Review Article

Multiple Myeloma, the Plasma Cell Cancer: An Overview

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Abstract

Multiple myeloma (MM), also known as plasma cell myeloma, is a cancer of plasma cells, a type of white blood cells that normally produce antibodies. The word myeloma is from the Greek (myelo), meaning "marrow" and (oma), meaning "tumor." It usually occurs around the age of 60 and is more common in men than women. It is uncommon before the age of 40. Usually, no symptoms are noticed initially. As the disease progresses, bone pain, bleeding, frequent infections, and anemia may occur. The cause of this disease is unknown. Risk factors include obesity, radiation exposure, family history, and certain chemicals. The abnormal plasma cells produce abnormal antibodies, which can cause kidney problems and overly thick blood. The plasma cells can also form a mass in the bone marrow or soft tissue. When one tumor is present, it is called a plasmacytoma; more than one is called MM. MM is diagnosed based on blood or urine tests finding abnormal antibodies, bone marrow biopsy finding cancerous plasma cells, and medical imaging finding bone lesions. Another common finding is high blood calcium levels. MM is considered treatable, but generally incurable. Remissions may be brought about with steroids, chemotherapy, targeted therapy, and stem cell transplant. Radiation therapy is sometimes used to reduce pain from bone lesions.

Keywords: Abnormal antibodies, anemia, multiple myeloma, plasma cells

Introduction

Multiple myeloma (MM) is a cancer originating from the terminally differentiated B-lymphocytes, the antibody-secreting plasma cells.[1] It is classified among the B-cell non-Hodgkin lymphomas, while both clinical course and treatment do substantially differ from the classical nodal lymphomas. MM is a systemic disease with the tumor cell compartment predominantly localizing to the bone marrow requiring systemic treatment for affected individuals. Despite significant progress, the disease remains largely incurable. The incidence of MM is approximately 6/100,000/year in the Western countries and affects African 2–3 times more often than White Americans, rendering it the most common hematologic cancer in this specific ethnic group.[2]

In most patients, MM plasma cells secrete immunoglobulin (Ig) molecules (which are nonfunctional) to the plasma. Incomplete molecules, the Ig light chains, can be secreted as an isolated plasma cell product as well as in excess to intact Igs. Light chains are readily secreted through the kidneys to the urine during which process severe renal impairment may occur. MM is now known to evolve from monoclonal gammopathy of undetermined significance (MGUS) in all cases: MGUS represents a state in which a small number of already clonally transformed plasma cells are present which do not yet feature a clearly malignant phenotype. MGUS may progress to smoldering myeloma and eventually to "overt" MM which, besides the presence of clonal bone marrow plasma cells and their secreted "M component," is characterized by related organ and tissue impairment [Figure 1]. Currently, several clinical parameters are used to estimate the risk of transition from the clinically indolent "precursor diseases" (i.e., MGUS and smouldering myeloma) to symptomatic myeloma.[3]

Patients' median age at diagnosis is 69 years with a slight male predominance. Fortunately, prognosis has improved for affected individuals during the last 15 years, with median survival having doubled from 3 to 6 years.[4,5]

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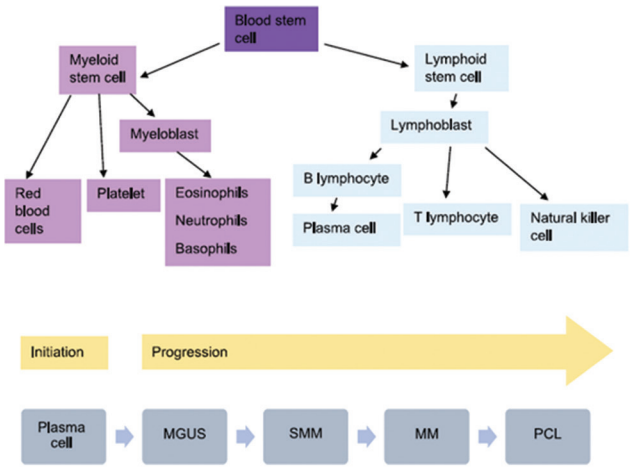

Figure 1: Hematopoietic stem cell differentiation pathways and the spectrum of plasma cell dyscrasias. MGUS: Monoclonal gammopathy of unknown significance, MM: Multiple myeloma, PCL: Plasma cell leukaemia, SMM: Smouldering multiple myeloma

Pathophysiology

B lymphocytes start in the bone marrow and move to the lymph nodes. As they progress, they mature and display different proteins on their cell surfaces. When they are activated to secrete antibodies, they are known as plasma cells. MM develops in B lymphocytes after they have left the part of the lymph node known as the germinal center. The normal cell line most closely associated with MM cells is generally taken to be either an activated memory B cell or the precursor to plasma cells, the plasma blast.[6]

The immune system keeps the proliferation of B cells and the secretion of antibodies under tight control. When chromosomes and genes are damaged, often through re-arrangement, this control is lost. Often, a promoter gene moves (or translocates) to a chromosome, where it stimulates an antibody gene to overproduction. A chromosomal translocation between the Ig heavy chain gene (on chromosome 14, locus q32) and an oncogene (often 11q13, 4p16.3, 6p21, 16q23, and 20q11) is frequently observed in people with MM. This mutation results in dysregulation of the oncogene which is thought to be an important initiating event in the pathogenesis of myeloma. The result is a proliferation of a plasma cell clone and genomic instability that leads to further mutations and translocations. The chromosome 14 abnormality is observed in about 50% of all cases of myeloma. Deletion of (parts of) chromosome 13 is also observed in about 50% of cases.[7]

Production of cytokines (especially interleukin-6) by the plasma cells causes much of their localized damage, such as osteoporosis, and creates a microenvironment in which the malignant cells thrive. Angiogenesis is increased. The produced antibodies are deposited in various organs, leading to kidney failure, polyneuropathy, and various other myeloma-associated symptoms.[8]

Clinical Presentation

The symptoms of MM are primarily related to bone infiltration by plasma cells or renal tubular damage by excess light chains. The clinical presentation of MM may be nonspecific. The most common presenting symptoms are fatigue, bone pain, and anemia. Renal failure may be a presenting feature, and about half of newly diagnosed MM patients have a raised creatinine level. Renal insufficiency can be due to hypercalcemia or a myeloma cast nephropathy caused by increased serum-free light chains. Other causes of renal failure include the use of nephrotoxic agents, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and secondary light-chain amyloidosis. Hypercalcemia may be found in approximately one-third of patients at diagnosis, and may require urgent therapy. While bone pain is present in up to 60% of patients when diagnosed with MM, a third of patients may also present with pathological fractures, usually of the axial skeleton, but also involving the long bones.[9]

Occasionally, MM may present as a medical emergency owing to spinal cord compression by an extradural plasmacytoma or vertebral fracture. Furthermore, patients with MM are at an increased risk of infections due to impaired cell-mediated and humoral immunity. Infections due to pneumococcal organisms are most common, but those due to hemophilus, Gram-negative organisms, and viruses are also increased.[10]

Approximately 7% of patients with MM may present with extramedullary disease only, which is associated with poorer survival. Less common clinical presentations include bleeding from platelet dysfunction or coagulation abnormalities, and hyperviscosity symptoms due to a very high M-protein level. Hepatosplenomegaly is unusual, except in cases of amyloid deposition. Some patients with MM may be diagnosed after an incidental finding of a raised globulin fraction on liver function tests performed for other reasons.[11]

Diagnostic Approach

Clinical evaluation

If a diagnosis of MM is suspected, history taking should pay particular attention to bone pain, constitutional symptoms, infections, and neurological complaints. A clinical examination should include assessment for pallor, bone tenderness, spinal deformities, and infections. A neurological examination is mandatory, especially with regard to signs of neuropathy and spinal cord compression.[10]

Investigations

Blood investigations

Baseline investigations for MM entail a full blood count (FBC) with a differential count and a smear, erythrocyte sedimentation rate, C-reactive protein and biochemical tests, including calcium, urea, and electrolytes, uric acid, and liver function tests. In some local setting, hepatitis B and C and HIV testing is usually performed.[11]

Common findings on the FBC include a normochromic, normocytic anemia in up to 73% of patients at diagnosis. More than 50% of patients demonstrate rouleaux formation on the peripheral smear due to high protein levels. Circulating plasma cells in the peripheral blood is an uncommon finding, but if present, may be indicative of a plasma cell leukemia. Patients who secrete a heavy-chain Ig have a raised globulin fraction (a high protein with normal-low albumin), while the globulin fraction is usually normal in patients with only light-chain secretion. The majority of patients with MM have decreased levels of uninvolved Igs (immune paresis), which predispose them to infection.[12]

Screening tests to demonstrate the M-protein include a serum protein electrophoresis (SPEP) with immune-fixation, and a serum free light-chain assay or urine protein electrophoresis (UPEP) with immune-fixation. More than half of patients with MM produce IgG heavy-chain M-protein, while 20% produce IgA and a similar number secrete only monoclonal light chains (light-chain myeloma). IgD and IgM monoclonal proteins are rare. Patients with light-chain myeloma have a normal SPEP, with light chains detected on the serum free light-chain assay and UPEP. About 2%–3% of patients have true nonsecretory MM with no detectable M-protein in the serum or urine; these patients require imaging and bone marrow biopsy for diagnosis and monitoring.[13]

Bone marrow examination

A bone marrow aspirate and trephine biopsy is key to the definitive diagnosis of MM. Plasma cell clonality is demonstrated on flow cytometry or immunohistochemistry. Fluorescent *in situ* hybridization studies aid with molecular characterization of MM, which is important for therapeutic decisions and prognostication[14] [Figure 2].

Imaging

Advanced imaging modalities are more sensitive for the diagnosis of MM and have largely replaced the skeletal survey in the developed world. Imaging techniques include whole-body, low-dose computed tomography (CT) scanning, ^{18}F-fluorodeoxyglucose positron emission tomography/CT (PET/CT) and magnetic resonance imaging (MRI).[15] PET/CT is more sensitive for soft-tissue lesions, while MRI has superior sensitivity for focal bone marrow involvement. MRI is also useful in cases of suspected spinal cord compression.[16]

A skeletal survey examination (skull, ribs, spine, pelvis, humerus, and femur radiographs) is useful in a setting where more specialized imaging is not available. Abnormalities on skeletal survey include punched-out lytic bone lesions, generalized osteopenia, and vertebral compression fractures[17-19] [Figures 3 and 4].

Management

Treatment is indicated in all patients who fulfill the criteria for the diagnosis of MM. Without treatment, the median survival is about 6 months[20,21] [Figure 5].

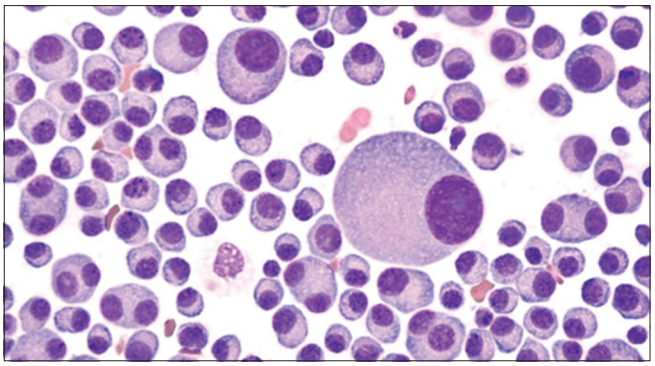

Figure 2: Bone marrow aspirate cytology of multiple myeloma

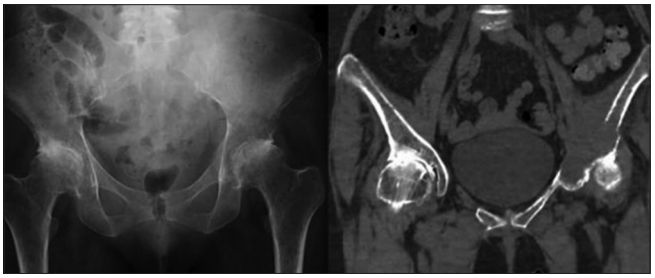

Figure 3: X-ray images such as the one on the left fail to indicate many cases of advanced bone destruction caused by multiple myeloma

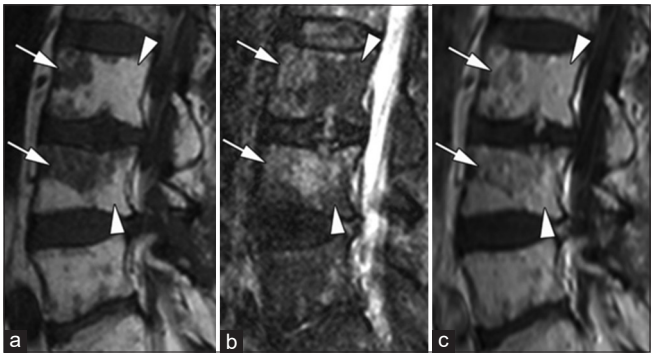

Figure 4: Magnetic resonant imaging appearance of multiple myeloma. Sagittal unenhanced T1-weighted (a), Short Tau Inversion Recovery (STIR) (b) and contrast material-enhanced T1-weighted (c) magnetic resonance images demonstrate areas of bone marrow with low signal intensity in a, intermediate signal intensity in b, and contrast enhancement in c (arrows). This signal intensity pattern is characteristic of active multiple myeloma lesions. The areas with high signal intensity in a, low signal intensity in b, and only mild or no enhancement in c (arrowheads) represent fat that has replaced the marrow as a result of radiation therapy

Supportive management and adjunctive therapies

The supportive aspect of management is crucial in MM. This is carried out by the observation of newly diagnosed patients, where there was a 10% rate of early death of patients with MM (within 60 days), mainly due to infection, followed by renal failure.[22]

Patients presenting as medical emergency cases require prompt intervention. Urgent radiotherapy is indicated in acute spinal cord compression. Severe hypercalcemia of rapid onset

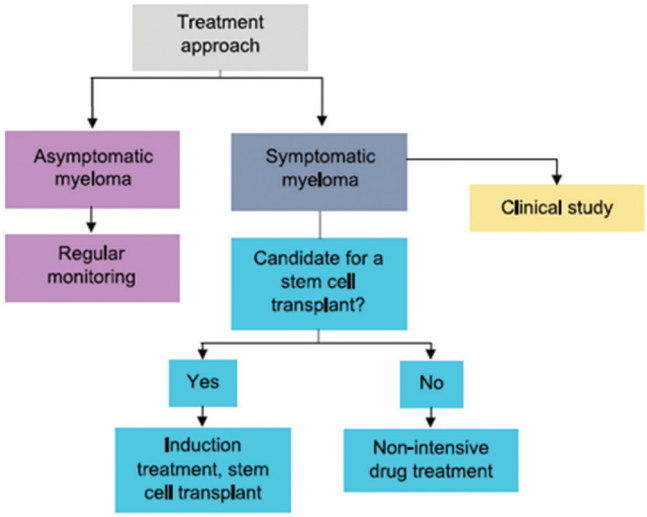

Figure 5: Treatment paradigm in multiple myeloma

requires urgent isotonic hydration, steroids and intravenous bisphosphonate therapy. Patients with uncommon presentations of hyperviscosity syndrome need prompt plasmapheresis.[23]

Care should be taken to avoid exacerbation of preexisting renal impairment. Nephrotoxic drugs such as aminoglycosides and NSAIDs must be avoided, and patients should maintain adequate hydration. Infections must be managed promptly, and patients must receive pneumococcal and influenza vaccines. Appropriate analgesia is important for the management of bone pain.[24]

Reversible underlying causes of anemia must be treated. Patients with acute, symptomatic anemia require blood transfusion. Erythropoiesis-stimulating agents may be used during the course of the disease, albeit with caution, owing to the increased risk of thrombosis associated with these agents. Bisphosphonate therapy is integral to the management of MM patients with symptomatic bone disease and lytic lesions or osteopenia on imaging. Apart from treating hypercalcemia, bisphosphonates improve bone pain, decrease skeletal-related events and have an antitumor effect. There is a role for surgery for fixation of pathological or impending fractures of the long bones, as well as spinal cord decompression of vertebral fragments. Vertebroplasty or kyphoplasty are useful adjuncts to pain control. Radiotherapy is also used for intractable bone pain and for the treatment of solitary plasmacytomas.[25]

Conclusion

Despite improvements in treatment and outcomes, most patients diagnosed with MM die as a result of their malignancy. Patients can be treated with multiples lines of therapy, but the depth and length of remission usually decrease with each relapse and the disease eventually becomes refractory.

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Conflicts of interest

There are no conflicts of interest.

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