

Pathobiology, Epidemiology, and Diagnosis of Multiple Myeloma

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Introduction

Multiple myeloma is the second most common hematologic malignancy, accounting for 10% of all cases (Rajkumar, 2016). Multiple myeloma is described as an increase in clonal altered plasma cells, characterized by plasmacytosis in bone marrow, production of monoclonal proteins, osteolytic bone lesions, renal disease, anemia, hypercalcemia, and immunodeficiency. The development of myeloma is a complex multistep process characterized by early and late genetic changes in the tumor cell, as well as unique supportive conditions within the bone marrow microenvironment (Abramson, 2018; Rajkumar & Kumar, 2016; Siegel et al., 2020). Although myeloma remains incurable, overall survival has improved over time because of advancements in the understanding of myeloma biology, ongoing development of novel therapies, and technological improvements of genetic sequencing affecting the therapeutic options and clinical outcomes (Dingli et al., 2017; Naymagon & Adul-Hay, 2016; Rajkumar, 2018).

The diagnosis of multiple myeloma is preceded by a premalignant phase known as monoclonal gammopathy of undetermined significance (MGUS). MGUS is associated with the presence of monoclonal immunoglobulins detected in blood or urine. The diagnosis of MGUS in the clinical setting includes a proportion of bone marrow plasma cells (BMPCs) at less than 10% and the absence of myeloma-related end-organ abnormalities, or specifically without hypercalcemia, renal impairment, anemia, and osteolytic bone lesions (known as CRAB symptoms). MGUS is detected in 3% of the population over the age of 50 years and progresses to active

multiple myeloma in 1% of these patients per year (Dhodapkar, 2016; Kyle et al., 2018; Pinto et al., 2020; van Nieuwenhuijzen et al., 2018).

If MGUS transforms, progression to smoldering multiple myeloma may be identified. Smoldering multiple myeloma is an asymptomatic clonal plasma cell disorder that is diagnosed with the following clinical findings (Jamet et al., 2020; Landgren, 2017; Zhao et al., 2019):

- BMPC proportion greater than 10%–60%
- Monoclonal protein of 3 g/dl or greater
- No CRAB symptoms or other myeloma-defining event

The progression of smoldering multiple myeloma to active multiple myeloma is complicated but reported at approximately 10% per year for the first 5 years after diagnosis, 3% per year for the next 5 years, and 1% per year for the subsequent 10 years (Jamet et al., 2020; Landgren, 2017; Zhao et al., 2019).

As previously described, active multiple myeloma arises from MGUS or smoldering multiple myeloma. Specific findings of active multiple myeloma include the presence of one myeloma-defining event in addition to evidence of either greater than 10% BMPC involvement or a biopsy-proven plasmacytoma. Other established myeloma criteria include the presence of CRAB symptoms and biomarkers consisting of the proportion of clonal BMPCs at 60% or greater, serum free light chain (SFLC) ratio of 100 or greater (i.e., involved SFLC divided by uninvolved SFLC is greater than 100 mg/L), and one or more myeloma lesions diagnosed by magnetic resonance imaging (MRI) (Palumbo et al., 2015; Rajkumar, 2019).

Molecular Pathogenesis

Underlying molecular variations affect the clinical course of multiple myeloma (Dhodapkar, 2016; Morelli et al., 2020; Schürch et al., 2020). Although some patients experience long periods of indolent disease, others relapse early and are refractory to therapy throughout the trajectory of their disease. Outcome improvement is contingent on developing a better understanding of molecular abnormalities that create differences in myeloma survival. These features may relate to messenger RNA (mRNA), DNA, or protein changes. The overall aim of healthcare providers and researchers is to identify chromosomal abnormalities to improve staging, outcome, or treatment relevant to a specific patient or subgroup of patients (Castaneda & Baez, 2019; Pawlyn & Davies, 2019; Rajkumar, 2016).

Bone Marrow Microenvironment

Clonal plasma cells compete for access to the bone marrow niche, and these abnormal cells suppress healthy plasma cell activity, leading to immunosuppression, impaired hematopoiesis, osteolytic bone lesions, and impaired renal dysfunction (Walker et al., 2018). A better understanding of the relationship between myeloma cells and the bone marrow microenvironment has resulted in identifica-

tion of new molecular targets, new treatment options, and experimental strategies (Fairfield et al., 2016).

Mesenchymal stem cells give rise to bone marrow stromal cells (BMSCs), which play an integral role in myeloma proliferation, survival, migration, drug resistance, osteoclastogenesis, and angiogenesis. BMSCs are multipotent progenitor cells that can differentiate into a variety of cells, such as adipocytes, endothelial cells, osteoblasts, and fibroblasts (Dehghanifard et al., 2018; Mekhloufi et al., 2020; Ramakrishnan & D'Souza, 2016; Xu et al., 2018). The communication between BMSCs and myeloma cells promotes a tumor-generating microenvironment within the bone marrow. BMSCs promote production of cytokines, such as interleukin (IL)-6 and tumor necrosis factor (TNF)-alpha, chemokines (e.g., stromal-derived factor-1, IL-8), and growth factors (e.g., insulin-like growth factor-1, hepatocyte growth factors), all of which cause disease progression and resistance to chemotherapy (Bieghs et al., 2016; Terpos et al., 2018; Vallet et al., 2018; Xu et al., 2018).

The interaction of myeloma cells with the bone marrow microenvironment involves the activation by cytokines, growth factors, and adhesion molecules in a cascade series that adds to the proliferation and antiapoptosis of myeloma cells (Dehghanifard et al., 2018; Fairfield et al., 2016). The unique cellular communication creates a milieu that allows for infiltration, growth proliferation, adhesion, and migration of myeloma cells, further providing an environment to create drug-resistant myeloma cells (Fairfield et al., 2016).

The pathophysiologic abnormalities are complex and interdependent with overlapping pathways that lead to myeloma progression. Several signaling pathways interact with myeloma cells, and a comprehensive discussion of these pathways is beyond the scope of this chapter. These pathways include the following (Hu & Hu, 2018; Parrondo & Sher, 2019; Terpos et al., 2018):

- Phosphatidylinositol-3 kinase/Akt/mechanistic target of rapamycin
- Inhibitor of nuclear factor-kappa B kinase
- Receptor activator of nuclear factor kappa-B (RANK)/RANK ligand (RANKL)/osteoprotegerin (OPG)
- Ras/Raf/mitogen-activated protein kinase
- Mitogen-activated protein kinase/extracellular signal-regulated kinase
- Janus kinase 2/signal transducer and activator of transcription 3
- Wingless-type pathway

Table 2-1 describes these pathways and additional factors associated with the growth and proliferation of myeloma cells.

The Interaction with Osteoclasts and Osteoblasts in Myeloma

A distinct characteristic of multiple myeloma is the development of bone disease. During osteoclastogenesis, osteoclastic cells remove bone tissue as bone remodeling occurs, whereas osteoblastic cells build bone tissue. It is common for myeloma cells to migrate to bone structures in the body. Skeletal involvement in this patient popu-

Table 2-1. Pathways That Lead to Myeloma Progression

Pathway	Function
JAK2/STAT3	JAK2/STAT3 pathway upregulates gene transcription. IL-6 signaling in bone marrow causes activation of the JAK2/STAT3 pathway, resulting in phosphorylation of STAT proteins. Activation is associated with multiple myeloma cell survival.
MAPK <ul style="list-style-type: none"> • ERK family • JNK family • p38 MAPK family 	Pathway regulates the production and secretion of cytokines. Pathway regulates key cellular processes, such as cell cycle progression, growth, differentiation, and apoptosis.
PI3K/Akt	When activated, PI3K binds to Akt. Akt then phosphorylates and modulates multiple proteins, leading to increased cell growth and survival, decreased apoptosis, and drug resistance. P13K/Akt pathway is upregulated in myeloma cells and interacts with nonmalignant cells in the microenvironment.
RANK/RANKL	RANK/RANKL activates downstream signaling pathways required for osteoclast development, differentiation, and maturation.
Wingless-type pathway <ul style="list-style-type: none"> • Dickkopf-1 • Sclerostin 	Wingless-type pathway regulates plasma and B-cell motility. Pathway plays a key role in bone disease by prompting proliferation and survival of osteoblastic cells. Dickkopf-1 is elevated in patients with multiple myeloma, inhibits wingless type pathway, and blocks transcription factor Runx2/Cbfa1 necessary for osteoblast cell differentiation. Pathway inhibits osteoblast cell differentiation. Pathway is associated with advanced multiple myeloma.

Akt—protein kinase 3; ERK—extracellular signal-regulated kinase; IL—interleukin; JAK—Janus kinase; JNK—c-Jun N-terminal kinase; MAPK—mitogen-activated protein kinase; PI3K—phosphatidylinositol 3-kinase; RANK—receptor activator of nuclear factor kappa-B; RANKL—receptor activator of nuclear factor kappa-B ligand; STAT—signal transducer and activator of transcription

Note. Based on information from Chong et al., 2019; Dehghanifard et al., 2018; Parrondo & Sher, 2019; Tai et al., 2018; Terpos et al., 2018; Vallet et al., 2018.

lation is related to the increased activity of osteoclasts and equally related to the lack of appropriate compensatory osteoblastic responses. Osteoclast activation and formation are involved in the development of osteolytic bone lesions that are characteristic in patients with myeloma (Brigle & Rogers, 2017; Fairfield et al., 2016).

Myeloma bone disease occurs in the setting of an imbalance of bone remodeling. Specifically, an increase in bone resorption occurs that is mediated by osteoclasts. A reduction in bone formation also occurs through the downregulation of the number of functional osteoblasts. Functionally, myeloma cells interfere with physiologic bone remodeling. Osteoclasts promote cytokines, such as RANKL, IL-1, IL-6,

and chemokine C-C motif ligand 3 and 20. Myeloma cells are also responsible for the inhibition of osteogenesis, as they upregulate osteoblast inhibitors, including dickkopf-1 and sclerostin (Vallet et al., 2018). Osteolytic bone resorption is caused by the stimulation of osteoclastogenesis and the suppression of osteoblastogenesis adjacent to the area of the tumor. Other growth factors involved in multiple myeloma bone disease include IL-1, IL-3, IL-11, IL-17, vascular endothelial growth factor, and stromal-derived factor-1-alpha (Espagnollet et al., 2020; Fairfield et al., 2016; Parrondo & Sher, 2019; Terpos et al., 2018; Vallet et al., 2018).

Osteoblastic cells regulate bone resorption by two processes. The first process is through OPG (osteoclastogenesis inhibitory factor), which is a member of the TNF receptor family. The second process is through RANKL, which is a transmembrane signaling receptor and a member of the TNF superfamily. RANKL is found on the surface of osteoclasts. RANK, RANKL, and OPG are considered key factors in regulating osteoclastic activity, and these factors form an important pathway of healthy and malignant bone remodeling. OPG binds to RANKL and inhibits bone resorption. RANKL stimulates osteoclast differentiation and activity, whereas OPG inhibits these processes. In multiple myeloma, the balance of RANKL and OPG is disrupted, leading to the activation of osteoclasts (Terpos et al., 2018; Vallet et al., 2018).

BMSCs secrete OPG, which prevents excessive activation of osteoclasts by serving as a decoy receptor and competing with RANK for binding to RANKL. The blockade of RANKL binding to RANK or the binding of OPG to RANKL inhibits osteoclast maturation and contributes to bone destruction. Elevated levels of soluble RANKL in patients with multiple myeloma are associated with disease burden and prognosis (Terpos et al., 2018). The consistent theme of bone damage in multiple myeloma is that myeloma cells affect the OPG-to-RANKL ratio in the bone marrow microenvironment, which results in bone disease.

The Role of Genetics in Multiple Myeloma

Active multiple myeloma develops over a period of time from several complex genetic events. This multistep process is initiated from premalignant diagnoses, such as MGUS and smoldering multiple myeloma (Manier et al., 2017; Robiou du Pont et al., 2017; Schürch et al., 2020). Abnormal karyotypes are identified in approximately 30%–50% of patients with myeloma (Saxe et al., 2019). Most genomic abnormalities in patients with myeloma are identified using metaphase cytogenetics, conventional karyotyping, or fluorescence in situ hybridization (FISH) analysis. More recently, array-comparative genomic hybridization and single-nucleotide polymorphism array have been utilized (Barilà et al., 2020).

Although the overall survival in myeloma has improved in recent years, patients identified as high risk have a progression-free survival of less than 18 months or an overall survival of less than 1.5–3 years. Genetic drivers are the important factors in identifying high-risk patients. Genetic abnormalities related to myeloma are described in two classifications. The first classification is translocation involving

immunoglobulin (Ig) heavy chain locus, also known as nonhyperdiploidy. Greater than 90% of genetic Ig heavy chain abnormalities are found on chromosome 14 and partner with chromosomes 4, 6, 11, and 20 (Barilà et al., 2020; Castaneda & Baz, 2019). The other category is hyperdiploidy or trisomies that involve odd chromosomes (3, 5, 7, 9, 11, 15, 19, and 21) and comprises approximately 40% of genetic abnormalities in patients with myeloma. Hyperdiploidy findings are generally associated with a more favorable outcome, except for trisomy 21. Nonhyperdiploidy and hyperdiploidy are associated with cyclin D genetic abnormalities (Bolli et al., 2018; Maes et al., 2017).

One identified high-risk driver is the loss of the tumor suppressor gene *TP53* (deletion of 17p), which is found in less than 10% of patients with newly diagnosed myeloma. *TP53* is also identified in patients with relapsed and refractory disease. Genetic drivers in patients with myeloma remain a focus of investigation. The goal of identifying genetic drivers is to improve treatment options and extend overall survival (Pawlyn & Morgan, 2017).

Genomic research has generated prognostic information and risk stratification, and it plays a significant role in precision medicine for patients with myeloma. Genomic abnormalities are associated with a variety of outcomes (i.e., favorable, neutral or standard, and poor). Table 2-2 describes genomic alterations, frequency of occurrence, and prognostic outcome. Examples of genomic findings associated with a poor outcome include translocations t(4;14), t(14;16), and t(14;20) and 1q and 17p deletion (Aktas Samur et al., 2019).

Secondary genetic abnormalities are also commonly found in patients with multiple myeloma. Translocation of *MYC* is a secondary chromosomal abnormality that is present in approximately 35% of newly diagnosed patients. *MYC* variation is more common in the relapsed and refractory setting, suggesting that *MYC* alterations promote disease progression (Barwick et al., 2019). Other secondary genomic events include 1q deletion, 17p deletion, and monosomy 17, all of which are associated with a poor prognosis. Monosomy 13 and 13q deletion are the most common secondary genomic abnormalities (Barilà et al., 2020; Flynt et al., 2020; Pawlyn & Davies, 2019; Robiou du Pont et al., 2017; Schürch et al., 2020).

Several initiatives are underway to investigate biomarker-driven personalized treatment approaches for patients with multiple myeloma. Studies such as the MyDRUG trial and CAPTUR trial will incorporate agents targeted to a large number of molecular drivers that are associated with preclinically determined treatment options (Auclair et al., 2019; Skamene et al., 2018). Advancement in myeloma research is directed at identifying therapies associated with genomic findings. One area of interest is the use of venetoclax. Recent studies have demonstrated superior progression-free survival in patients with relapsed or refractory multiple myeloma with translocation t(11;14) genetic abnormalities (Auclair et al., 2019; Kumar et al., 2017; Paner et al., 2020; Pawlyn & Davies, 2019).

Abundant multiple myeloma research suggests that defining high-risk characteristics in the context of the bone marrow microenvironment will be the key to further improvement in treatment options for patients with myeloma. The goal

Table 2-2. Chromosomal Findings in Multiple Myeloma

Class	Description	Genes Affected	Frequency in Newly Diagnosed (%)	Risk
Primary Events				
Translocation	t(4;14)	<i>MMSET</i>	10–15	High
	t(6;14)	<i>CCND3</i>	3	Standard
	t(11;14)	<i>MAF</i>	15–20	Standard
	t(14;16)	<i>MAF</i>	3	High
	t(14;20)	<i>MAFB</i>	1	High
Copy number aberrations	Hyperdiploidy (trisomy) 3, 5, 7, 9, 11, 15, 19, or 21	Odd-numbered chromosomes	50	Favorable
Secondary Events				
Translocation	<i>MYC</i>	<i>MYC</i>	20	High
Copy number aberrations	1q21 gain	<i>CKS1B</i>	30–35	High
	1p deletion	<i>CDKN2C, FAF1, FAM46C</i>	20	High
	13q deletion	<i>RB1, LAMP1</i>	20	Standard/ high
	17p deletion	<i>TP53</i>	10	High

Note. Based on information from Bergstrom et al., 2020; Binder et al., 2017; Caers et al., 2018; Castaneda & Baz, 2019; Maes et al., 2017; Pawlyn & Morgan, 2017; Rajkumar, 2020; Saxe et al., 2019; Sonneveld et al., 2016.

of ongoing genomic analysis is to identify targets that can be incorporated into such studies that will improve the progression-free survival and overall survival in myeloma (Auclair et al., 2019; Maes et al., 2017; Pawlyn & Morgan, 2017).

Diagnosis of Plasma Cell Disorders

The diagnosis of MGUS, smoldering multiple myeloma, and active multiple myeloma is based on the clinical, biologic, and radiologic clinical presentation. The incidence of MGUS increases with age, and approximately 3% of people aged 50 years and older meet the criteria for MGUS. The hallmark of this clinical finding is the increase in plasma cells not associated with clinical symptoms or high-risk lab-

oratory abnormalities. MGUS and smoldering multiple myeloma are commonly discovered as incidental findings investigated in the setting of abnormal laboratory values. Some of these abnormalities include an increase in total protein or globulin and an abnormal serum protein electrophoresis panel (SPEP) obtained for a variety of symptoms, such as neuropathy, increase in infections, and chronic inflammatory demyelinating polyneuropathy.

Monoclonal Gammopathy of Undetermined Significance

MGUS is a diagnosis of exclusion after smoldering multiple myeloma and active multiple myeloma have been excluded. MGUS is categorized in three ways: IgM, non-IgM (consisting of IgG and IgA), and light chain (Bergstrom et al., 2020; Rajkumar et al., 2014). In 2014, the International Myeloma Working Group (IMWG) described the following clinical findings in MGUS: the absence of CRAB criteria, monoclonal protein less than 3 g/dl, urinary protein less than 500 g/24 hours, and BMPC involvement less than 10% (Rajkumar et al., 2014). Imaging is necessary to rule out bone lesions. Imaging should include positron-emission tomography-computed tomography (PET-CT), whole-body low-dose CT, or whole-body MRI (Dhodapkar, 2016; Rajkumar et al., 2014).

Literature supports that certain high-risk factors are associated with MGUS progression. A study in Sweden reported that in 728 patients with MGUS, the suppression of one or two immunoglobulins (immunoparesis) was associated with a greater risk of progression than in participants without suppression (Turesson et al., 2014). The overall risk of progression in that study was 0.5% per 2.5 years (Turesson et al., 2014). A monoclonal protein concentration greater than 1.5 mg/dl and a SFLC ratio less than 0.26 or greater than 1.65 were also found to be risk factors (Turesson et al., 2014). IgD MGUS is also considered high risk.

Transformation to active multiple myeloma occurs most often in patients with IgA MGUS. IgM MGUS is more likely to develop into Waldenstrom macroglobulinemia. IgG MGUS is not a high-risk feature (van Nieuwenhuijzen et al., 2018). Bone marrow biopsy and aspiration should be considered in patients suspected of having MGUS. Cytogenetic testing with FISH should be obtained. Patients diagnosed with MGUS should be monitored closely for disease transformation to smoldering or active multiple myeloma, and a plan of care should be determined and communicated early in the MGUS diagnosis. Initial follow-up should be scheduled for six months and annually if the clinical status remains stable (Bergstrom et al., 2020; Caers et al., 2018).

Smoldering Multiple Myeloma

Smoldering multiple myeloma is a preclinical malignancy that precedes the diagnosis of active multiple myeloma. Patients diagnosed with smoldering multiple myeloma are previously diagnosed with MGUS and are at increased risk for developing active multiple myeloma. IMWG defines smoldering multiple myeloma

as 10%–60% BMPC involvement, and/or serum monoclonal protein greater than 3 g/dl or urine monoclonal protein greater than 500 mg/24 hours. Smoldering multiple myeloma does not present with CRAB criteria (Bergstrom et al., 2020; Lakshman et al., 2018; Rajkumar et al., 2014; San Miguel et al., 2019). The risk of smoldering multiple myeloma progressing to active disease is approximately 10% annually in the first five years, 3% in the subsequent five years, and 1% after that time frame (Bergstrom et al., 2020; Jamet et al., 2020; Landgren, 2017; Zhao et al., 2019).

The Mayo Clinic and the Spanish models are classification systems that describe high-risk smoldering multiple myeloma. The Mayo Clinic model measures risk factors as monoclonal protein 3 g/dl or more, BMPC involvement of 10% or more, and involved to uninvolved SFLC ratio of 8 or more. This method results in the classification of patients into three risk categories (Lakshman et al., 2018). Patients with smoldering multiple myeloma who have all three risk factors have a 76% chance of progression over a five-year period (Lakshman et al., 2018). The Spanish model uses the proportion of BMPCs with aberrant plasma cell phenotype on flow cytometry ($\geq 95\%$) and immunoparesis of uninvolved immunoglobulins to identify high-risk patients. Based on these parameters, the five-year cumulative probability of progression was 4% with no risk factors, 46% with one risk factor, and 73% with two risk factors (Pérez-Persona et al., 2007). Imaging should be obtained to assess for bone involvement by one of the following: PET-CT, whole-body low-dose CT, or whole-body MRI (Pérez-Persona et al., 2007).

San Miguel et al. (2019) reported that high-risk factors for smoldering multiple myeloma were serum monoclonal protein of 2 g/dl, involved to uninvolved SFLC ratio of 20, and BMPC involvement greater than 20%. Similar to other models, the number of factors defined risk: low with no risk factors, intermediate with one risk factor, and high with two or more risk factors (San Miguel et al., 2019). Underlying cytogenetic abnormalities are essential to identify high-risk patients. Patients diagnosed with translocation t(4;14) and deletion of 17p are classified as having high-risk smoldering multiple myeloma (Madhira et al., 2020; Pérez-Persona et al., 2007).

Patients with high-risk smoldering multiple myeloma should be closely monitored for disease progression, and clinicians should evaluate clinical status on a routine basis. It is suggested that individuals with high-risk characteristics continue with ongoing clinical evaluation consisting of blood work and clinical assessment every two to three months following the initial diagnosis. Imaging should be obtained when clinically indicated. Clinical assessment can be extended to every four to six months if clinical condition remains stable. Patients with low-risk smoldering multiple myeloma should be followed with blood work and clinical assessment every three to four months for the first year and every six months after the first year with stable disease (Bergstrom et al., 2020).

Active Multiple Myeloma

Multiple myeloma is highly suspected when individuals report or present with the following clinical findings: bone pain and subsequent osteolytic lesions reported

on imaging, symptomatic or asymptomatic hypercalcemia, acute renal failure, and unexplained anemia or an increase in infections. It is estimated that bone pain and anemia are described at diagnosis in approximately 70% of patients. Fatigue occurs in nearly all patients (98%) with active multiple myeloma. Renal failure is also a presenting symptom and occurs in approximately 20% of patients with myeloma. Hypercalcemia and an increase in infections are reported in approximately 15% of individuals with newly diagnosed myeloma. Other presenting symptoms include peripheral neuropathy, headaches which suggest hyperviscosity, visual disturbances, and mucosal bleeding (Bergstrom et al., 2020; Pawlyn & Jackson, 2019; Ramsenthaler et al., 2016). Howell et al. (2017) reported that patients with newly diagnosed myeloma who presented to the emergency department or were emergently hospitalized with myeloma symptoms were found to have advanced disease and poorer outcomes compared to patients with newly diagnosed disease who did not present in an emergency setting.

The diagnosis of multiple myeloma requires the presence of one or more myeloma-defining events in addition to BMPC involvement greater than 10% or biopsy-proven plasmacytoma. A myeloma-defining event is determined by the presence of an established CRAB feature in addition to BMPC involvement greater than 60% or a SFLC ratio of greater than 100 (Bergstrom et al., 2020; Caers et al., 2018; Rajkumar, 2018).

Diagnostic Tests

Diagnostic workup of multiple myeloma should begin with basic blood work consisting of complete blood count with differential and complete metabolic panel, including electrolytes, renal studies, liver function test, calcium, phosphorus, uric acid, albumin, and globulin. A lactate dehydrogenase test should be obtained, as it is a marker that is often elevated in aggressive disease (Rajkumar, 2019). Based on initial testing, more advanced laboratory work and tests should be obtained when myeloma is suspected.

Beta-2 microglobulin should be included in the initial workup. Beta-2 microglobulin is a biomarker that can accumulate in patients with renal dysfunction and ultimately can correlate to systemic myeloma disease burden. Other laboratory work that should be obtained is an SPEP with immunofixation and SFLC (Bergstrom et al., 2020; Caers et al., 2018). In a study of patients with plasma cell proliferative diseases, SFLC, SPEP, and immunofixation were found to detect monoclonal immunoglobulin in 74%, 79%, and 87%, respectively (Willrich & Katzman, 2016). A 24-hour urine collection for protein and urine protein electrophoresis panel should also be included in the workup. Table 2-3 describes a list of comprehensive tests that should be ordered to diagnose multiple myeloma.

Many patients are referred to a hematology specialist or oncologist when multiple myeloma is suspected. It is common for the specialist to order a bone marrow biopsy and aspirate, as well as imaging to include whole-body low-dose CT scan,

Table 2-3. Initial Tests to Diagnose Multiple Myeloma

Test	Description	Clinical Significance
Blood chemistries	Beta-2 microglobulin	Beta-2 microglobulin correlates to systemic myeloma burden and is used in staging.
	Blood urea nitrogen, creatinine	Aggressive myeloma can affect the kidneys and is measured by an increase in creatinine and blood urea nitrogen.
	Calcium	Increase in calcium and alkaline phosphatase is caused by bone disease in myeloma.
	Electrolytes	Electrolytes imbalances could reflect renal dysfunction. Decrease in sodium can be noted in patients with high protein levels.
	Liver function tests, alkaline phosphatase, albumin	Increase in calcium and alkaline phosphatase is caused by bone disease in myeloma. Albumin levels are decreased.
	Total protein, globulin	Immunoglobulins are proteins. Total protein is often elevated in myeloma, and most is globulin.
Bone marrow biopsy and aspirate	Cellular assessment and bone marrow plasma cell quantification	Cellular assessment measures disease burden and is used in staging. See also Table 2-2.
	Chromosomal abnormalities (chromosome analysis and FISH) to detect unfavorable cytogenetic aberrations	The following high-risk cytogenetic findings are associated with poor prognosis: <ul style="list-style-type: none"> • Translocations t(4;14), t(14;16), t(14;20) • Deletion 17/17p • Gain 1q
	Immunophenotype (flow cytometry)	Flow cytometry identifies biomarkers.
Complete blood count with differential	Platelets	Platelets are decreased with significant bone marrow involvement.
	Red blood cells	Anemia is common at diagnosis.
	White blood cells	White blood cell count may be elevated in plasma cell leukemia. Absolute plasma cell count is > 2,000/mm ³ .
Diagnostic imaging	Low-dose whole-body CT, MRI, PET-CT	Imaging detects bone involvement and plasmacytoma found in bone or soft tissue.

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Table 2-3. Initial Tests to Diagnose Multiple Myeloma (Continued)

Test	Description	Clinical Significance
Monoclonal proteins	Immunoglobulins: IgG, IgA (IgM, IgD, and IgE myeloma are not common.)	Plasma cells make antibodies (immunoglobulins). An increase in abnormal plasma cells occurs in myeloma, commonly producing IgG or IgA, and IgM is less common.
	Monoclonal protein	Malignant plasma cells secrete a monoclonal protein (M protein or M spike), which is characteristically detected in multiple myeloma.
	Serum protein electrophoresis and urine protein electrophoresis	Protein electrophoresis separates proteins in blood or urine into several groups based on their size and electrical charge, and monoclonal protein is found in myeloma.
	Monoclonal spike/monoclonal protein	Immunofixation identifies the specific type of protein that is being produced by the malignant plasma cells and is often more specific than the monoclonal protein.
	Serum free light chains Immunofixation	
	Serum free light chain	An increase in light chains (kappa and lambda) in the blood is commonly found in myeloma and reported individually and as a ratio.

CT—computed tomography; FISH—fluorescence in situ hybridization; MRI—magnetic resonance imaging; PET—positron-emission tomography

Note. Based on information from Bashiti, 2016; Bergstrom et al., 2020; Gerecke et al., 2016; Michels & Petersen, 2017; Saxe et al., 2019.

MRI, and PET-CT. Skeletal survey is considered suboptimal in staging and diagnosing myeloma bone damage because osteolytic lesions are difficult to determine unless significant bone damage has occurred (Caers et al., 2018; Pawlyn & Jackson, 2019).

Bone marrow biopsy and aspirate are necessary to quantify and qualify disease burden and staging. Although bone marrow testing is crucial in identifying multiple myeloma, specimen collection is not uniform and is based on technique. Another consideration in testing is that bone marrow is not evenly distributed. Consequently, the bone marrow results may not be interpreted consistently or be uniformly applicable in the clinical setting. The number of BMPCs is quantified as a percentage of plasma cells. Al Saleh et al. (2020) reported that the percentage of bone marrow involvement was associated with progression-free survival and overall survival. The study reported BMPC involvement of 60% or more in 562 patients (39%), and the median progression-free survival was shorter in this group compared to BMPC involvement less than 60% (22.6 vs. 32.1 months; $p < 0.0001$). The study also noted that the median overall survival was shorter in

the group with greater BMPC involvement (53.4 vs. 75.4 months; $p < 0.0001$) (Al Saleh et al., 2020).

Information from bone marrow aspirate is needed to identify the immunophenotype or flow cytometry to detect myeloma markers. Immunophenotyping is an important diagnostic tool in identifying plasma cell disorders and is utilized to identify biomarkers. These immunophenotypic biomarkers are described and categorized by cluster of differentiation (CD). CD138 or CD38 are commonly identified as multiple myeloma biomarkers. CD38 can be expressed on other cells, such as activated T cells; therefore, the expression of biomarkers such as CD45 and CD19 allows for greater certainty in abnormal plasma cell identification. Although CD38 and CD138 are generally indicative of abnormal plasma cells, CD19 is generally not expressed in abnormal plasma cells. The expression of CD45 is variable (Caers et al., 2018; Flores-Montero et al., 2016). Bone marrow aspirate is also sent for FISH testing to identify chromosomal abnormalities. See Table 2-2 for an outline of genetic abnormalities.

IMWG updated the diagnostic multiple myeloma criteria to include specific biomarkers and the use of improved diagnostic scans to identify bone disease. IMWG further defines other plasma cell disorders, such as solitary plasmacytoma with and without bone marrow involvement (Kumar et al., 2017; Rajkumar, 2016). Solitary plasmacytoma is an early-stage plasma cell malignancy that is categorized along the spectrum of MGUS, smoldering myeloma, and active myeloma. In this disorder, a solitary lesion is found on the bone or soft tissue without CRAB criteria. Solitary plasmacytomas are classified into two types, defined by the presence of a single biopsy-proven plasmacytoma (bony or extramedullary). The first category is plasmacytoma with a normal bone marrow examination. The second category is solitary plasmacytoma with minimal bone marrow involvement of less than 10%. The risk of recurrence or progression to myeloma within three years in solitary plasmacytoma without bone marrow involvement is approximately 10%, compared to 20%–60% for patients with minimal marrow involvement (Rajkumar, 2016).

Myeloma Staging

In the past, multiple myeloma was assessed using two staging systems: the Durie-Salmon Staging System and the International Staging System (ISS). Both systems have their own limitations (Rajkumar, 2020). Durie-Salmon staging is a tumor burden system allowing for subjective interpretation. Although the ISS is based on laboratory values and creates a simplistic interpretation, factors incorporated into staging could be influenced by nonmyeloma health problems, such as renal dysfunction. Neither staging system considers chromosomal abnormalities.

Genetic abnormalities, such as translocations t(4;14), t(14;16), and t(14;20); 1q gain; and 1p and 17p deletion, influence prognosis and response to therapy. Palumbo et al. (2015) published a study revising the ISS (R-ISS). The R-ISS combines elements of tumor burden and biomarkers, such as the presence of high-risk cytogenetic abnormalities or elevated lactate dehydrogenase.

The R-ISS was developed based on a study of 4,445 patients with newly diagnosed myeloma from 11 international trials. The study reported five-year survival rates of patients with stage I disease at 82%, stage II at 62%, and stage III at 40% (Palumbo et al., 2015). Figure 2-1 describes the criteria for the R-ISS. The R-ISS offers a more comprehensive and objective evaluation of staging for newly diagnosed myeloma. In the R-ISS, clinical presentation and cytogenetic abnormalities are incorporated across healthcare settings based on objective clinical similarities.

Treatment options have significantly improved over the past decade. Understanding the pathophysiology and the role of genetic abnormalities in myeloma is the basis for clinical advancement with an improvement in the overall survival of patients. The availability and standardization of diagnostic tests have enabled oncology practitioners to make accurate clinical assessments. The utilization of the R-ISS allows for objective staging that enables treatment to be tailored based on these findings.

Epidemiology

It is essential for nurses to understand the epidemiology of multiple myeloma, which is the second most common hematologic malignancy after non-Hodgkin lymphoma and represents approximately 1% of all cancers (Kazandjian, 2016).

Incidence

Over the past 25 years, the incidence of multiple myeloma cases has been on the rise. It is estimated that approximately 34,920 new cases will be diagnosed in the United States in 2021 and will account for approximately 12,410 deaths (Siegel et al., 2021). The incidence of myeloma is higher in men than in women: 19,320 and 15,600 cases, respectively (Siegel et al., 2021). This is also true of myeloma deaths, which are estimated at 6,840 deaths in the male population and 5,570 deaths in the female population (Siegel et al., 2021). Myeloma is most frequently diagnosed in people aged 65–74 years, with the median age of 69 years at diagnosis (National Cancer Institute, n.d.).

Based on age-adjusted rate measured from 2013 to 2017, the Surveillance, Epidemiology, and End Results (SEER) database estimated new cases of multiple myeloma at approximately 7 per 100,000 people per year (National Cancer Institute, n.d.). The death rate was approximately 3 per 100,000 people per year (National Cancer Institute, n.d.). In 2017, approximately 140,779 people were living with myeloma in the United States (National Cancer Institute, n.d.). These statistics are comparable to data from Europe and Canada (Blimark et al., 2018; European Union, n.d.; Tsang et al., 2019). North America, Australia, and Western Europe are the three regions of the world where myeloma is most prevalent. In contrast, several Asian countries have the lowest incidence of multiple myeloma. The incidences reported by Japanese and Korean studies were 2 and 1.5 per 100,000 people per

year, respectively (Cowan et al., 2018; Wang et al., 2020). The worldwide five-year prevalence is estimated at 230,000 cases, and more than 120,000 cases of myeloma are diagnosed annually across the world (Ferlay et al., 2018; Landgren et al., 2019; Ruzafa et al., 2016).

Survival Data

Survival of patients living with multiple myeloma has significantly improved over the past decade. Nandakumar et al. (2019) reported that the overall survival in myeloma improved from 2004 to 2017. The study grouped patients by year of diagnosis: 2004–2007, 2008–2012, and 2013–2017. The estimated four-year survival rates were 50% for the 2004–2007 group, 62% for the 2008–2012 group, and 75% for the 2013–2017 group (Nandakumar et al., 2019). The median overall survival was 3.9 in the first group, 6.3 in the second group, and not reported in the third group (Nandakumar et al., 2019). The five-year relative survival rates improved to 49% in the time frame of 2005–2011 (Kazandjian, 2016). This improvement coincided with the approval of proteasome inhibitors and immunomodulatory drugs. This survival statistic is greatly improved from 25% during 1975–1977 and 27% during 1987–1989 (Kazandjian, 2016).

The Swedish Cancer Register conducted a study collecting data over a 40-year period. The goal of the study was to define changes in survival of patients with myeloma (Thorsteinsdottir et al., 2018). Data were collected from 1973 to 2013, and the study included 21,502 patients with myeloma. Relative survival ratios were grouped into four intervals (1973–1982, 1983–1992, 1993–2002, and 2003–2013) and six age categories (20–40 years, 41–50 years, 51–60 years, 61–70 years, 71–80 years, and older than 80 years). The 10-year relative survival ratios did not improve significantly between the first three decades: 0.1 (95% confidence interval [CI] [0.09, 0.12]) during 1973–1982, 0.12 (95% CI [0.11, 0.13]) during 1983–1992, and 0.14 (95% CI [0.13, 0.15]) during 1993–2002 (Thorsteinsdottir et al., 2018). However, the relative survival ratio increased significantly to 0.2 (95% CI [0.18, 0.23]) for 2003–2013 (Thorsteinsdottir et al., 2018).

Survival improvement is attributed to several treatment factors. During the past decade, the development of novel treatments has changed the clinical course of the disease and ultimately has improved survival. Laboratory advancements, such as cytogenetic developments, SFLC access, and capability of measuring minimal residual disease, have significantly improved detection and response to disease progression. Supportive care of patients with myeloma is another important factor contributing to improved survival (Blimark et al., 2018; Kazandjian, 2016; Thorsteinsdottir et al., 2018).

Risk Factors

Several risk factors for multiple myeloma have been identified in the literature, MGUS being one of the most influential. Other risk factors include older age, male

sex, Black race, and genetic factors. Environmental factors, such as exposure to benzene, petroleum products, and Agent Orange, are also described in the literature. Agricultural or industrial occupation have been acknowledged, whereas obesity and dietary characteristics are less frequently described but are associated with an increased risk of myeloma (Kazandjian, 2016; Marinac et al., 2019; Sergeantanis et al., 2015).

Monoclonal Gammopathy of Undetermined Significance

MGUS is a well-documented risk factor for multiple myeloma. Epidemiologic studies in Olmsted County, Minnesota, estimated MGUS to affect approximately 3% of individuals aged 50 years or older, with prevalence increasing with age (Kyle et al., 2006). It is important to note that the individuals in this study were mostly Caucasian. The cohort was heavily skewed toward the Caucasian race, and the 3% figure does not reflect the higher incidence of MGUS in Black Americans and Black people from Africa or the decreased incidence in Asians and Mexicans in comparison to the Caucasian population (Kelly et al., 2016; Smith et al., 2018). The prevalence of MGUS increases in the aging population. The median age at diagnosis of MGUS is 70 years, and it affects 3.2% of individuals older than 50 years (Atkin et al., 2018). This incidence increases to 8.9% in people older than 85 years (Atkin et al., 2018). MGUS is most often diagnosed as an incidental finding while investigating other medical conditions in patients with presenting symptoms (Atkin et al., 2018; Go & Rajkumar, 2018).

In a prospective study conducted by the National Cancer Institute Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, 685 individuals were identified with MGUS (Landgren et al., 2019). The participants were followed for 16 years. Of the 685 individuals identified, 187 (27%) were found to have progression from non-IgM or light-chain MGUS to active multiple myeloma. The remaining 498 individuals diagnosed with non-IgM or light-chain MGUS did not progress to myeloma (Landgren et al., 2019).

Figure 2-1. Revised International Staging System for Multiple Myeloma

<p>Stage I</p> <ul style="list-style-type: none"> • Serum albumin \geq 3.5 g/dl, beta-2 microglobulin < 3.5 mg/L • No high-risk cytogenetics • Normal lactate dehydrogenase <p>Stage II: Neither stage I nor III</p> <p>Stage III</p> <ul style="list-style-type: none"> • Beta-2 microglobulin > 5.5 mg/L • High-risk cytogenetics • Elevated lactate dehydrogenase

Note. Based on information from Palumbo et al., 2015; Rajkumar, 2016; Tandon et al., 2017.

Using samples from the National Health and Nutrition Examination Survey (NHANES) III, Landgren et al. (2017) studied the prevalence of MGUS in a younger population (10–49 years). Of 12,373 individuals included, 63 were diagnosed with MGUS. The prevalence of MGUS was higher in Black people (0.88%) than White people (0.22%). The most striking difference noted in the 40–49-year age group was a 3.26% prevalence in the Black cohort compared to 0.53% in the White cohort (Landgren et al., 2017).

African Ancestry

Numerous epidemiologic reports have described the increased incidence of multiple myeloma in the African American population as two- to threefold times higher than other ethnicities. Multiple myeloma is the leading hematologic malignancy in African Americans, Afro-Caribbeans, and Africans compared to people of European, Japanese, and Mexican descent (Ailawadhi et al., 2019; Banavali et al., 2018; Kelly et al., 2016; Pierre & Williams, 2020; Smith et al., 2018). The mortality rate for Black American patients is higher, and the time to initial treatment is prolonged compared to White patients. The reasons for racial disparity in the Black American population are multifactorial and involve access to health care, including clinical trials; increased comorbidities; inferior treatment utilization, and socioeconomic factors (Ailawadhi et al., 2018; Marinac et al., 2020; Pierre & Williams, 2020; Smith et al., 2018).

Data on more than 30,000 patients with myeloma, obtained from the SEER registry, show that Black patients with myeloma had better overall survival than their White counterparts (Waxman et al., 2010). Although Black patients with myeloma have improved overall survival, they have a higher mortality rate than White patients. This discrepancy can be attributed to mortality being measured by the frequency of deaths, which is partly dependent on incidence, and survival is not dependent on incidence (Smith et al., 2018). A study by Ailawadhi et al. (2019) identified 3,504 White, 858 Black, and 468 Hispanic patients with myeloma using SEER data from 2007–2013. The study found that the median time from myeloma diagnosis to the initiation of therapy was longer for Black (5.2 months) and Hispanic people (4.6 months) than for White people (2.7 months) (Ailawadhi et al., 2019). Median multiple myeloma-specific survival was longer for Black patients (5.4 years) compared to 4.5 years in the Hispanic and White group.

Utilizing a SEER-Medicare database, Fiala and Wildes (2017) evaluated treatment strategies for Black Americans with myeloma. The study reported that Black patients were 37% less likely to utilize hematopoietic stem cell transplantation. The study also reported that Black patients were 21% less likely to receive bortezomib. Fiala and Wildes (2017) found that the underutilization of these treatment modalities was associated with a 12% increase in hazard ratio for death among Black patients.

One hypothesis for the superior overall survival in the Black population compared to White people is that Black people may have a more indolent subtype of

multiple myeloma. A study by Greenberg et al. (2015) compared the primary cytogenetic abnormalities in 292 Black and 471 White patients. The study found that Black patients had a lower prevalence of several cytogenetic abnormalities. These abnormalities included translocations t(11;14) and t(4;14) and deletions of 13q and 17p (Greenberg et al., 2015). The clinical and biologic differences among race and the rate of transformation from MGUS to myeloma are thought to be similar between patients of African descent and European descent. The disparities between racial groups related to MGUS and myeloma raise questions about the role of genetics and environmental risk factors. More epidemiologic investigations are needed to better understand the role of race in the development and treatment of myeloma.

Genetic or Ancestral History

The etiology of multiple myeloma is unclear; however, several studies suggest the development of the disease may be associated with inherited factors. Epidemiologic cohort studies have shown an increased risk of myeloma or MGUS in first-degree relatives of patients with myeloma or MGUS (Morgan et al., 2014). Familial clustering of multiple myeloma among first-degree relatives described a twofold increased risk of developing myeloma and a twofold increased risk of MGUS (Kristinsson et al., 2009).

Several studies have reported that families of individuals with MGUS have an increased risk of developing lymphoproliferative and plasma cell proliferative disorders, suggesting an underlying genetic link of all lymphocytic malignancies (Landgren & Weiss, 2009). The biologic impact of inherited myeloma has only recently been studied thanks to advancements in technology and the feasibility of gathering data from large, diverse populations.

Schinasi et al. (2016) published data from 11 case-control studies from the International Multiple Myeloma Research Consortium to describe the relationship of myeloma risk with having a first-degree relative diagnosed with lymphocytic malignancy. Logistic regression models were used to describe the relationship between myeloma and having a first-degree relative with a history of non-Hodgkin lymphoma, Hodgkin lymphoma, leukemia, or myeloma. A total of 2,843 cases and 11,470 controls were included (Schinasi et al., 2016). Multiple myeloma risk was elevated in individuals with a first-degree relative with any lymphocytic malignancy (odds ratio = 1.29, 95% CI [1.08, 1.55]) (Schinasi et al., 2016). Risk of myeloma was greater in people who had a first-degree relative with myeloma, especially among men and Black people (Schinasi et al., 2016).

Age

The incidence of multiple myeloma increases with age. The incidence of myeloma in people aged 65 years and older is expected to increase by 77% by 2030 as the result of the overall increase in the older adult population (Manapuram & Hashmi, 2018). Although the overall survival for patients with myeloma has improved over the past decade, survival improvements are minimal in aging populations. One

explanation for the lack of improved survival may be the presentation of more severe disease in older patients. Another reason for the lack of survival benefit in this population may be related to patient characteristics, such as performance status, comorbidities, and organ dysfunction associated with aging (Manapuram & Hashmi, 2018; Mina et al., 2019).

In a multiple myeloma survival study reported by Thorsteinsdottir et al. (2018), 21,502 patients were followed for a 40-year period from 1973 to 2013. The 5-year and 10-year relative survival rate increased significantly for all age groups except for the youngest (aged 20–40 years at diagnosis) and the oldest (older than 80 years at diagnosis), which showed no change in survival (Thorsteinsdottir et al., 2018).

Myeloma is often described as a disease of the older adult population. The development of novel therapies is associated with improved survival; however, these improvements have not been as robust in older populations. Treating older adults with myeloma is complicated and requires close monitoring. A study by Puyade et al. (2018) reported that age was related to inadequate provision of care in treating myeloma, particularly in first-line treatment. More studies are necessary to determine survival in older adults related to comorbidity, disease biology, and increases in treatment- and disease-related complications.

Environmental and Lifestyle Risk Factors

Several environmental and lifestyle risk factors in the development of multiple myeloma have been described in the literature. Environmental risk factors associated with myeloma include exposure to radiation, chemicals used in agriculture, aromatic hydrocarbon solvents, and Agent Orange. Several lifestyle risks factors, such as diet and obesity, as well as socioeconomic status, are associated with the development of multiple myeloma.

Radiation: The increased risk of developing hematologic malignancies associated with radiation exposure has been documented since the 1940s and was noted in Hiroshima and Nagasaki atomic bombing survivors (Hsu et al., 2013; Kuznetsova et al., 2016). Since then, extensive data have been collected, and studies have reported an increase in lymphatic and hematopoietic cancers among Japanese atomic bombing survivors, large groups of radiation workers, and patients who received radiation therapy. In a study by Neriishi et al. (2003), the transformation from MGUS to active multiple myeloma was accelerated in individuals who were exposed to radiation when compared to nonexposed individuals. Transformation from MGUS to myeloma occurred in 16% of nonexposed people, 17% of people whose radiation dose was unknown, and 26% of the radiation-exposed people (Neriishi et al., 2003).

Other studies have not identified radiation exposure as a myeloma risk factor. A large cohort of 22,373 radiation workers was followed for 50 years (Kuznetsova et al., 2016). Workers were exposed to external gamma radiation and internal plutonium. Leukemias were increased in this cohort; however, it was found that there was not an increase in Hodgkin lymphoma, non-Hodgkin lymphoma, or myeloma

(Kuznetsova et al., 2016). The data are inconclusive, and more epidemiologic studies are needed.

Occupational Risk Factors: A number of occupational exposures have been implicated in the development of multiple myeloma. Agricultural workers exposed to hazardous substances, such as pesticides, may be at greater risk for myeloma. Tsang et al. (2019) analyzed the geographical distribution of myeloma cases in Canada from 1992 to 2015. More than 32,000 patients were diagnosed with myeloma in that time. The study reported lower incidence rates of myeloma in metropolitan areas and higher incidence rates in rural and farming areas.

The AGRICAN cohort epidemiologic study conducted in France analyzed the associations between multiple myeloma and crop- or animal-related activities resulting in pesticide exposure (Tual et al., 2019). Information from more than 155,000 participants was collected from 2005 to 2007, and 269 of them were diagnosed with myeloma (Tual et al., 2019). Myeloma risk was increased in farmers using pesticides on crops in the 1960s. Farmers who used pesticides on corn, insecticides on animals, and disinfectants in animal barns were found to have an increased risk of developing myeloma (Tual et al., 2019).

Benzene, toluene, and xylene are hydrocarbons that are found in gasolines. They are more water soluble than other hydrocarbons and are often found in aquifers because they can migrate from contaminated soils. These compounds are biodegradable under certain laboratory conditions. However, without appropriate cleanup measures, benzene, toluene, and xylene can contaminate subsoils for long periods of time. De Roos et al. (2018) investigated the association between occupational exposures to benzene, toluene, and xylene (aromatic hydrocarbon solvents) with the development of myeloma. In a large epidemiologic study of more than 13,000 individuals, those exposed to any of the three solvents had a 42%–63% increased risk of myeloma (De Roos et al., 2018). The association was stronger in exposures that occurred within 20 years than in exposures that occurred beyond that time frame.

It is estimated that more than three million Americans deployed to Vietnam in the 1960s and 1970s were exposed to Agent Orange, which is a defoliant mixture. Many studies have been conducted to prove the relationship between Agent Orange and the development of hematologic malignancies (Gleason, 2015). Landgren et al. (2015) used data and specimens from the Air Force Health Study to compare veterans who conducted aerial missions to spray Agent Orange in Vietnam during 1962–1971 to veterans who were not exposed to Agent Orange. The prevalence of MGUS in those exposed to Agent Orange (7.1%) was higher than those who were not exposed (3.1%) (Landgren et al., 2015).

A study by Bumma et al. (2020), conducted in the Veterans Administration, identified 211 patients with MGUS. Of the 211 individuals, 96% were male and 122 were Black. Eleven patients had reported Agent Orange exposure. Cumulative risk of progression in the overall population was 1.4% at one year. Risk of transformation in the population exposed to Agent Orange was significantly higher, with a hazard ratio of 11.19 (95% CI [2.10, 59.47], $p = 0.005$). Overall survival was shorter

in exposed patients (median overall survival of 7 years) compared to those who were not exposed (11.1 years) (Bumma et al., 2020).

Lifestyle and Socioeconomic Factors: The overall survival of patients with multiple myeloma may be influenced by socioeconomic factors, income, education, and high body mass index. The International Agency for Research on Cancer has recently concluded that there is now adequate evidence to support the association between body weight and myeloma. However, body mass index and the increased risk of MGUS and myeloma remain controversial. Information obtained from the Age, Gene/Environment Susceptibility–Reykjavik Study (AGES-RS) reported that body mass index was not associated with the development of MGUS. However, this investigation reported that high midlife body mass index increased risk of progression to myeloma and other lymphoproliferative diseases (Thordardottir et al., 2017).

In a prospective study utilizing data from the Nurses' Health Study and Health Professionals Follow-Up Study, 20-year weight patterns in adulthood, body shape trajectory from ages 5–60 years, and body fat distribution were assessed to determine association with myeloma (Marinac et al., 2019). Researchers recorded 582 myeloma cases. Individuals who experienced weight cycling and at least one intentional episode of weight loss of 20 pounds or more had a higher risk of developing myeloma compared to individuals with stable weight (Marinac et al., 2019). This study also identified four body shapes: lean-stable, lean-increase, medium-stable, and medium-increase. Multiple myeloma risk was higher in the medium-increased group than in the lean-stable group (Marinac et al., 2019).

Information from the AGES-RS study suggests that certain foods may affect the development of multiple myeloma (Thordardottir et al., 2018). Fruit intake of three times per week during adolescence was associated with lower risk of MGUS when compared to lower fruit consumption. Fruit intake after MGUS onset was also associated with reduced risk of progressing to myeloma. Fruit intake of three times per week later in life correlated to a decreased risk of progressing from MGUS to myeloma when compared to lower intake (Thordardottir et al., 2018). These findings suggest that diet may alter the risk of developing MGUS, as well as decrease the risk of progressing to multiple myeloma.

Numerous studies have reported that cancer mortality and survival are decreased in individuals with low socioeconomic status (Jang & Chang, 2019; Tomic et al., 2018). This is also true for patients with myeloma. Using SEER data, Costa et al. (2016) evaluated the overall survival for younger individuals diagnosed with myeloma from 2007 to 2012. Researchers analyzed several socioeconomic variables and found that lower socioeconomic status was associated with a decrease in survival of younger patients. Similarly, Fiala et al. (2015) conducted an institutional study and compared socioeconomic status to SEER data. The study concluded that patients with low socioeconomic status had a 54% increase in mortality rate relative to patients with high socioeconomic status (Fiala et al., 2015). The study also found that Black patients were more likely to be in the lowest or middle socioeconomic cohort compared to White patients, and Black patients were less likely to

have insurance at time of diagnosis (Fiala et al., 2015). This information is vital in caring for patients with myeloma. Individuals of lower incomes are vulnerable and at risk for poorer outcomes compared to patients of a higher income. This population requires close monitoring and involvement of social services, as well as hospital financial administrators, to support them throughout the trajectory of their disease.

Summary

It is estimated that approximately 34,920 new cases of multiple myeloma were diagnosed in the United States and accounted for approximately 12,410 deaths in 2021 (Siegel et al., 2021). Several risk factors have been identified, including MGUS, older age, male sex, Black race, and hereditary factors. Environmental risk factors for myeloma include exposure to radiation aromatic hydrocarbons, agricultural chemicals, and Agent Orange. Weight and dietary characteristics may also play a role in development of myeloma.

Numerous epidemiologic reports have described the greater incidence of myeloma in Black people as two- to threefold higher than other ethnicities. The mortality rate for Black patients is higher, and the time to initial treatment is prolonged compared to that of White patients. The reasons for these disparities are multifactorial and include access to health care and clinical trials, higher incidence of comorbidities, inferior treatment utilization, and socioeconomic factors.

Epidemiologic cohort studies have shown an increased risk of myeloma or MGUS in first-degree relatives of patients with these diseases. This is important information to obtain in a health history and may aid in early diagnosis of plasma cell disorders.

Although myeloma often affects older people, improvements in survival contributed to novel therapies have not yet been observed in older populations. Treatment of older adults is complex as a result of comorbidities, lower performance status, and altered cognitive capacity, which may result in treatment toxicities and delays, thus affecting outcomes.

The epidemiology of multiple myeloma is ever-changing as more epidemiologic research is being published. It is imperative that nurses continue to incorporate these epidemiologic findings into their practice. Understanding of risks and disease patterns aids in identifying patients at risk for developing myeloma, as well as patients at risk for poor outcomes related to the disease. Epidemiologic information is instrumental in providing comprehensive care to patients with myeloma.

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