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MULTIPLE MYELOMA: A COMPREHENSIVE REVIEW OF CLINICAL FEATURE AND MANAGEMENT

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ABSTRACT Multiple myeloma (MM) is a hematologic malignancy that accounts for 1-2% of all cancers and 17% of hematologic malignancies worldwide. It predominantly affects older adults, with a higher incidence in males and African American populations. Clinical manifestations often include bone pain, anemia, renal insufficiency, and hypercalcemia, due to the proliferation of malignant plasma cells. Diagnosis is based on clinical, laboratory, and imaging findings, including the detection of monoclonal proteins in serum or urine, and the presence of clonal plasma cells in bone marrow biopsy. Imaging techniques such as MRI and PET/CT play a key role in identifying osteolytic lesions and assessing disease progression. The management of MM has advanced with the use of autologous hematopoietic cell transplantation, triple drug regimens, and maintenance therapies.

KEYWORDS : Multiple myeloma, hematologic malignancy, bone pain, monoclonal protein, autologous transplantation.

INTRODUCTION

Multiple myeloma (MM) is a hematologic malignancy characterized by the clonal proliferation of plasma cells, predominantly within the bone marrow. These abnormal plasma cells produce monoclonal immunoglobulins or light chains, leading to clinical manifestations such as bone pain, anemia, renal insufficiency, and hypercalcemia. The disease has a significant impact on skeletal integrity, with up to 60% of patients presenting with bone-related complications at diagnosis, including osteolytic lesions and fractures. MM accounts for approximately 1-2% of all cancers globally, with an estimated 180,000 new cases and 117,000 deaths annually. advances in treatment, including immunomodulatory drugs and proteasome inhibitors, the prognosis remains poor for many patients, especially those with high-risk cytogenetic abnormalities (1-3).

METHODS

For this narrative review, a comprehensive search was conducted across four major databases: PubMed, Scopus, Web of Science, and Embase. The search strategy included the following keywords: "multiple myeloma," "clinical features," "diagnosis," "laboratory manifestations," and "plasma cell neoplasms." Studies were selected based on their relevance to the clinical and laboratory aspects of multiple myeloma, and their methodological quality, encompassing case studies, clinical trials, and systematic reviews. Articles that lacked sufficient data, were published prior to 2000, or were duplicates were excluded from the analysis. Ultimately, 15 references were included to provide a current and comprehensive overview of the clinical features, laboratory findings, and diagnostic strategies in multiple myeloma.

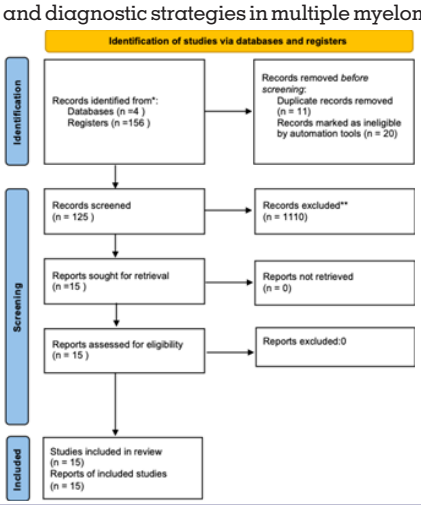

Figure 1. Prisma.

Epidemiology

Multiple myeloma (MM) is a relatively uncommon hematologic malignancy, accounting for approximately 1-2% of all cancers and over 17% of hematologic malignancies globally. The annual incidence in the United States is approximately 7 cases per 100,000 people, with 36,000 new cases and 13,000 deaths reported annually. Globally, MM accounts for around 180,000 new cases and 117,000 deaths each year. The disease predominantly affects older adults, with a median age at diagnosis between 65 and 74 years, and only 10% of patients are younger than 50 years. MM is more common in males and African American populations, with African Americans having a two to three times higher incidence compared to White populations (4,5).

Clinical Features

Multiple myeloma (MM) presents with a range of clinical manifestations primarily due to the proliferation of malignant plasma cells in the bone marrow and the production of monoclonal immunoglobulins. The most common presenting symptom is bone pain, reported by approximately 60% of patients, which is often associated with osteolytic lesions, osteoporosis, or pathologic fractures. These lesions predominantly affect the axial skeleton, including the spine, ribs, and pelvis (6,7).

Anemia is another common feature, present in 73% of patients at the time of diagnosis. This normocytic, normochromic anemia often results from bone marrow replacement by malignant plasma cells, relative erythropoietin deficiency, and, in some cases, dilution due to elevated levels of monoclonal protein. Renal insufficiency occurs in nearly 50% of patients, often as a result of light chain cast nephropathy, commonly referred to as "myeloma kidney." Other causes of kidney impairment include hypercalcemia and amyloidosis. Hypercalcemia is present in 28% of cases, often resulting from bone resorption due to osteoclast activation by the malignant plasma cells. This can lead to symptoms such as nausea, vomiting, confusion, and, in severe cases, coma (7).

Other less common clinical manifestations include recurrent infections due to immunosuppression, hyperviscosity syndrome, and neurologic symptoms such as spinal cord compression, which can occur in 5% of patients. The acronym "CRAB" (Calcium elevation, Renal insufficiency, Anemia, and Bone lesions) is frequently used to summarize the key defining features of MM. Early recognition and diagnosis of these clinical manifestations are crucial for improving patient outcomes (8,9).

Pathophysiology And Morphologic Characteristics

The pathophysiology of multiple myeloma (MM) is characterized by the malignant proliferation of clonal plasma cells within the bone marrow. These abnormal plasma cells produce monoclonal immunoglobulins or light chains, leading to several clinical and laboratory manifestations. One of the key hallmarks of MM is the production of a monoclonal (M) protein, which can be detected in the serum or urine of more than 97% of patients. The detection of this protein is crucial for diagnosis and monitoring of the disease. The monoclonal protein typically appears as a single sharp peak on serum protein electrophoresis (SPEP) and is confirmed by immunofixation (9).

In MM, bone marrow infiltration by clonal plasma cells often exceeds 10% of total cellularity, a critical diagnostic criterion. These plasma cells exhibit a range of morphologic features, from mature plasma cells with typical eccentric nuclei and abundant basophilic cytoplasm to more atypical forms with prominent nucleoli and higher nuclear-to-cytoplasmic ratios. Abnormal accumulations of immunoglobulin within the cytoplasm can result in the formation of Mott cells or Russell bodies, both of which are characteristic of MM (10).

In terms of immunophenotyping, MM cells commonly express plasma cell markers such as CD38, CD138, and CD79a. However, they often lack expression of CD19 and show variable expression of CD45. Notably, around 70% of myeloma cells express CD56, a marker typically absent in normal plasma cells. This pattern of expression helps differentiate myeloma from reactive plasmacytosis and other plasma cell disorders. Cytogenetic abnormalities are common in MM, although no single genetic mutation defines the disease. Common abnormalities include translocations involving chromosome 14q32, as well as deletions of 13q. These genetic changes contribute to the disease's heterogeneity and are associated with different prognoses. Bone destruction is a hallmark of MM pathophysiology, driven by the increased activity of osteoclasts and suppressed osteoblast function. This leads to the characteristic osteolytic lesions observed on imaging and contributes to the significant morbidity of the disease, including pathologic fractures and hypercalcemia. Understanding the pathophysiology and morphologic characteristics of MM is essential for diagnosis, prognosis, and therapeutic strategies (11).

Diagnosis And Imaging

The diagnosis of multiple myeloma (MM) is primarily based on a combination of clinical, laboratory, and imaging findings. The identification of a monoclonal (M) protein in the serum or urine is a cornerstone of diagnosis, detected in over 97% of patients through serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP), or free light chain (FLC) assays. These tests, alongside immunofixation, allow the detection and classification of the monoclonal protein. Nonsecretory myeloma, characterized by the absence of detectable M protein, is rare, but in these cases, diagnosis relies heavily on bone marrow biopsy and imaging studies (12).

Bone marrow biopsy is essential to confirm the diagnosis of MM, with the presence of clonal plasma cells in greater than 10% of the bone marrow cellularity being a diagnostic criterion. Flow cytometry and immunohistochemistry are used to establish the clonal nature of the plasma cells, typically revealing a light chain restriction (kappa or lambda) and aberrant expression of markers such as CD38, CD138, and CD56 (12).

Imaging plays a critical role in both the diagnosis and staging of MM. Conventional radiography, while useful, is limited in its ability to detect early bone lesions. More advanced imaging modalities, such as low-dose computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET)/CT, are now preferred. These techniques provide greater sensitivity in identifying osteolytic lesions, soft tissue plasmacytomas, and spinal cord compression. MRI is particularly valuable for assessing marrow infiltration and detecting vertebral fractures or spinal cord involvement. PET/CT offers additional functional information, helping to identify extramedullary disease and evaluate the metabolic activity of myeloma lesions. Incorporating both laboratory and imaging modalities is essential for an accurate diagnosis of MM, enabling better disease monitoring and guiding treatment decisions to improve patient outcomes (12,13).

Management Of Multiple Myeloma

The treatment of multiple myeloma (MM) has evolved significantly over the past decades, offering patients extended survival and improved quality of life. The management strategy typically depends on the patient's eligibility for autologous hematopoietic cell transplantation (HCT), risk stratification, and disease stage. For patients eligible for HCT, induction chemotherapy followed by stem cell collection and transplant is the standard of care. The induction phase generally involves the use of triple drug regimens, such as bortezomib, lenalidomide, and dexamethasone (VRd), aiming to reduce tumor burden and alleviate symptoms (13).

After successful induction, eligible patients undergo high-dose chemotherapy with melphalan followed by autologous stem cell transplantation. This approach has been shown to significantly improve progression-free survival (PFS) compared to chemotherapy alone (13).

For those not eligible for HCT, primarily older adults or those with significant comorbidities, treatment typically includes 8 to 12 months of induction chemotherapy, followed by maintenance therapy to delay disease progression. Regimens for non-transplant candidates may involve the same agents used for transplant-eligible patients but at adjusted dosages to minimize toxicity. Maintenance therapy, commonly with lenalidomide, helps maintain disease control but requires careful monitoring for potential long-term toxicities (14).

For patients with relapsed or refractory MM, treatment selection depends on the nature of the relapse. Early relapses or those with high-risk cytogenetic features often necessitate more aggressive approaches, potentially including multi-agent chemotherapy or participation in clinical trials. For later relapses, treatment options may include repeat use of previous therapies or the introduction of novel agents like monoclonal antibodies, proteasome inhibitors, or immunomodulatory drugs (14,15).

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