REVIEW

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Multiple Myeloma for the Primary Care Provider: A Practical Review to Promote Earlier Diagnosis Among Diverse Populations

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ABSTRACT

Multiple myeloma is the second most common hematologic malignancy in the United States and the most common hematologic malignancy among Blacks/African Americans. Delay in diagnosis is common and has been associated with inferior disease-free survival and increased rates of myeloma-related complications. Despite a roughly 2-times higher risk of multiple myeloma, diagnostic delay appears more common, and improvements in 5-year survival rates have been slower among Blacks/African Americans than their White counterparts. When patient symptoms and basic laboratory findings are suggestive of multiple myeloma, the primary care provider should initiate extended laboratory work-up that includes serum protein electrophoresis, serum immunoglobulin free light chain assay, and serum immunofixation. Heightened awareness within high-risk populations such as Blacks/African Americans may help to eliminate racial disparities in the diagnosis and treatment of multiple myeloma.

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KEYWORDS: Diagnosis; Disparities; Early diagnosis; Multiple myeloma; Race

INTRODUCTION

Multiple myeloma is a hematologic malignancy of terminally differentiated plasma cells in the bone marrow that can lead to destructive bone lesions, renal injury, and laboratory abnormalities such as anemia and hypercalcemia. Representing the second most common hematologic malignancy (behind non-Hodgkin lymphoma),[1] multiple myeloma comprises 1.8% of all new cancer cases and 18% of all hematologic malignancies in the United States.[2,3] In 2022, an estimated 34,470 cases will be diagnosed and the malignancy will result in 12,640 deaths.[4]

Multiple myeloma is slightly more common in men than in women and is most frequently diagnosed among people aged 65-74 years.[2] The rate of new cases is over 2 times higher among Blacks/African Americans than Whites,[2] and Black/African American patients are younger, on average, at diagnosis than their White and Asian counterparts.[5,6] In fact, multiple myeloma is the most common hematologic cancer among Blacks/African Americans.[2,6] In 2019, nearly 33,000 Blacks/African Americans were alive with the malignancy, with an incidence rate of 16.1 per 100,000 people.[2] An estimated 7810 new cases are expected to be diagnosed within the Black/African American population in 2022.[7] Although Blacks/African Americans currently comprise only 14.2% of the total US population,[7] it is estimated that they will comprise roughly 24% of the newly diagnosed multiple myeloma population by 2034.[8]

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The majority of patients diagnosed with multiple myeloma initially present to their primary care provider (PCP).[9,10] Unfortunately, the highly variable presentation of multiple myeloma often echoes signs and symptoms of conditions more commonly encountered by the generalist, such as diabetes, arthritis, and chronic renal insufficiency. This nonspecific presentation contributes to delays in both diagnosis and time to treatment. Early referral to Hematology has the potential to improve survival and quality of life, underscoring the need for PCPs to be adept at recognizing typical signs and symptoms of multiple myeloma so that an appropriate diagnostic algorithm can be initiated. This review will summarize the pathophysiology, prognosis, and clinical presentation of the disease, while focusing on key diagnostic considerations for the general practitioner. Disparities between Black/African American and White patients in both disease characteristics and access to appropriate care will be discussed throughout.

CLINICAL SIGNIFICANCE

- Most patients diagnosed with multiple myeloma see their primary care provider several times prior to Hematology referral.
- A series of protein assays can substantially increase the diagnostic sensitivity for multiple myeloma and may prevent delays in treatment.
- Blacks/African Americans are less likely than Whites to receive a full diagnostic workup for multiple myeloma.
- When access to health care is equal, Blacks/African Americans have equivalent, if not better, myeloma outcomes than Whites.

PATHOPHYSIOLOGY

Abnormal, clonal myeloma cells primarily reside in the bone marrow and can invade adjacent bone, causing bone pain and fractures from associated skeletal destruction.[11,12] These cells typically secrete an intact, abnormal monoclonal immunoglobulin (M protein), which can lead to both hyperviscosity of the blood and renal failure.[12] The complete M protein is not found in all cases of multiple myeloma, as myeloma cells secrete only monoclonal free light chains in up to 20% of patients (Figure 1).[11]

Multiple myeloma belongs to a class of disorders known as plasma cell dyscrasias, which include an often-progressive spectrum of conditions ranging from asymptomatic and premalignant states (monoclonal gammopathy of undetermined significance and smoldering multiple myeloma) to active, clinical disease. Monoclonal gammopathy of undetermined significance progresses to multiple myeloma or another lymphoproliferative disorder at a rate of roughly 1% per year,[13] whereas smoldering multiple myeloma progresses at a faster pace and in over 70% of patients at 15 years.[14] The presence of certain high-risk cytogenetic features, such as deletion of 17p [del(17p)] and translocation t(4;14), influence the likelihood of progression to multiple myeloma and are associated with more refractory disease.[15,16]

As a key precursor to multiple myeloma, monoclonal gammopathy of undetermined significance presents at an

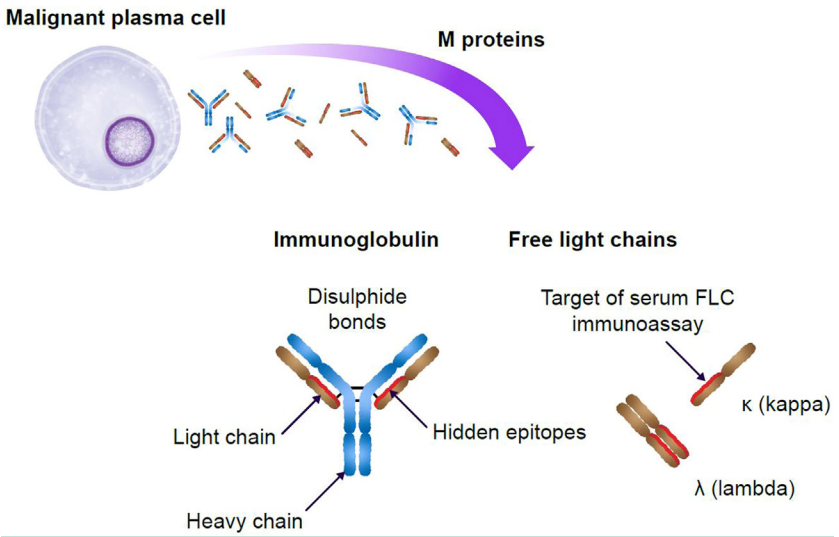

Figure 1 Intact M protein and free light chain (FLC) structure. In MM, malignant plasma cells in the bone marrow secrete an abnormal immunoglobulin called M protein. Intact M protein is composed of 2 heavy chains and 2 light chains. In up to 20% of patients, only FLCs are present; these FLCs feature exposed epitopes that are targets of the serum FLC assay. Overproduced free light chains are of either the kappa or lambda type. Hence, monoclonality is suggested by an abnormal kappa: lambda ratio (<0.26 or >1.65).

earlier age and is up to 4 times more common among Blacks/African Americans, in whom the prevalence may be as high as 17%.[17-19] The higher risk of both conditions among Blacks/African Americans with affected family members suggests that genetic predisposition may play a role in this population.[19-21]

PROGNOSIS

The 5-year relative survival rate among all patients with multiple myeloma is 55.6%.[2] Survival has improved for patients over the last several decades with the advent of novel therapies including autologous stem cell transplant, immunomodulatory agents (IMiDs), proteasome inhibitors (PIs), and monoclonal antibodies. However, improvement in survival rates was generally slower among Blacks/African Americans than Whites through 2012.[6,22]

Black race has been associated with underuse of transplant and novel medications such as the PI bortezomib.[6,23] Underuse of these treatments significantly increases the hazard ratio for death among this population of patients.[23] Blacks are also less likely to receive other novel therapies, including the IMiDs lenalidomide and pomalidomide, as well as the PI carfilzomib.[24] Triplet induction therapies, which may contain a PI, IMiD, or monoclonal antibody as well as dexamethasone, are preferred regimens for newly diagnosed patients,[3] as they are more likely than doublet therapies to induce a response, slow disease progression, and extend survival.[25,26] Importantly, the use of frontline triplet induction therapy containing a PI and IMiD is less common in Blacks than Whites.[27] Access barriers such as lower socioeconomic status, inadequate health insurance, and geographical location do not fully explain treatment disparities between Blacks/African Americans and Whites.[23] Additional contributors likely include structural barriers within the health care system (eg, bias among physicians, cultural barriers, a lack of coordination of care) as well as differences in individual decision-making that may be influenced by personal preferences or a general mistrust of the medical system.[23]

When Blacks/African Americans receive equal access to care, their survival outcomes are equal and, in patients <65 years old, often better than their White counterparts.[28] This survival benefit has been partially attributed to more favorable cytogenetics, as African ancestry has been associated with a higher prevalence of low-risk cytogenetic features such as t(11;14) and a numerically lower prevalence of high-risk features such as del(17p).[29,30] Contributions from other differences in disease biology are also suspected.[31]

CLINICAL PRESENTATION

Patients with multiple myeloma present with variable and oftentimes nonspecific symptoms (Figure 2). A study of 1027 patients found that bone pain and fatigue were present in 58% and 32% of patients, respectively, at diagnosis. Additional findings included anemia in 73% of patients,

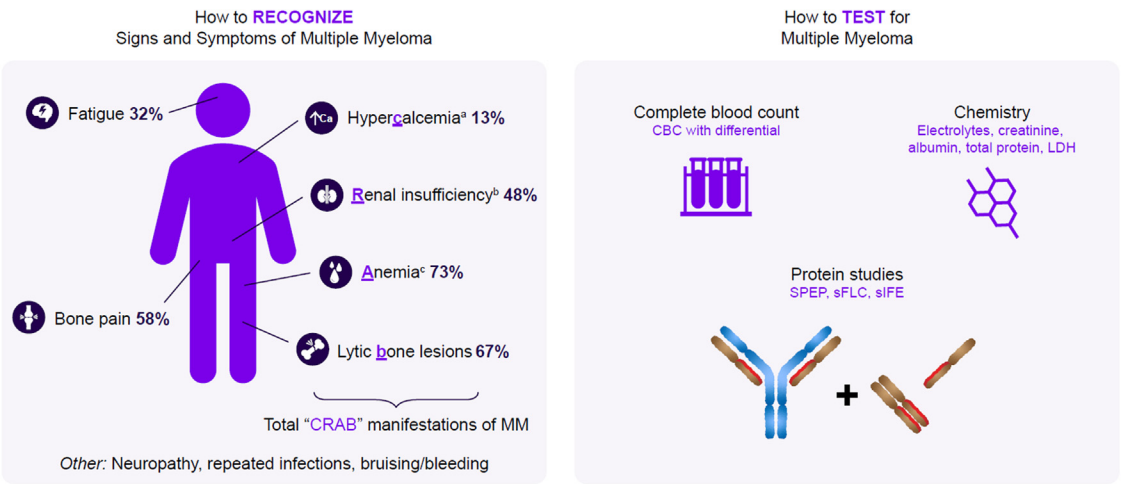

Figure 2 Key points to help the primary care provider recognize and test for multiple myeloma.[12,33] Ca = calcium; CBC = complete blood count; Hgb = hemoglobin; LDH = lactate dehydrogenase; MM = multiple myeloma; sFLC = serum free light chain assay; sIFE = serum immunofixation electrophoresis; SPEP = serum protein electrophoresis.
[a]Defined as serum calcium ≥11 mg/dL. Corrected calcium can be calculated using the following equation: corrected calcium = serum calcium + 0.8 (4 - serum albumin).
[b]Defined as serum creatinine ≥1.3 mg/dL. If a serum creatinine of ≥2 mg/dL is used as the cutoff for renal insufficiency, the incidence changes to 19%.
[c]Defined as Hgb concentration ≤12 g/dL. SI conversion factors: To convert serum calcium to mmol/L, multiply values by 0.25; to convert serum creatinine to μmol/L, multiply values by 88.4; to convert Hgb to g/L, multiply values by 10.

elevated creatinine in 48%, hypercalcemia in 13%, and bone abnormalities (primarily lytic lesions followed by fractures and osteoporosis) in 79%.[12] These latter findings reflect the most typical "CRAB" (hypercalcemia, renal impairment, anemia, or lytic bone lesions) manifestations of multiple myeloma.[32] Other common symptoms include neuropathy, repeated infections, unintentional weight loss, and bruising/bleeding.[33] Notably, Blacks/African Americans are more likely to present with certain markers of aggressive disease, including anemia and elevated lactate dehydrogenase.[34-37]

Many symptoms of multiple myeloma overlap with other conditions, including low back pain, diabetes, chronic kidney disease, and arthritis. Diabetes and multiple myeloma have multiple symptoms in common, including excessive thirst and urination, fatigue, frequent infections, and neuropathy. Similarly, without targeted testing, renal insufficiency caused by multiple myeloma can be difficult to distinguish from that caused by diabetes or chronic kidney disease. Bone pain or low back pain are often attributed to arthritis or osteoporosis and not taken seriously.

Attributing symptoms of multiple myeloma to comorbidities has been associated with prolonging the diagnostic process.[38,39] This may be particularly problematic among Black/African American patients who, despite a younger mean age at diagnosis, present with a greater number of pre-existing comorbidities, including renal disease, diabetes, and mild liver disease.[35,40] Notably, the US Centers for Disease Control and Prevention estimates the crude prevalence of diabetes (diagnosed and undiagnosed) as higher among patients identified as Black, non-Hispanic than as White, non-Hispanic (17.4% vs 13.6%, respectively),[41] underscoring the heightened need for PCPs to be able to distinguish multiple myeloma symptoms from those caused by diabetes in this population.

DIAGNOSIS

Time to Diagnosis and Implications of Delayed Diagnosis

The time between first symptom of multiple myeloma and actual diagnosis is often substantial, with a mean diagnostic interval (time from first presentation to diagnosis) of roughly 100 days.[38,39] A recent real-world analysis of 104 patients with newly diagnosed multiple myeloma found that 62% of patients experiencing diagnostic delay were African American.[42] Black patients have also been shown to be less likely than White patients to undergo a complete initial diagnostic evaluation, including Revised/International Staging System testing and proper imaging.[43]

Initial presentation for multiple myeloma is most commonly via primary care, and patients, on average, visit their PCP 3 times prior to Hematology referral.[9] The diagnostic interval is twice as long (6 vs 3 months) in patients presenting to their PCP vs a hematologist.[10] Delay in diagnosis has been associated with a higher incidence of myeloma-related complications and a significant decrease in disease-free survival, but not overall survival.[10,38,44,45] Presenting with late-stage complications (eg, severe infection, spinal cord compression, fractures, renal failure) has been associated with inferior outcomes.[46,47]

Testing and Differential Diagnosis

In addition to findings of anemia, hypercalcemia, and elevated creatinine, routine laboratory testing may reveal other abnormalities, including an elevated total protein level, low anion gap, low albumin, elevated lactate dehydrogenase, and elevated erythrocyte sedimentation rate. Key takeaways for the PCP are presented in Figure 2; expanded signs and symptoms of multiple myeloma, as well as a full primary-care–appropriate diagnostic algorithm, are provided in Figure 3.

When multiple myeloma is suspected based on clinical presentation and routine blood testing, serum protein electrophoresis and serum free light chain assays should be ordered to detect M protein and/or monoclonal excess of free light chains. Serum protein electrophoresis will separate serum proteins based on size and charge and provides a quantitative and relatively inexpensive, though somewhat insensitive, measure of serum M protein.[48,49] By targeting the hidden epitopes normally found at the interface of the heavy and light chains of an intact M protein (Figure 1), the serum free light chain assay detects both kappa and lambda free light chains. Although not specific for monoclonal light chains, monoclonality is inferred when an abnormal kappa: lambda ratio is found, with a ratio of <0.26 indicating a lambda clone and a ratio of >1.65 suggesting a kappa clone.[48]

As 20% of patients with multiple myeloma will have light chains only,[11] adding serum free light chain testing to serum protein electrophoresis is critical and improves detection rates (Table 1) to the extent where reliance on burdensome 24-hour urine testing for detection of Bence Jones protein is eliminated.[49] Additional testing should include serum immunofixation electrophoresis, a qualitative assay that detects the type of abnormal monoclonal protein (eg, immunoglobulin [Ig]A, IgM, IgG) and light chain type (kappa or lambda) present in the serum.[48] Although combining all 3 assays does not improve the diagnostic sensitivity for multiple myeloma (Table 1), it does increase the diagnostic sensitivity for monoclonal gammopathy of undetermined significance by 8% and smoldering multiple myeloma by 0.5%.[49]

Where available and financially feasible, low-dose whole-body computed tomography (CT) should be considered, as it offers better sensitivity than a basic skeletal survey for the detection of osteolytic lesions, particularly within the spine and pelvis.[50] Because lytic lesions become visible on plain radiographs only once 30% of the trabecular bone substance is lost,[51] a skeletal survey should be reserved for instances where whole-body CT is not possible. In cases where bony pain is present but lytic lesions are

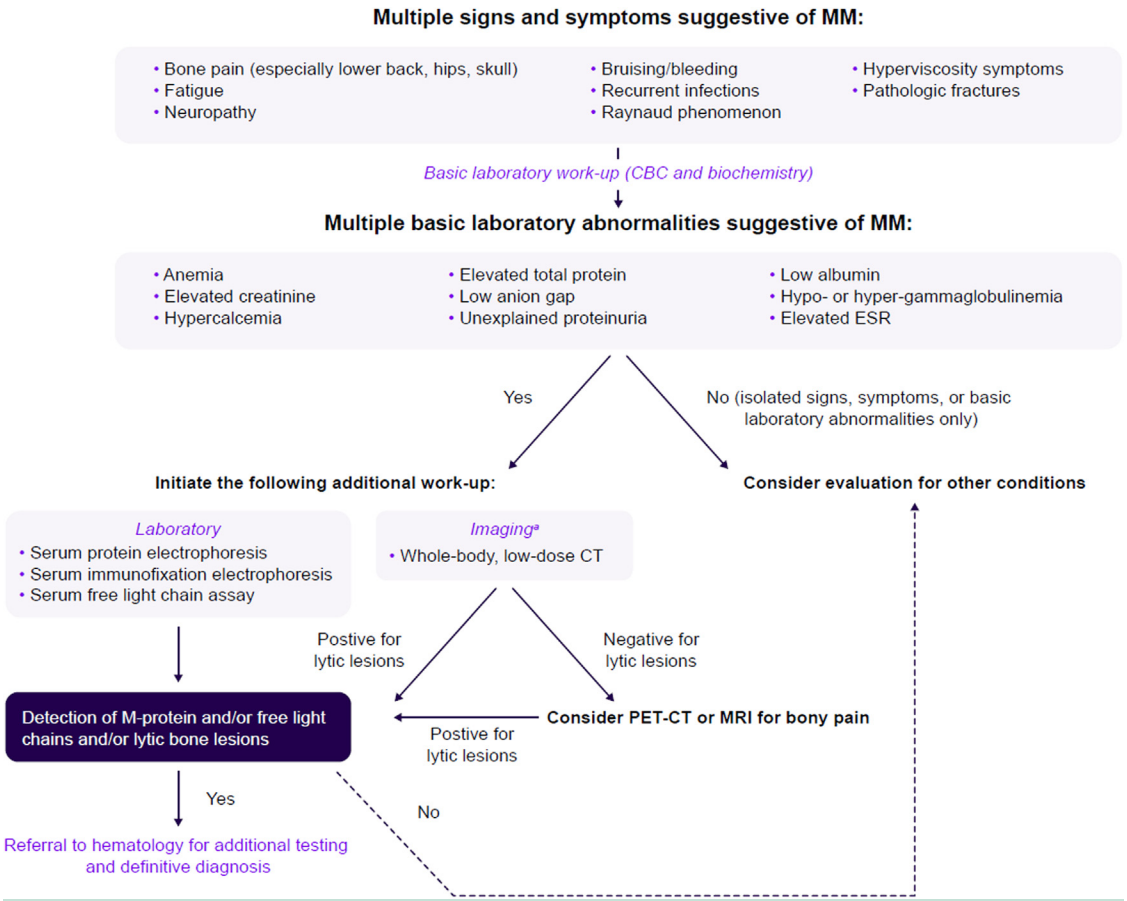

Figure 3 Inclusion of multiple myeloma in the differential diagnosis and primary care-appropriate diagnostic work-up. CT = computed tomography; ESR = erythrocyte sedimentation rate; MM = multiple myeloma; MRI = magnetic resonance imaging; PET-CT = positron emission tomography-computed tomography.
[a]Where available and financially feasible, whole-body, low-dose CT is preferable to a basic skeletal survey due to improved sensitivity for detecting lytic lesions. When CT is not possible, a basic skeletal survey can be considered. When bony pain exists but CT does not detect lytic lesions, advanced imaging with PET-CT or MRI can be considered, though ordering of such imaging is generally reserved for Hematology.

absent on CT, advanced imaging with positron emission tomography CT or magnetic resonance imaging (MRI) can be considered,[32] though these are typically reserved for ordering by the hematologist/oncologist.

Table 1 Diagnostic Sensitivity of Various Screening Algorithms Among 467 Patients with Multiple Myeloma[49]

Screening Algorithm	Diagnostic Sensitivity for Multiple Myeloma n (%)
SPEP alone	409 (87.6)
sIFE alone	441 (94.4)
sFLC alone	452 (96.8)
SPEP + sIFE + uIFE	461 (98.7)
SPEP + sIFE + sFLC	467 (100)
SPEP + sFLC	467 (100)

sFLC = serum free light chain; sIFE = serum immunofixation electrophoresis; SPEP = serum protein electrophoresis; uIFE = urine immunofixation electrophoresis.

Referral of Appropriate Patients to Hematology/Oncology

Detection of serum monoclonal protein, an abnormal free light chain ratio, or an elevated involved free light chain level may be suggestive of multiple myeloma or another plasma cell disorder. In the absence of overt signs and symptoms of multiple myeloma, these abnormalities may indicate the premalignant stages of either monoclonal gammopathy of undetermined significance or smoldering multiple myeloma. To establish a definitive diagnosis of a plasma cell disorder and determine the type of disorder (Table 2),[32,52] patients with abnormal serum protein electrophoresis and/or serum free light chain results should be referred to Hematology/Oncology, as should patients whose test results lead to diagnostic uncertainty. Presence of other signs or symptoms indicative of multiple myeloma (eg, bone pain, fatigue, or CRAB features) can be used to inform the urgency of the referral.

Table 2 International Myeloma Working Group Diagnostic Criteria for Multiple Myeloma and Certain Related Plasma Cell Disorders[32,52]

Disorder	Disorder Definition
MGUS (non-IgM[a])	All 3 criteria must be met: • Serum monoclonal protein (non-IgM type) <3 g/dL • Clonal bone marrow plasma cells <10%[b] • Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) or amyloidosis that can be attributed to the plasma cell proliferative disorder
SMM	Both criteria must be met: • Serum monoclonal protein (IgG or IgA) of ≥3 g/dL, or urinary monoclonal protein ≥500 mg/24 h, or clonal bone marrow plasma cells 10%-60% • Absence of MDEs or amyloidosis
MM	Both criteria must be met: • Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma • ≥1 of the following MDEs: ○ Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically: □ Hypercalcemia: serum calcium >1 mg/dL higher than the ULN or >11 mg/dL □ Renal insufficiency: CrCl <40 mL/min or serum creatinine >2 mg/dL □ Anemia: Hgb of >2 g/dL below the LLN or <10 g/dL □ Bone lesions: ≥1 osteolytic lesion(s) on skeletal radiography, CT, or PET-CT ○ Clonal bone marrow plasma cell percentage ≥60% ○ Involved:uninvolved sFLC ratio ≥100 (involved FLC level must be ≥100 mg/L) ○ >1 focal lesions on MRI (at least 5 mm in size)
Solitary plasmacytoma	All 4 criteria must be met: • Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells • Normal bone marrow with no evidence of clonal plasma cells • Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion) • Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, or bone lesions (CRAB) that can be attributed to a lympho-plasma cell proliferative disorder

CrCl = creatinine clearance; CT = computed tomography; FLC = free light chain; Hgb = hemoglobin; Ig = immunoglobulin; LLN = lower limit of normal; MDE = myeloma-defining events; MGUS = monoclonal gammopathy of undetermined significance; MM = multiple myeloma; MRI = magnetic resonance imaging; PET-CT = positron emission tomography-computed tomography; sFLC = serum free light chain; SMM = smoldering multiple myeloma; ULN = upper limit of normal.

SI conversion factors: To convert serum calcium to mmol/L, multiply values by 0.25; to convert serum creatinine to μmol/L, multiply values by 88.4; to convert Hgb to g/L, multiply values by 10.

[a]For diagnostic criteria associated with other types of MGUS (ie, IgM MGUS and light-chain MGUS), see Rajkumar et al, 2014.[52]

[b]Bone marrow biopsy can be deferred in patients with low-risk MGUS (IgG-type, M protein <15 g/L, normal FLC ratio) who lack clinical features concerning for MM.

Prompt treatment is clearly indicated for multiple myeloma, and asymptomatic patients with intermediate or high-risk smoldering multiple myeloma may be eligible for treatment or clinical trials rather than monitoring.[3] Similarly, monoclonal gammopathy of undetermined significance may indicate the presence of another plasma cell-related disorder (eg, immunoglobulin light-chain amyloidosis, light chain deposition disease, POEMS (Polyneuropathy, Organomegaly, Endocrinopathy/edema, Monoclonal protein, Skin changes) syndrome, monoclonal gammopathy of renal significance, or lymphoma) that can be appropriately diagnosed and managed by Hematology/Oncology. Notably, patients with low-risk monoclonal gammopathy of undetermined significance (eg, those with small M protein spikes <1.5 g/dL, IgG-type, and normal free light chain ratio) may be considered for follow-up within primary care, as they do not routinely require bone marrow examination or extensive imaging.[53] Such patients should be followed with serum protein electrophoresis at 6 months and, if stable, every 2 to 3 years unless symptoms suggestive of a plasma cell malignancy arise.[53]

Upon Hematology/Oncology referral, a bone marrow biopsy will likely be used to determine clonal bone marrow plasma cell percentage.[52] Urine evaluation (via a 24-hour urine sample and urine protein electrophoresis) may be used to monitor disease and detect albuminuria, while advanced imaging can help judge the extent of skeletal involvement.[32] Together with serum free light chain results, bone marrow biopsy and MRI results can be used to diagnose multiple myeloma in patients who lack traditional CRAB features. These additional "SLiM" criteria (greater than or equal to Sixty percent clonal plasma cells in the bone marrow; involved:uninvolved free light chain ratio of ≥100 with the involved free light chain being ≥100 mg/L; MRI with more than one focal marrow lesion) were added to the diagnostic criteria in 2014 (Table 2); each of these

criteria is associated with an approximately 80% risk of progression to symptomatic end-organ damage.[32,52]

The diagnosis of multiple myeloma requires evidence of either 10% or more clonal plasma cells in the bone marrow or a biopsy-proven plasmacytoma. In addition, 1 or more myeloma-defining events (any of the traditional CRAB criteria or any of the SLiM criteria added in 2014) must be present (Table 2).[32,52] If the diagnosis of multiple myeloma is made, additional work-up used to determine prognosis and stage of disease will include fluorescent in situ hybridization to detect high-risk cytogenetic abnormalities [eg, t(4;14), t(14;16) or del(17p)], serum β_2 microglobulin, and lactate dehydrogenase.[16]

FUTURE DIRECTIONS FOR CARE

To avoid unnecessary anxiety for patients and financial toxicity to both patients and the health care system, heightened awareness of multiple myeloma must be accompanied by the appropriate level of discretion for testing. Routine screening is not currently recommended, as it can lead to overtesting and overdiagnosis of monoclonal gammopathy of undetermined significance, which requires costly annual monitoring and can negatively impact quality of life.[54-56] Interestingly, recent research suggested that screening for monoclonal gammopathy of undetermined significance among patients at high risk for progression to multiple myeloma (eg, Black/African Americans or first-degree relatives of patients with hematologic malignancies) may be appropriate, and that such screening may not increase cancer-related worry or compromise quality of life.[57]

A recent study found that investigations to evaluate all CRAB criteria for multiple myeloma were underused in the primary care setting.[58] Diagnostic pathways aided by electronic medical record (EMR) functionality and/or artificial intelligence may assist PCPs in evaluating appropriate patients for possible multiple myeloma. Clinical prediction rules that estimate a patient's risk of disease and trigger interventions can be built into EMR systems. These have been shown to reduce time to diagnosis in colorectal and prostate malignancies,[59] and recently developed prediction rules for multiple myeloma show promise but must be validated.[60] EMRs that facilitate consultation with a hematologist/oncologist may expedite diagnosis of multiple myeloma; such "E-consults" to Hematology have been shown to aid in the evaluation of monoclonal gammopathy of undetermined significance.[61] Various artificial intelligence techniques are being investigated for their ability to integrate routine laboratory results into screening models to expedite diagnosis.[62]

In addition to utilizing appropriate and validated advances in technology, the ability of PCPs to improve multiple myeloma diagnostic speed and accuracy is likely to be informed by future research and influenced by heightened educational efforts. Most publications detailing time to diagnosis, impacts of diagnostic delay on outcomes, and disparities in access to novel and improved therapies (particularly within the Black/African American population) arise from data collected over a decade ago. Recent research presented at conferences[9,43] has presented emerging data on these topics, and their associated publications are eagerly awaited.

CONCLUSION

As the majority of patients diagnosed with multiple myeloma initially present to their PCP, generalists must be adept at recognizing typical signs and symptoms of the disease, with a heightened awareness among particularly high-risk groups such as Blacks/African Americans. When multiple myeloma is included in the differential diagnosis, a basic initial testing strategy that includes a complete blood count, basic chemistry, serum protein electrophoresis, serum free light chain assay, and serum immunofixation electrophoresis can expedite early referral to a hematologist/oncologist and prevent delays in both accurate diagnosis and treatment.

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