Multiple Myeloma

AUTHORS: Michal Moshkovich & Matthew Lynn
ARTIST: Wendy Zhang

Pathoprofile

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INTRODUCTION

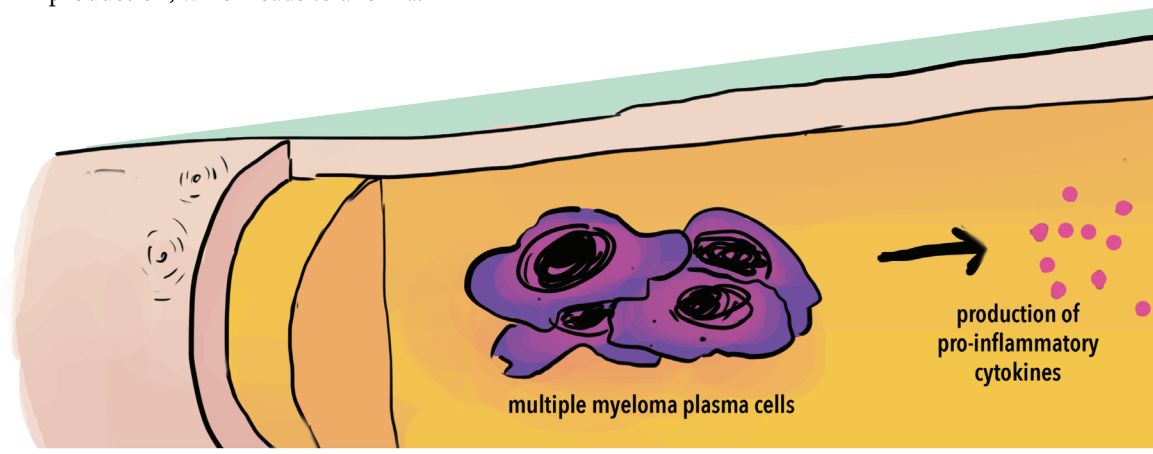
Multiple myeloma (MM) is a build-up of tumour plasma cells in the bone marrow.[1] Although considered a rare cancer, making up only ~1% of all cancer types, MM is the second most common hematologic malignancy.[2] This disease starts out in the premalignant stages as monoclonal gammopathy of undetermined significance (MGUS) defined by the presence of plasma cell-made monoclonal protein (M-protein) in the blood. MGUS leads to smouldering multiple myeloma, an intermediate stage which presents a greater amount of bone marrow plasma cells and M-protein in the blood.[3,4] Finally, symptomatic multiple myeloma takes the form of cancer and causes damage to the body.[3]

SYMPTOMOLOGY: CRAB

MM exhibits heterogeneous clinical symptoms.[1] The cause for this remains uncertain, but it has been proposed that the variety of symptoms experienced is related to chromosomal abnormalities located on the tumour plasma cells.[1] There is a standard set of symptoms that MM patients experience, represented by the CRAB criteria: calcium (hypercalcemia), renal impairment, anemia, and bone involvement.[5] Proliferating plasma cells produce immunoglobulins, specifically paraproteins (myeloma proteins), which can result in plasma hyperviscosity and kidney damage.[6] This proliferation can also cause bone marrow suppression and hypercalcemia.[6] These resulting conditions are reflected in the symptoms, such as fatigue as a result of anemia, or headaches due to hyperviscosity.[6] Due to the heterogeneity of symptoms, diagnosis of MM requires patients to exhibit these general symptoms, as well as abnormal plasma cells in the bone marrow, bone lesions, and/or a monoclonal protein in the serum or urine.[5] Of all common cancers, MM has the longest interval of time between presentation of primary symptoms and diagnosis.

SIGNALING PATHWAYS

There is a variety of signalling pathways involved in apoptosis, cell growth, survival, and drug resistance of MM cells. One family of dimer transcription factors called NF-κB, is involved in intracellular functions such as apoptosis, inflammation, angiogenesis, and immunity.[7] Mutations and pro-inflammatory cytokines in the microenvironment of MM cells activate this NF-κB pathway, while several clinical drugs aim to inhibit it to overcome drug resistance and prompt apoptosis.[7] Hypercalcemia present in MM occurs due to an increase of osteoclastic bone resorption as a result of local cytokine release by MM cells.[8] Bone resorption further initiates the entrance of calcium into extracellular fluid.[8] While the development of anemia in MM patients can be explained through several factors, the most common factor is inadequate production of erythropoietin (EPO), a hormone synthesized by the kidney that plays a significant role in the synthesis of red blood cells.[9] The production of inflammatory cytokines such as Interleukin-1 and tumor necrosis factor in MM patients downregulates EPO production, which leads to anemia.[9,10]



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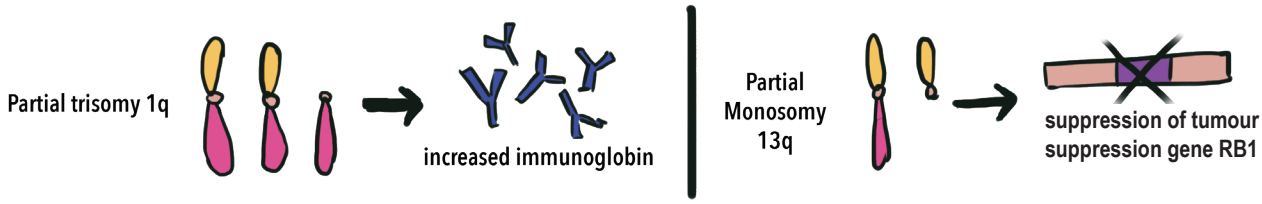
Risk Factors

Although the cause of MM is uncertain, recent studies have sought to investigate the complex interrelation between genetic, demographic, and environmental factors that may increase the risk of developing MM.[3] Genetic findings often vary across studies due to the complexity of the disease; however, research has primarily focused on chromosomes 1 and 13. 35-40% of MM cases exhibited trisomy 1q, where three copies of the q arm on chromosome 1 are present instead of the normal two.[3,11] Furthermore, an additional 45-50% of cases exhibited chromosome 13q deletion, possessing only 1 copy of the q arm on chromosome 13.[11] Trisomy 1q was associated with increased immunoglobin levels, while 13q deletion was correlated with lower levels of tumour-suppressor gene RB1. These are characteristics associated with MM and cancer development.[11] Considering these abnormalities were not present in all cases, genetic factors alone may not be sufficient in determining MM risk. MM is most common among elderly populations with median age of diagnosis ranging from 66 to 70; patients under 30 comprised only 0.02% of cases.[12] Studies show that MM occurs twice as frequently in African-American populations than among European-Americans, suggesting that ethnicity may also play a role. As with most cancers, exposure to external radiation appears to increase the risk of MM, as seen in a 1948-2004 cohort study of Russian plutonium production workers.[13]



Treatment

Treatment of MM depends on a patient's eligibility for autologous stem cell transplantation (ASCT) as assessed by the clinician. In ASCT- eligible patients, blood-forming stem cells are harvested from a patient's bone marrow following 3-4 cycles of pharmaceutical induction therapy. This is often achieved with Bortezomib, a proteasome inhibitor that disrupts the cell cycle and induces apoptosis.[14] Patients may then be given dexamethasone to improve the sensitivity of myeloma cells, before treatment with high doses of chemotherapy.[14] The stem cells are then released back into the bloodstream to allow the bone marrow to produce new blood cells.[14] Patients ineligible for ASCT will be provided with 8-12 cycles of Bortezomib and dexamethasone.[14] Both ASCT and non-ASCT patients then undergo maintenance therapy with lenalidomide in order to prevent the growth of residual myeloma cells.[15] Although these treatments have proved quite effective in improving prognosis, almost all MM patients eventually relapse and require multiple treatment cycles throughout their lives. In addition to pharmaceutical interventions, studies have shown that low inflammatory diets, high in fruits and vegetables, may also decrease risk for MM.[16]

REVIEWED BY: TOM KOUROUKIS

Dr. Kouroukis is an Associate Professor in the Department of Oncology and Division Head of Malignant Hematology at McMaster University. His clinical interests include the treatment of older patients with hematological malignancies.