma cells in bone tissue, along with sustained activation of proinflammatory proteins and cytokines, leads to gradual remodeling and destruction of bone. At the time of diagnosis, approximately 80% of patients show multiple osteolytic lesions. Localized osteoporosis and osteolysis contribute to the development of pathological fractures [2].

2. Review methodology

This review was conducted as a narrative review of the literature. A non-systematic search was performed using PubMed, Scopus, Google Scholar, and Polish medical databases. Keywords included: multiple myeloma, bone disease, osteolytic lesions, rehabilitation, physical therapy, orthopedic devices, spinal orthoses, and pathological fractures.

Original articles, review papers, clinical guidelines, and consensus statements published in English or Polish were included. Publications focusing on adult patients with multiple myeloma and skeletal complications were analyzed. The collected data were qualitatively synthesized.

3. Research results

3.1 Criteria for the diagnosis of multiple myeloma

A prerequisite for the diagnosis of multiple myeloma is the demonstration of clonal plasma cells, either by immunophenotyping of the bone marrow or by immunohistochemical analysis

of a trephine biopsy or extramedullary plasmacytoma tissue. The proportion of clonal plasma cells in the bone marrow must exceed 10% [3,6]. Another criterion for the diagnosis of multiple myeloma is the presence of at least one feature of end-organ damage according to the SLiM-CRAB criteria (Table 1) [5].

C (calcium)	Hypercalcemia, corrected serum calcium level > 0.25 mmol/L (> 1 mg/dL) above the upper reference limit or > 2.75 mmol/L (11 mg/dL)
R (renal insufficiency)	Creatinine clearance < 40 mL/min or serum creatinine > 173 μmol/L (2 mg/dL)
A (anemia)	Hemoglobin 2 g/dL below the lower reference value or < 10 g/dL
B (bones)	Osteolytic lesions in bone radiography, computed tomography or positron emission tomography
S (sixty)	Clonal plasma cells in the bone marrow greater than or equal to 60%
Li (light chains)	Involved/uninvolved free light chain ratio of 100 or more
M (magnetic resonance)	More than one focal marrow lesion

Table 1. SLiM CRAB criteria for end-organ damage and biomarkers related to multiple myeloma[5].

3.2 Pathophysiology of Bone Disease in Multiple Myeloma

Bone tissue consists of both organic and inorganic components. The organic components include osteocytes, bone-lining cells, osteoclasts, osteoblasts, collagen fibers, proteoglycans, and glycoproteins [8]. Normal maintenance and remodeling of bone tissue in healthy individuals is a continuous process, tightly regulated by the interplay between osteoclast activity, which resorbs bone, and osteoblast activity, which synthesizes bone [9,10].

In multiple myeloma, this balance is disrupted. Malignant cells produce factors that both activate osteoclasts and inhibit osteoblasts, leading to increased bone resorption and, consequently, multiple pathological fractures [7,11]. As a result of bone destruction, components of the bone matrix, including cytokines, are released and activated; these, in turn, act as growth factors for tumor cells. This establishes a vicious cycle of interactions between malignant cells, bone marrow stromal cells, and bone tissue, promoting myeloma cell

proliferation and further osteolysis [10].

This bone loss is generally irreversible, and even in patients achieving complete remission, bone regeneration rarely occurs [12].

3.2.1 The Role of RANK/RANKL/OPG in the Pathophysiology of Bone Lesions

In recent years, significant progress has been made in understanding bone biology, thanks to the discovery of a functional system comprising three molecules from the TNF family: the receptor activator of nuclear factor-κB (RANK), its ligand (RANKL – receptor activator of nuclear factor-κB ligand), and osteoprotegerin (OPG). These molecules play a central role in osteoclastogenesis [10]. Their actions are antagonistic: RANK/RANKL stimulate osteoclast activity, whereas OPG promotes osteoblast activity.

Myeloma cells can disrupt the balance among these three molecules through several mechanisms. First, they can directly produce RANKL, which directly stimulates osteoclast-mediated bone resorption. Second, they can increase local RANKL expression in bone marrow stromal cells, indirectly promoting osteolysis. Third, malignant cells can inhibit OPG production, thereby suppressing bone formation [10,12,13].

3.3 Bone Pain and Pathological Fractures as the First and Most Common Manifestation of Multiple Myeloma

Back and/or bone pain is often one of the first symptoms of multiple myeloma. At the time of diagnosis, it affects between 30% and 68% of patients [2,15,16,17]. Proliferating plasma cells in the bone marrow cause destruction of bone structure, which may lead to pathological fractures. Osteolytic lesions occur primarily in the lumbar and sacral spine, pelvis, ribs, long bones, and skull, and most commonly present as multiple lesions [18]. Osteolytic changes are observed in up to 66% of patients with newly diagnosed multiple myeloma [2].

Skeletal involvement can be detected in most patients using X-ray imaging. However, lytic lesions are visible on X-rays only after more than 30% of trabecular bone is lost. Therefore, in certain situations, computed tomography (CT) is required, and when spinal cord compression is suspected, magnetic resonance imaging (MRI) is the imaging modality of choice (Figure 1) [15]. Other diagnostic methods for bone lesions include whole-body low-dose CT (WBLDCT) and positron emission tomography (PET) [3].

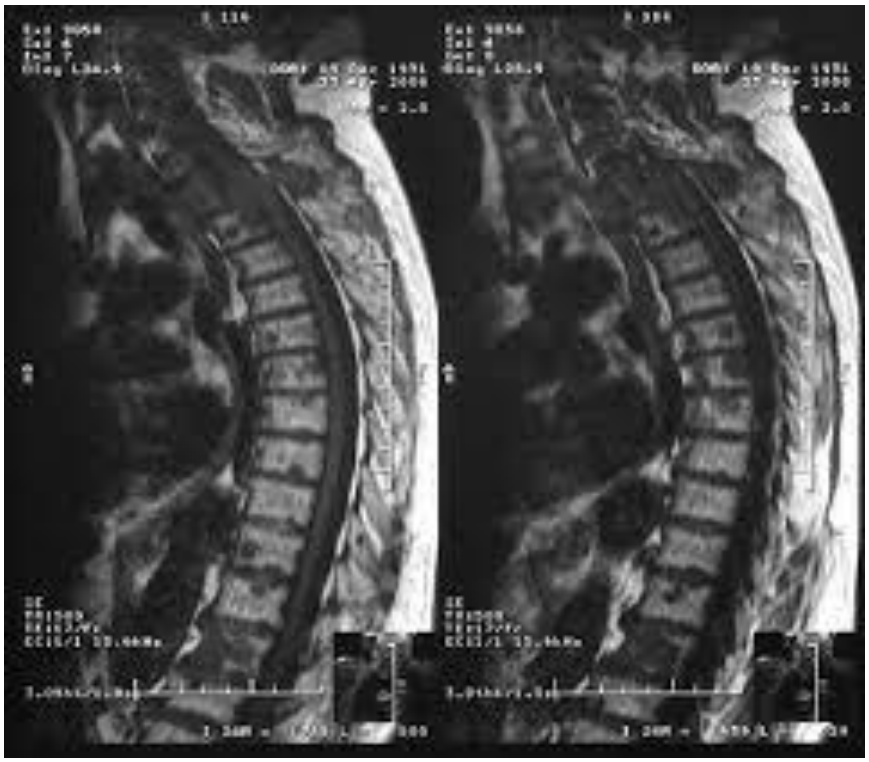

Figure 1. MRI of thoracic spine, showing numerous osteolytic foci in vertebral bodies. [14]

3.4 Functional Motor Impairment

Skeletal involvement in multiple myeloma manifests as bone pain, pathological fractures, and their neurological consequences, including spinal cord compression and cranial nerve palsies. The disease directly impairs the musculoskeletal system including motor function, affecting balance and posture. These impairments are often accompanied by comorbidities, which further negatively influence motor performance and overall functional capacity. Mobility problems tend to worsen as the disease progresses. Consequently, patients are frequently unable to perform basic activities independently or to ambulate without assistance [11,24].

3.5 Treatment of Bone Disorders in Multiple Myeloma

3.5.1 Pharmacological Treatment

All medications used in the treatment of multiple myeloma directly or indirectly inhibit excessive osteoclastic activity. However, only bortezomib has an additional effect of stimulating osteoblasts to induce bone formation [3]. Therefore, in all patients undergoing chemotherapy for multiple myeloma, it is recommended to initiate adjunctive treatment with

intravenous bisphosphonates [3].

Unfortunately, already established osteolytic lesions rarely heal; however, their progression can be slowed or even halted through the administration of intravenous bisphosphonates (e.g., pamidronate or zoledronic acid), which are pyrophosphate analogues. These agents inhibit osteoclast activity and promote osteoclast apoptosis. Additionally, they induce apoptosis of myeloma cells [3,11,19].

When zoledronic acid therapy is used, oral supplementation with calcium and vitamin D is recommended. Routine use of bisphosphonates is not advised in patients who do not require chemotherapy, such as those with monoclonal gammopathy of undetermined significance (MGUS), due to the risk of adverse effects, including renal insufficiency, hypocalcemia, and osteonecrosis of the jaw [3].

3.5.2 Local Radiotherapy

Local radiotherapy has demonstrated proven efficacy in the treatment of multiple myeloma. It is primarily employed in palliative care, particularly for spinal cord compression. The objectives of radiotherapy are both pain relief and improvement of functional capacity, which contribute to enhanced quality of life. Furthermore, radiotherapy may facilitate fracture healing [3,24].

3.5.3 Surgical Treatment Methods

Vertebral compression fractures represent one of the potential pathological fractures in patients with multiple myeloma. These fractures not only cause significant pain but also lead to functional impairment and reduced quality of life [11,20]. In such cases, surgical intervention may be required.

Currently, two vertebral reconstruction techniques are commonly used in patients with multiple myeloma: percutaneous vertebroplasty and kyphoplasty. Percutaneous vertebroplasty involves the injection of bone cement into the vertebral defect under fluoroscopic guidance. In kyphoplasty, bone cement is introduced into the vertebral cavity after initial expansion of the collapsed vertebra using a balloon. Both procedures are minimally invasive and have demonstrated high efficacy [11,21].

3.6 The Role of Rehabilitation as Supportive Treatment

Rehabilitation plays a significant role in improving both survival outcomes and quality of life, as well as in enhancing overall functional capacity. Its effects extend beyond physical improvement to include benefits in psychological well-being. Rehabilitation in oncology patients should encompass the following phases: the initial phase (inpatient treatment during the acute stage of the disease), the early phase (outpatient rehabilitation up to one year after completion of primary treatment), the late phase (during remission), and the palliative phase (after completion of oncological treatment) [11].

The rehabilitation program should be individually tailored to each patient and appropriately modified throughout the course of treatment. Due to variability in health status, disease progression, and the presence of comorbidities, it is not possible to develop a single standardized rehabilitation plan applicable to all patients with multiple myeloma. Additionally, it should be acknowledged that functional problems in oncological patients may result not only from the disease itself but also from applied oncological treatments and coexisting conditions [25].

A valuable tool supporting appropriate assessment of patients' functional status during rehabilitation is the International Classification of Functioning, Disability and Health (ICF). Developed by the World Health Organization (WHO) in 2001, the ICF provides a universal framework and standardized language for describing health, disability, and functioning in the context of environmental factors. It emphasizes an individual's abilities and limitations rather than focusing solely on disease, encompassing body functions, activities, and participation in social life. As such, it represents an internationally accepted standard for health assessment and health policy development [11].

3.6.1 Kinesiotherapy and Daily Physical Activity

Oncological patients commonly experience elevated levels of stress, pain, and general fatigue, which may adversely affect sleep quality and overall well-being. A key component of comprehensive rehabilitation is movement-based therapy, referred to as kinesiotherapy. Available evidence suggests that even low levels of physical activity may contribute to

improvements in pain perception, fatigue, sleep quality, and psychological well-being [11,22,23]

Physical activity does not necessarily need to involve specialized or supervised exercise programs. Patients may engage in various forms of home-based activity, such as Nordic walking, stretching exercises, resistance training using elastic bands, endurance exercises, and low- to moderate-intensity aerobic activity. Importantly, all forms of physical activity should be individually prescribed and adjusted according to the patient's clinical condition, functional limitations, and overall health status [11,22,23].

Prior to initiating therapeutic intervention, it is essential to obtain a detailed patient history and to assess individual dysfunctions as well as general physical condition. Objective evaluation of functional capacity may be performed using standardized functional tests, scored according to the patient's ability to perform specific activities (Table 2). Such assessments support appropriate planning and monitoring of the rehabilitation process [11].

Activity	Scoring
Standing up from and sitting down on a chair	1 2 3 4 5
Walking on the flat surface and over small obstacles	1 2 3 4 5
Single-leg stance	1 2 3 4 5
Wall sitting followed by arm elevation	1 2 3 4 5
Towel test (wiping movement)	1 2 3 4 5
Marching in place with high knee elevation	1 2 3 4 5
Standing with eyes closed	1 2 3 4 5
Lying down on a mattress or bed	1 2 3 4 5

Table 2. Functional tests – a questionnaire assessing the patient's function on a point scale, where: 1– does not cause any difficulties, 2–causes a certain difficulty, 3–is quite difficult to perform, 4–is very difficult to perform, 5–it is not possible to perform [11]

3.6.2 Physical Therapy

Until recently, physical therapy was considered absolutely contraindicated in active neoplastic disease. However, scientific studies increasingly report beneficial effects of modalities such as

thermotherapy, local infrared radiation, and transcutaneous electrical nerve stimulation (TENS). Classical massage may also be applied locally to promote relaxation of soft tissues [11,25].

3.6.3 Adaptation of the Living Environment

The comprehensive nature of rehabilitation involves consideration of all aspects of a patient's life. One of the roles of physiotherapists and medical specialists is to ensure appropriate adaptation of the patient's living environment to their current functional status. Providing patients with toilet seat raisers, grab bars to assist standing, shower stools, bedside ladders, or anti-decubitus mattresses may significantly improve quality of life [11,25].

3.6.4 Orthopedic Equipment

As the neoplastic disease progresses and numerous mobility limitations develop, patients are often required to use various forms of orthopedic assistive devices. For ambulation, elbow crutches or a walking frame may be helpful (Figure 2). To protect the spine, orthopedic braces are used, such as the Jewett brace, which unloads the thoracic and lumbar segments of the spine. Importantly, the maximum recommended duration of brace use during the day is 3 hours [11,26]. The use of medical devices aims to improve patient safety and functional capacity at every stage of the disease; therefore, these products constitute an important supportive element of therapy in patients with multiple myeloma [11].

Figure 2. Rehabilitation walker [11]

4. Conclusions

A review of the literature clearly indicates that bone pain and pathological fractures are the primary causes of mobility limitations in patients with multiple myeloma. The severity of pain

symptoms and the number of osteolytic lesions correlate with reduced physical functioning and quality of life. The implementation of a comprehensive rehabilitation program, individually tailored and adjusted to the patient's condition, together with the early initiation of pharmacological or surgical treatment, is associated with improved mobility and a reduction in the degree of disability. Appropriately selected exercises and physical activity may not only enhance patients' physical performance but also improve their psychological well-being and reduce stress related to cancer and its treatment.

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