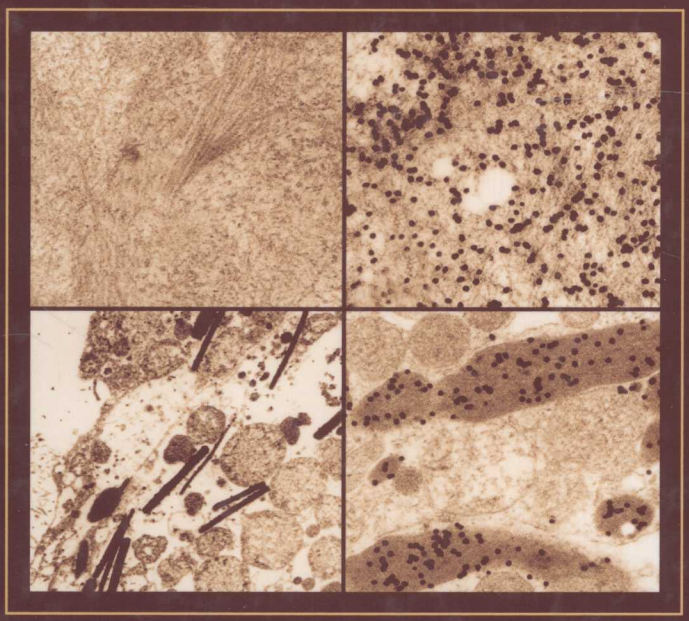
Biology and Management of Multiple Myeloma

Edited by

James R. Berenson, MD



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Dedication

I dedicated this book to my wife, Debra,
and my children, Shira and Ariana.

Also, a special thanks to Christine Pan James
for her assistance in the preparation and editing of this volume

Preface

Biology and Management of Multiple Myeloma is intended to serve as an authoritative, comprehensive, and detailed interpretation of published studies related to this B cell malignancy.

The book, written by a group of international experts on this disease, should provide insights into the newest breakthroughs—from the basic pathogenesis to the clinical aspects of myeloma. The first part of the book is devoted to the biology of myeloma, where important discoveries have been made in the last few years, many of which are clinically relevant. The characteristics of the malignant cell are shown, and the important roles of oncogenic changes, chromosomal anomalies, Kaposi's sarcoma herpes virus, and cytokines are described. New epidemiological findings and prognostic factors are analyzed in subsequent chapters. The increasing importance of renal disease, anemia, and bone disease has provided a basis for the inclusion of chapters devoted to the etiology and treatment of these complications. A thorough analysis of conventional treatment regimens is provided, as well as discussion of newer experimental approaches involving immunologic targeting, inhibitors of drug resistance, and new anti-tumor agents. The role of high-dose therapy is discussed in the chapters on allogeneic and autologous transplantation.

We have tried to provide a thorough, objective overview of each area. We hope that this book provides the reader with a thorough understanding of where
myeloma research is in the clinic and research laboratory.

James R. Berenson, *MD*

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Robert A. Kyle, MD and
Daniel E. Bergsagel, MD

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1. INTRODUCTION

Multiple myeloma (MM) is a neoplastic disorder characterized by the proliferation of a single clone of plasma cells derived from B cells in the bone marrow. Frequently, the myeloma invades adjacent bone, destroying skeletal structures and resulting in bone pain and fractures. Occasionally, plasma cells infiltrate multiple organs and produce other symptoms. The excessive production of a monoclonal (M) protein can lead to renal failure caused by Bence Jones proteinuria or hyperviscosity caused by excessive amounts of M protein in the blood. The diagnosis depends on the identification of abnormal monoclonal plasma cells in the bone marrow, M protein in the serum or urine, osteolytic lesions, and a clinical picture consistent with the diagnosis.

2. CLINICAL FINDINGS

2.1. Symptoms

The most important symptom of myeloma is bone pain, which is reported by approximately two-thirds of patients at the time of diagnosis *(1)*. The pain, which is often severe and incapacitating, occurs most often in the back or ribs and less often in the extremities. Spasms of back pain, usually induced by movement, do not occur at night, except with a change of position in bed. The pain is usually

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relieved by lying down. Sudden pain in the ribs followed by localized tenderness indicates a rib fracture, even when the radiograph is negative. Sudden, severe back pain caused by a compression fracture may occur after a fall or after lifting an object. The trauma responsible for the pain is often minimal. The patient's height may decrease by 4 to 6 inches during the course of the disease as a result of vertebral collapse.

The most common symptoms are weakness and fatigue caused primarily by anemia, which occurs in approximately two-thirds of patients. Fever caused by the myeloma itself occurs much less frequently than in patients with lymphoma or acute leukemia. In patients with myeloma, fever is most often caused by a bacterial or (less frequently) viral infection. The physician must search diligently for the source of fever because myeloma is responsible in only 1% of patients. Fever is not uncommon in the patient with preterminal myeloma characterized by dedifferentiation and extramedullary disease *(2)*. Pneumococcal pneumonia or septicemia is also not uncommon. Gross bleeding, seen in fewer than 10% of patients, most often consists of epistaxis or gastrointestinal (GI) bleeding, with thrombocytopenia frequently a contributing factor. The major symptoms may result from renal insufficiency, hypercalcemia, neurologic features, and other less common symptoms that will be discussed separately.

2.2. Physical Findings

The most frequent physical finding is pallor; skeletal deformity, pathologic fractures, bone tenderness, tumors, and purpura may also be observed. The liver is palpable in 4% of patients, and the spleen in 1% *(1)*. Lymphadenopathy is uncommon. Extramedullary plasmacytomas, which result in large subcutaneous masses with a purplish hue, are rare at diagnosis, but are common seen late in the course of the disease.

2.3. Patient Manifestations

Patients may present with features of other organ involvement, with MM identified only after further evaluation. This disorder occurs primarily in the older patient (median age: approx 65 yr); only 3% of our patients are younger than 40 yr, and 18% are younger than 50 yr *(3)*.

2.4. Renal Involvement

Patients with MM may present with acute or, more commonly, chronic renal failure. The serum creatinine value is 2 mg/dL or more in one-fifth of patients at diagnosis. Two major causes of renal failure are "myeloma kidney" and hypercalcemia. Myeloma kidney is characterized by the presence of large, waxy, laminated casts consisting mainly of precipitated monoclonal light chains (Bence Jones protein), which are seen in the distal and collecting tubules. The extent of cast formation correlates with the amount of free urinary light chain and the severity of renal

insufficiency. Hypercalcemia, present in about 25% of patients at the initial evaluation, is a major but treatable cause of renal insufficiency.

Hyperuricemia is usually associated with renal failure. Primary amyloidosis (AL), which is seen in 10% of patients, may result in the development of nephrotic syndrome, renal insufficiency, or (more commonly) both. In fact, the occurrence of heavy albuminuria in patients with MM suggests the possibility of amyloidosis.

Acute renal failure may be the initial manifestation of MM. Patients may appear to be in good health and present with acute renal failure; the diagnosis of myeloma is not considered until the recognition of Bence Jones proteinuria or other features of MM. Acute renal failure is often precipitated by dehydration or hypotension. Intravenous urography may be the precipitating factor, but the risk is low if dehydration is avoided.

Patients may present with an acquired Fanconi syndrome or light-chain deposition disease. Acquired Fanconi syndrome is characterized by proximal tubular dysfunction that results in glycosuria, phosphaturia, and aminoaciduria. Light-chain deposition disease is characterized by proteinuria, often in the nephrotic range, or renal insufficiency *(4)*.

2.5. Neurological Involvement

Radiculopathy is the most frequently observed neurological complication. It is caused by compression of the nerve by a paravertebral plasma cell tumor or occasionally by the collapsed bone itself. Pain is aggravated by movement or change of position. Spinal cord compression may result when a myeloma arising in the marrow cavity of the vertebra extends into the extradural space. This condition occurs in about 5% of patients, mainly in the thoracic cord. Paraplegia may be the presenting event. Leptomeningeal myelomatosis is uncommon but is being recognized more frequently *(5)*. Fatigue, drowsiness, headaches, reduced mentation, and associated symptoms are features of this complication. Examination of the cerebrospinal fluid reveals abnormal monoclonal plasma cells. Sensorimotor peripheral neuropathy is rare in MM; when present, it is usually a result of primary AL. Occasionally hyperviscosity is observed, manifested by blurred vision, oronasal bleeding, headache, ataxia, and drowsiness. It is found in patients with immunoglobulin (Ig)A myeloma but rarely in those with IgG.

2.6. Hypercalcemia

Hypercalcemia may be indicated by the presence of weakness, fatigue, polydipsia, polyuria, constipation, anorexia, nausea, vomiting, confusion, stupor, or coma. It is important to keep in mind that hypercalcemia will lead to dehydration, renal insufficiency, and death unless treated promptly.

2.7. Other Organs

Other organ systems, e.g., the GI tract, may become involved. Occasionally, plasma cells infiltrate the rugal folds of the stomach or a plasmacytoma develops

in the stomach, with bleeding and pain as the initial symptoms. Hepatomegaly, jaundice, ascites, and plasma cell infiltration are uncommon. Rarely, the gallbladder, bile ducts, pancreas, and large and small bowel are involved by tumor. IgA myeloma is more likely to be present when the GI tract is involved.

The ribs and sternum are frequently involved, with such involvement often characterized by localized, painless swelling associated with plasma cell tumors; in fact, this may be the first manifestation of the disease. Pain develops when a pathological fracture occurs. Asymptomatic plasmacytomas may appear as soft tissue masses on a routine chest radiograph. Occasionally, the radiograph finding is interpreted as a primary tumor of the lung, and the rib involvement is overlooked. In some cases, extramedullary involvement of the mediastinum, mediastinal lymph nodes, or lung is the initial finding. Pleural effusion associated with plasma cell deposits in the pleura may occur later in the disease.

Occasionally, myeloma involves the pericardium and may result in pericardial effusion and tamponade. Plasmacytomas have been reported in the atria. Myeloma rarely involves the orbit, although extramedullary myeloma may involve the base of the brain and be accompanied by destruction of the clivus, thereby producing neurological symptoms from cranial nerve involvement.

2.8. Other Forms of Systemic Involvement

Patients with MM are at increased risk for infection, particularly pneumonia, septicemia, or meningitis. *Streptococcus pneumoniae* and Gram-negative organisms are the most frequent pathogens in these infections *(6)*. The propensity to infection results from an impaired antibody response, a reduction in normal polyclonal immunoglobulin levels, neutropenia, and glucocorticoid therapy.

Both excessive bleeding and thrombotic events may occur. Excessive bleeding may result from thrombocytopenia or qualitative platelet abnormalities, presumably owing to M protein activity. Inhibitors of specific coagulation factors have been recognized, and abnormal clot retraction contributes to bleeding, along with hyperviscosity, hepatic involvement, intravascular coagulation, and amyloid. Deep vein thrombosis and pulmonary embolism have been observed in these patients; whether they are due to older age, debilitation, or myeloma is unclear.

3. LABORATORY FINDINGS

3.1. Anemia

Normocytic normochromic anemia is present during the initial examination in about 70% of cases. Although leukocyte and neutrophil counts are usually normal, thrombocytopenia is present in about 5% of patients at diagnosis. The proportion of plasma cells is low, except in patients with plasma cell leukemia. In fact, only an occasional plasma cell is found in the Wright-stained smear in

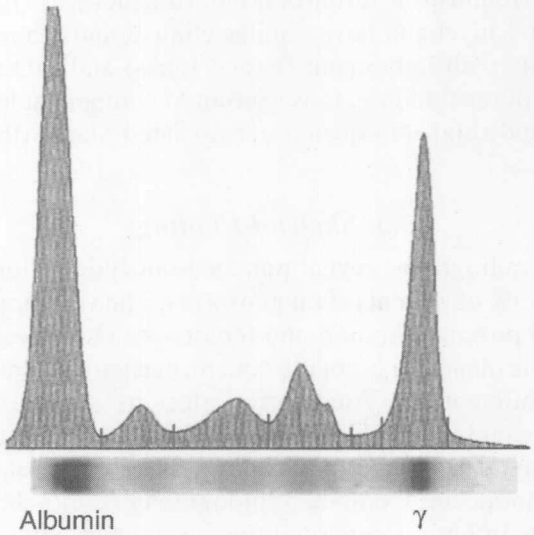

Fig. 1. *Top*, Monoclonal pattern of serum protein as traced by densitometer after electrophoresis on agarose gel: tall, narrow-based peak of γ mobility. *Bottom*, Monoclonal pattern from electrophoresis of serum on agarose gel (anode on left): dense, localized band representing monoclonal protein of γ mobility. (From ref. *6a*. By permission of Blackwell Munksgaard.)

about 15% of patients. Rouleau formation is common and found in nearly two-thirds of patients. Hypercalcemia is present in 25% of patients, and approx 20% have an increased serum creatinine value *(at least 2.0 mg/dL at diagnosis)*.

Overt hemolytic anemia is rare in patients with MM. When it does occur, it is often characterized by the presence of megaloblastoid changes associated with a folic acid or vitamin B_{12} deficiency. The erythrocyte sedimentation rate is frequently increased; however, a normal sedimentation rate does not exclude a diagnosis of myeloma. Serum alkaline phosphatase values are usually normal.

3.2. Serum and Urine M Protein

The serum protein electrophoretic pattern shows a peak or localized band in 80% of patients (Fig. 1; *6a*). Hypogammaglobulinemia is present in 10%; the rest of these patients have an equivocal abnormality or a pattern that appears normal. In our practice, IgG accounts for 52% of cases, IgA for 21%, light chain for only 16%, IgD for 2%, biclonal for 2%, and IgM for 0.5%. In 7% of cases, M protein is not detected in the serum with immunofixation; in 78%, it is detected in urine using this method *(1)*. κ Light chains are found twice as often as λ.

An M protein is found in the serum or urine at diagnosis in 97% of patients with MM. IgG and IgA myeloma have similar clinical and laboratory features at diagnosis. Patients with light-chain (Bence Jones) and IgD myeloma have a higher incidence of renal failure, lower serum M component levels, more light-chain excretion, and a higher frequency of associated AL than those with IgG and IgA myeloma.

3.3. Skeletal Findings

Conventional radiographs reveal punched-out lytic lesions, osteoporosis, and fractures in 79% of patients at diagnosis *(1)*. The vertebrae, skull, thoracic cage, pelvis, and proximal humeri and femora are most frequently involved. Involvement of the mandible is not infrequent, and patients may suffer a pathologic fracture while eating. Osteosclerotic lesions are rare *(7)*. Technetium (Tc) 99m bone scanning should not be used because it is inferior to conventional radiography, e.g., large lytic lesions may be overlooked because bone formation does not occur. Computed tomography (CT) is helpful in patients who have bone pain but no abnormalities on radiography *(8)*. In one study, abnormal magnetic resonance imaging (MRI) patterns were obtained in 50 of 61 patients (82%) with MM *(9)*. MRI in the evaluation of spinal cord compression is very useful *(10)*.

Plasma cells usually comprise more than 10% (range: <5–100%) of all nucleated cells in bone marrow. Bone marrow involvement may be more focal than diffuse, and some patients may require repeat bone marrow examinations for diagnosis. In our experience with 1027 cases of MM in which a bone marrow aspirate and biopsy were both obtained at diagnosis, 4% had fewer than 10% plasma cells. The median plasma cell value was 50% *(1)*.

3.4. Morphologic Appearance of Plasma Cells

Plasma cells may show striking variations on light microscopy. "Flaming" plasma cells are characterized by diffuse eosinophilic coloring of the cytoplasm resembling a sunset glow. Large flaming cells with the nucleus pushed to the side (which have been called thesaurocytes) were originally reported in patients with IgA myeloma; however, they are not specific to this type of myeloma. More often, the cytoplasm of the plasma cells is blue. It is also commonly fragmented, ragged, and extended, and may appear enormous and distended by lacunae. Some plasma cells contain Russell bodies, which are acidophilic, hyaline, crystalline, usually periodic acid-Schiff-positive structures composed of M protein that ordinarily appear as red granules within the cell, but may take the form of rods, amorphous red globs, clear crystals, or spicules resembling Auer rods. The nuclei of the plasma cells are usually eccentric and exceeded two- to threefold in volume by the cytoplasm. The chromatin pattern may be dense and either lymphoidal or reticular, with some degree of blocking or clumping. Nucleoli are

common and may be large and multiple. Frequently, a relatively clear area (hof) is seen in the cytoplasm adjacent to the nucleus, representing the Golgi region.

Electron microscopy reveals a prominent, well-developed endoplasmic reticulum and a prominent, well-organized Golgi region. The endoplasmic reticulum is typically abundant and lamellar in configuration. Variations in shape and amount lead to varying degrees of endoplasmic dilation and dense body formation. Asynchrony in the nuclear and cytoplasmic maturation process in plasma cells is a prominent feature. Mature plasma cells have a relatively small, eccentrically located nucleus with a typical spoke-wheel pattern, whereas the malignant plasma cell is characterized by a large, centrally located nucleus, possibly with abundant cytoplasm and a marked perinuclear hof. The larger the nuclei and nucleoli, the greater the protein-producing capacity of the cell and the greater the likelihood of neoplasia. Cleaved, multilobulated, convoluted, or even cerebriform nuclei of variable size have been seen. The cytologic features most useful in establishing a diagnosis of myeloma are nuclear–cytoplasmic asynchrony with large nuclei and nucleoli, abnormal nuclear configuration, and variations in cell size and cytoplasmic staining.

Myeloma cells may have a very lymphoid appearance on light microscopy; this may result in myeloma being confused with lymphoma. Electron microscopy has shown a spectrum ranging from lymphocytes to plasma cells. A plasmablastic morphology is characterized by a fine reticular chromatin pattern in the nucleus, with no or minimal chromatin clumping. The nucleus must be more than 10 μm in diameter or at least one nucleolus of at least 2 μm in diameter must be seen. The cytoplasm must have little or no hof region and be less abundant in cytoplasm (<50% the volume of the nuclear area). The morphology is considered plasmablastic when plasmablasts comprise 2% or more of the plasma cells *(11)*.

The morphologic features of MM have been reviewed *(12)*. Identification of a monoclonal immunoglobulin in the cytoplasm of plasma cells using immunoperoxidase staining or immunofluorescence is helpful for recognizing polyclonal plasma cell proliferation caused by plasmacytosis owing to an autoimmune disease, metastatic carcinoma, liver disease, acquired immunodeficiency syndrome, or infection.

4. DIAGNOSIS

Suggested tests for patients in whom MM is suspected are listed in Table 1 *(13)*. The diagnosis of MM is usually not difficult, because most patients present with typical symptoms or laboratory abnormalities. Minimal criteria for the diagnosis include a substantial portion of the bone marrow composed of plasma cells (>10%) or a tissue biopsy specimen containing monoclonal plasmacytosis plus one of the following: M protein in serum (usually >3 g/dL), M protein in urine, or lytic lesions.

Table 1
Evaluation of a Patient With a Monoclonal (M) Protein

1. Obtain a complete history and perform a physical examination.
2. Measure the M protein content:
   - Serum M proteins: measure with SPEP (in g/dL)
   - Urine M proteins: measure the total protein excreted in a 24-h urine collection (g/24 h), then determine the light-chain fraction by electrophoresis of concentrated urine (UPEP) and calculate the M protein as grams per 24 h
3. Identify the light- and heavy-chain class of M protein using immunofixation.
4. Use SPEP to measure M protein levels; nephelometric immunoglobulin assays for IgG, IgA, or IgM overestimate the M protein level.
5. Measure hemoglobin, leukocyte, differential, and platelet levels.
6. Perform a bone marrow aspirate and biopsy for cytogenetic study, and plasma-cell labeling index test, if available.
7. Take needle aspirates of a solitary lytic bone lesion or extramedullary tumor(s) if the diagnosis is in doubt.
8. Evaluate renal function based on the serum creatinine value; use UPEP to distinguish proteinuria caused by glomerular lesions (urine contains an unselected mixture of all serum proteins) vs tubular lesions (urine protein consists mostly of light chains, which cannot be reabsorbed by damaged tubular cells).
9. Measure serum calcium and alkaline phosphatase levels; when indicated by clinical findings, measure serum cryoglobulin and viscosity, as well.
10. Obtain radiographs of the skull, ribs, spine, pelvis, humeri, and femora.
11. Obtain an MRI scan if a paraspinal mass is suspected or if symptoms suggest spinal cord or nerve root compression.
12. If amyloidosis is suspected, carry out needle aspiration of abdominal fat and bone marrow biopsy specimen staining for the easiest and safest ways to confirm the diagnosis.
13. Measure β_2-microglobulin, C-reactive protein, and lactate dehydrogenase levels, which are useful and independent prognostic factors.

M protein, monoclonal protein; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis; Ig, immunoglobulin; MRI, magnetic resonance imaging.

The patient must also have the usual clinical features of MM, including end-organ damage, as defined in Table 2 *(14)*. Connective tissue disorders, metastatic carcinoma, lymphoma, leukemia, and chronic infections must be excluded.

5. DIFFERENTIAL DIAGNOSIS

The main conditions to consider in the differential diagnosis are monoclonal gammopathy of undetermined significance (MGUS), smoldering MM (SMM), AL, and metastatic carcinoma *(15)*. In MGUS, the M component is less than 3 g/dL, the bone marrow contains fewer than 10% plasma cells, skeletal radiography shows no osteolytic lesions or fractures, and the patient has no evidence of