Multiple Myeloma

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KEYWORDS

• Fluorodeoxyglucose • PET • PET/CT • Multiple myeloma • Monoclonal gammopathy • Plasmacytoma

KEY POINTS

- Multiple myeloma is a heterogeneous disease process exhibiting a wide range of biological behaviors.
- PET/computed tomography (CT) imaging is useful in identifying additional bone lesions in patients with a plasmacytoma, and it is an important adjunct in the risk assessment of patients with multiple myeloma.
- Active myeloma can be identified from its indolent precursor states, allowing appropriate initiation of therapy.
- In the evaluation of patients with multiple myeloma, PET/CT is highly sensitive and specific for the detection of extraosseous disease.
- PET/CT aids therapy assessment before and after stem cell transplantation.

INTRODUCTION

Multiple myeloma (MM) arises from a single clone of differentiated plasma cells and typically produces high levels of a monoclonal immunoglobulin. These malignant plasma cells proliferate primarily within the marrow space and commonly produce osseous lesions.[1,2] MM is the most common malignant bone neoplasm in adults and incidence increases with age. Most patients with myeloma are diagnosed initially at 50 to 70 years of age.[2,3] Patients with MM present with a variety of symptoms: bone pain, fatigue, and lethargy from anemia, renal failure, and hypercalcemia.[2,4,5] Many patients are detected incidentally with laboratory tests demonstrating a monoclonal protein in the serum or urine. The treatment of myeloma is continuously evolving and currently uses thalidomide, protease inhibitors, chemotherapy, and long-acting steroids. Stem cell transplantation plays an important role in a patient with aggressive and extensive disease.[6–8]

Diagnostic imaging plays a critical role in the evaluation of patients with known or possible hematologic malignancies. Skeletal surveys covering the axial and proximal appendicular skeleton have been traditionally used in the workup of MM.[1] Computed tomography (CT) and magnetic resonance (MR) play a large role in staging patients with extraosseous hematologic malignancies, but, until recently, were used in MM for problem-solving only. ^{18}F fluorodeoxyglucose (FDG) PET identifies tumor sites based on their elevated glucose metabolism.[9,10] With the integration of PET and CT into a single scanner, it has become the modality of choice for the assessment of patients with hematologic malignancies.[10,11]

This article reviews myeloma and other plasma cell dyscrasias. The use of FDG PET/CT at crucial junctures in patients with myeloma adds additional clinical information, which provides an opportunity to impact medical management positively and therefore impact patient outcomes.

PLASMA CELL DYSCRASIAS

MM is one of many plasma cell dyscrasias resulting from a proliferating clone of plasma cells typically secreting a paraprotein (**Table 1**). Monoclonal gammopathy of undetermined significance

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Table 1
Plasma cell dyscrasias

	Incidence (%)
Common	
MGUS	59
MM	18
Uncommon/rare	<10
Solitary plasmacytoma	
SMM	
WM	
Plasma cell leukemia	
Nonsecretory myeloma	
Solitary plasmacytoma	
Primary amyloidosis	
Heavy chain disease	
POEMS	

Adapted from Kyle RA, Rajkumar SV. Monoclonal gammopathy of undetermined significance and smoldering multiple myeloma. Hematol Oncol Clin North Am 2007;21:1093.

(MGUS) is a most frequent member of this group. MGUS occurs in 1% to 3% of adults over the age of 50 and is typically detected incidentally on screen laboratory studies. A serum monoclonal protein less than 3 g/dL, bone marrow containing less than 10% plasma cells, and no evidence of end-organ damage (**Box 1**) caused by the plasma cell clone defines MGUS. MGUS is a premalignant state and is a precursor for MM, primary amyloidosis, light chain deposition disease, Waldenström macroglobulinemia (WM), lymphoma, and other plasma cell dyscrasias. The annual rate of progression to MM is approximately 1% (**Table 2**). At 25 years, nearly 70% of patients with MGUS have remained stable with no symptoms or evidence of progression. MGUS must be differentiated from less common but far more aggressive plasma cell dyscrasias.[12–16]

Smoldering myeloma (SMM) is a premalignant plasma cell dyscrasia, which is intermediate between MGUS and MM. SMM is differentiated from MGUS by higher serum monoclonal protein levels (≥3 g/dL) and a greater percentage of plasma cells in the bone marrow (≥10% and <60%), but no evidence of myeloma end-organ damage.[17,18] SMM patients are at much higher risk of progressing to MM than MGUS patients (see **Table 2**). The annual rate of progression to symptomatic MM is about 10%, with more than 50% conversion in 5 years.[19,20] Significant research is currently underway in SMM patients to determine which factors are associated with a higher risk for progression to active MM. If the SMM patient is completely asymptomatic, close observation is preferred and treatment is restricted to enrollment in prospective clinical trials.[21]

Box 1
End organ damage in multiple myeloma

C = elevated calcium level (Ca >11.5 mg/dL)

R = renal insufficiency (Cr >2.0 mg/dL)

A = anemia (Hgb <10 g/dL)

B = lytic bony lesions

Adapted from Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia 2009;23:3.

Table 2
Progression to multiple myeloma

	Monoclonal Protein (g/dL)	Marrow Plasma Cells (%)	Annual MM Progression (%)
MGUS	<3	<10	1
SMM	≥3	or ≥10 to <60	10
SPB	<3	<10	15–20[a]

[a] Assessment without FDG PET/CT.

Adapted from Rajkumar SV, Dispenzieri A, Fonseca R, et al. Thalidomide for previously untreated indolent or smoldering multiple myeloma. Leukemia 2001;15:1274; and Rajkumar SV, Larson D, Kyle RA. Diagnosis of smoldering multiple myeloma. N Engl J Med 2011;365:474, with permission.

Solitary plasmacytomas are composed of plasma cells, which on biopsy are histologically identical to those seen in MM. Solitary plasmacytomas most frequently occur in bone (SPB), but can also be found in soft tissues.[22–24] SBP is characterized by a biopsy-proven clone of plasma cells, bone survey evidence of no additional lesions, and no end-organ damage. A monoclonal protein is present in a highly variable percentage (30%–70%) of SBP patients. Radiation therapy (40–50 Gy) to the SPB is a very effective treatment. The distinction between SBP and MM is the number of lesions found; 3 or more plasmacytomas are treated systemically as MM. SPB patients are at high risk of progression to MM compared with MGUS or SMM patients, with 40% to 60% progression at 4 years.[22,25,26]

PET/COMPUTED TOMOGRAPHY IMAGING

FDG PET/CT plays important clinical roles in the management of MM patients and in the evaluation