Diagnosis and Risk Stratification in Multiple Myeloma

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KEYWORDS

• Multiple myeloma • Prognosis • Risk stratification • Diagnostic workup
• Chromosomal abnormalities

KEY POINTS

- Multiple myeloma (MM) is a tumor of monoclonal plasma cells, which produce a monoclonal antibody and expand predominantly in the bone marrow.
- Patients present with hypercalcemia, renal impairment, anemia, and/or bone disease (CRAB criteria). Only patients with symptomatic MM require therapy, whereas asymptomatic patients receive regular follow-up. Survival of patients with MM is very heterogeneous.
- Gene expression profiling is emerging as a prognostic tool to further improve risk stratification.
- Incorporation of imaging techniques, such as positron emission tomography/computed tomography and magnetic resonance imaging, will add valuable information to the standard response assessment.
- New therapeutic strategies for high- and low-risk MM should be explored in the setting of clinical trials.

CLINICAL PRESENTATION

Multiple myeloma (MM) is a tumor of terminally differentiated monoclonal B cells (plasma cells) that produce a monoclonal protein and .expand predominantly in the bone marrow (BM). Hypercalcemia, renal impairment, anemia, and bone disease represent the CRAB criteria for symptomatic MM requiring therapy.

Symptoms of anemia develop as a result of displacement of normal hematopoiesis. Thrombocytopenia occurs rarely with only 5% of patients with newly diagnosed MM presenting with platelets less than 100×10^9/L.[1] Alterations in the BM microenvironment result in reduced bone formation by osteoblasts and increased bone destruction

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by osteoclasts, which lead to diffuse osteoporosis, osteolytic lesions, and painful pathologic fractures. There is also a higher incidence of infections because of immune dysfunction, especially during active disease. Approximately 20% of the patients with newly diagnosed MM present with renal impairment (creatinine $\geq$2 mg/dL); it is most frequently caused by light-chain cast nephropathy, which results in extensive destruction of tubular cells.[1] Several other factors, such as dehydration, hypercalcemia, infections, nephrotoxic drugs, and contrast media, may also contribute to renal impairment.[2] Also amyloidosis and monoclonal immunoglobulin deposition disease are causes of renal impairment in MM, leading to usually nonselective proteinuria.

DIFFERENTIAL DIAGNOSIS

Sixty-three percent of the patients with MM present at more than 65 years of age, and 37% of the patients newly diagnosed with MM are older than 75 years.[3] Therefore, patients may present with renal impairment that is not related to MM but a result of other underlying medical conditions that are prevalent in elderly patients, such as hypertension and diabetes. Similarly, primary hyperparathyroidism should be considered for hypercalcemia; deficiencies of iron, vitamin B_{12}, and folic acid for anemia; and metastatic carcinoma for lytic bone lesions. Other symptomatic plasma cell diseases that have to be excluded include solitary plasmacytoma and primary plasma cell leukemia (pPCL) (**Table 1**). Symptomatic MM is virtually always preceded by monoclonal gammopathy of uncertain significance (MGUS) that progresses to smoldering myeloma (SMM) (see **Table 1**).[4] MGUS and SMM do not require therapy but only clinical observation, except in the setting of clinical trials.

DIAGNOSTIC WORKUP OF MM

At the time of MM diagnosis, the authors obtain a detailed medical history and physical examination and perform laboratory studies, such as full blood count and differential, peripheral blood smear, blood chemistry including tumor lysis parameters, beta-2 microglobulin, serum protein electrophoresis, and free light chains (**Box 1**). Staging procedures should also include the evaluation of urine M protein in 24-hour urine and a skeletal survey. Whole-body radiographs still remain the standard tool for the evaluation of MM bone disease.[5] However, it is well recognized that this imaging technique underevaluates the extent of skeletal lesions. Low-dose whole-body computed tomography (CT), which is faster and has greater sensitivity compared with standard radiography, is a valuable alternative.[5] Magnetic resonance imaging (MRI) is useful for the evaluation of cord compression or a painful area of the skeleton. Furthermore, MRI is recommended in patients with radiographs suggesting a solitary plasmacytoma of the bone.[4]

In addition, the authors perform a BM biopsy and BM aspiration for morphology, immunophenotyping by flow cytometry, and cytogenetic analysis by fluorescence in situ hybridization (FISH), which should include at least t(4;14)(p16;q32), t(14;16)(q32;q23), ampl(1q21), and del(17p13) (see **Box 1**). Lumbar puncture, MRI, or CT is performed when extramedullary (EM) involvement is suspected.

PROGNOSTIC FACTORS

Response to treatment and survival of patients with MM is very heterogeneous, with some patients dying of refractory MM within a few weeks, whereas others live for more than 10 years. This variety in outcome is related to intrinsic tumor cell characteristics, including sensitivity to active MM drugs,[6] tumor burden, and several host factors. Risk stratification of patients with MM is important in order to define which