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Multiple myeloma

Gautam Raju Mehta, MD, Faten Suhail, MD, Rami Y. Haddad, MD, Ghassan Zalzaleh, MD, Edgar V. Lerma, MD

Multiple myeloma is defined as a malignant proliferation of a single clone of plasma cells resulting in monoclonal immunoglobulin production. It is often associated with extensive skeletal destruction, infections, anemia, hypercalcemia, and renal failure. Due to its multi-system consequences, it is important to be able to identify patients at risk and those who present with classical and non-classical signs and symptoms. It is equally as important to understand the pathophysiology of the disease to be able to treat specific disease processes adequately.

Epidemiology

Multiple myeloma (MM) accounts for nearly 1% of all cancers and for approximately 13% of all hematologic malignancies. The annual incidence in the United States ranges from 4 to 6 cases per 100,000 persons.[1] The incidence of myeloma increases with age, with the median age of diagnosis being 66 years old. It is very rare in individuals under the age of 40 years. Males are more commonly affected than females and the incidence in African–Americans is 2–3 times that in Caucasians.[1] Renal dysfunction in multiple myeloma is also quite common. In two large studies, it was found that 43% of patients had a plasma creatinine concentration > 1.5 mg/dL.[2] Renal disease often plays an important role in the survival of these patients.[2] One report found that the one-year survival in patients with plasma creatinine concentrations less than 1.5 mg/dL was upwards of 80% versus 50% in those with plasma creatinine concentrations greater than 2.3 mg/dL.[2] There is a general association between the severity of renal disease in MM and the long-term prognosis for patients.

Pathophysiology

Multiple myeloma (MM) is thought to develop from the malignant transformation of post-germinal center plasma cells. Multiple genetic and environmental changes lead to the transformation of these progenitor cells into a malignant neoplasm.[3]

It appears that the majority of cases of MM are preceded by monoclonal gammopathy of unknown significance (MGUS). It is thought to be the result of an abnormal plasma cell response to

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antigenic stimulation.[4] The progression from MGUS to MM occurs at random via genetic lesions, which include gene mutations, translocations, and alterations in the bone marrow microenvironment. Symptoms begin at this stage with plasma cell infiltration beginning to take effect.[4,5]

Osteolytic bone lesions result from an imbalance between osteoclastic and osteoblastic activity.[6] Mediated by the RANKL/OPG system and via increased interleukin production, osteolytic bone lesions often signal the onset of active malignancy. This increase in osteoclastic activity also mediates the hypercalcemia commonly found in multiple myeloma.[6,7]

Bone marrow crowding with malignant plasma cells is a hallmark of multiple myeloma, and thus anemia is a common consequence due to the replacement of hematopoietic tissue with tumor.[6]

Renal disease is a common complication and often one of the first clinical findings in multiple myeloma. It occurs through a variety of mechanisms and is often described based on the physiologic site of injury.[8] Glomerular damage results from multiple processes including primary amyloidosis, monoclonal immunoglobulin deposition disease of light or heavy chains, and monoclonal cryoglobulinemia. Tubular damage has also been identified in the setting of light chain cast nephropathy and proximal tubulopathy. Interstitial disease is a common secondary finding due to plasma cell infiltration.[8,9]

Light chains, or less commonly heavy chains, are often implicated in the pathogenesis of renal dysfunction in multiple myeloma. Normally light chains are filtered, reabsorbed in tubules, and broken down. Due to the significant increase in light chain production in multiple myeloma, the tubules become overwhelmed.[8] The normal rate of light chain excretion is <30 mg/day. In MM, the increased light chain excretion can reach levels of 100 mg to >20 g/day. Tubular damage will result either due to the toxic effects of light chains themselves, intratubular cast formation, or due to the intracellular release of lysosomal enzymes.[10] Tamm–Horsfall proteins (THMP) are usually secreted into the thick ascending loop of Henle.[11] Light chains will thus precipitate into the tubules through binding with THMP, creating obstructing and dense casts.[11]

In one study, kidney injury developed in up to 54% of patients who were found to have high urinary free light chains, but it was found in only 2% of those with no free light chains. A picture similar to type II proximal renal tubular acidosis occurs in this setting. The kidneys initially lose the ability to retain glucose and amino acids, which is combined with a loss in ability to acidify and concentrate the urine. Early proteinuria secondary to MM is predominantly light chains with very little albumin loss. However, once glomerular damage occurs, non-selective proteinuria (including albumin) becomes a feature.[9] Biochemically, patients with multiple myeloma are also prone to reduced anion gaps as a result of chloride retention secondary to the cationic M protein. Pseudohyponatremia often develops in the setting of elevated protein, and thus myeloma patients are more susceptible to acute kidney injury with dehydration.

Acute kidney injury is also seen in multiple myeloma as a result of intravenous radiocontrast use, non-steroidal anti-inflammatory drugs, bisphosphonate use, and hyperuricemia.

Diagnosis + laboratory studies

The clinical presentation of multiple myeloma varies, and the disease process often follows an insidious course. Once discovered, MM has often progressed extensively. A thorough history, physical examination, and routine laboratory testing should precede further investigation. Multiple myeloma is often suspected with clinical presentations including, but not limited to, bone pain; lytic lesions on imaging; unexplained hypercalcemia; acute renal failure; systemic signs suggestive of malignancy such as fatigue, weakness, and weight loss; or increased total serum protein levels.[1]

Clinical suspicion should prompt further evaluation. A complete blood count, serum electrolytes, urine and serum electrophoresis with immunofixation, and quantification of monoclonal protein should be sought after.[1] Trephine biopsy plus aspirate of bone marrow for cytogenic analysis or fluorescence in situ hybridization (FISH) should also be performed. A skeletal survey is essential in the identification of bone lesions.[1,9,12]

Diagnostic criteria include at least 10% clonal bone marrow cells and serum or urinary monoclonal proteins. Myeloma-related organ dysfunction is assessed with a serum