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Multiple myeloma: an overview of diagnosis and management

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■ **BACKGROUND** Multiple myeloma, a lethal disease resulting from proliferation of immunoglobulin-secreting cells, accounts for approximately 1% of malignant neoplasms in the United States and affects blacks twice as often as whites.

■ **OBJECTIVE** To review the historic, epidemiologic, diagnostic, and therapeutic features of multiple myeloma.

■ **SUMMARY** Multiple myeloma is often diagnosed when a monoclonal protein is found in the serum or urine or both. No single test differentiates benign from malignant plasma cell proliferation. The clinical features of multiple myeloma develop from tissue damage secondary to the monoclonal gammopathy, plasma cells, and cytokines excreted by the cells. Increased vulnerability to infection is due to depressed normal immunoglobulins. The melphalan-and-prednisone regimen improves median survival from 7 months to 3 years in the 50% to 60% of patients who respond. Cure is exceedingly rare. Refractory and resistant multiple myeloma patients should be treated on investigational protocols.

■ **CONCLUSIONS** There has been substantial advancement in our understanding of the biology of multiple myeloma and related plasma cell neoplasms over the past two decades. We can reasonably hope that improvements in treatment will ensue.

■ INDEX TERMS: MULTIPLE MYELOMA
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MULTIPLE MYELOMA, a lethal, progressive, malignant disease, works its damage throughout the body, causing bone pain, pathologic fractures, anemia, hypercalcemia, and renal failure. Patients who do not undergo chemotherapy or who make up the 40% of patients for whom chemotherapy is not effective can expect to survive less than a year. Responders have a median survival of only 3 to 4 years.

Not all patients with the characteristic monoclonal proteins have multiple myeloma. The disease can range from monoclonal gammopathy of unknown significance to aggressive disease. Certain clinical and laboratory features can help refine the diagnosis. Remarkable advances in our understanding of the pathogenesis of multiple myeloma in the past few years may afford improvements in its treatment.

DEFINITION

Myeloma is a prototype of a group of conditions known as plasma cell neoplasms. Plasma cell neoplasms are a group of related disorders, each of which is associ-

ated with proliferation and accumulation of immunoglobulin-secreting cells that are derived from the B-cell series of immunocytes. Monoclonal components occur in both the malignant plasma cell disorders (ie, multiple myeloma and Waldenström's macroglobulinemia) as well as in the clinically unclear or idiopathic benign, premalignant, or early malignant disorders.

B lymphocytes and plasma cells synthesize five major classes of immunoglobulins: IgG, IgA, IgM, IgD, and IgE. These antibodies have a monomeric structure composed of two identical heavy chains and two identical light chains, each of which has constant and variable regions of amino acid sequences. The constant regions of the heavy chain for the various classes are gamma (IgG), alpha (IgA), mu (IgM), delta (IgD), and epsilon (IgE). The constant regions of the light chains are kappa and lambda. The constant regions define the molecule's class specificity and other biologic characteristics. The monoclonal immunoglobulins secreted in malignant plasma cell disorders are similar to normal homogenous antibodies, but in most instances the antigen they bind to is unknown.

EARLY DESCRIPTIONS

Although skeletal evidence for the existence of myeloma in ancient times has been obtained from Egyptian mummies and other anthropologic remains, the first case report was published in 1850 in England.[1] Later that year, Dr. Henry Bence Jones[2] tested urine specimens from a patient with myeloma and established the heat properties of urinary light chains, which are now called Bence Jones proteins.

In 1873, Rustizky[3] independently described a similar patient and employed the term "multiple myeloma" for the first time to describe the multiple bone tumors that were present. Kahler[4] published a major review of multiple myeloma in 1889, and the disease became known as Kahler's disease, particularly in Europe. In 1900, Wright[5] published a case report indicating that myeloma does not arise from the red marrow but from specific plasma cells. This was probably the first case in which roentgenograms were used to show abnormalities in the ribs.

The development of bone marrow aspiration in 1929[6] and protein electrophoresis in 1937[7] facilitated the diagnosis and enhanced the understanding of myeloma. In 1938, Magnus-Levy described amyloidosis as a complication of multiple myeloma. In 1953, Graber and Williams[8] developed immune electrophoresis, which can precisely identify the heavy and light chains in monoclonal immunoglobulins, thereby enhancing the diagnosis of monoclonality of an immunoglobulin. In the 1970s, methods were developed to estimate the total-body burden of tumor cells and to define the relationship of tumor burden to clinical manifestations of this disease. This led to the development of a useful staging system.[9]

Systemic therapy was essentially without effect until 1947, when Alwall[10] reported two cases in which chemotherapy was of value. In 1958, Block[11] described the use of phenylalanine mustard in myeloma. In 1962, the Southwest Oncology Group reported that melphalan could induce remission in approximately one third of myeloma patients.[12]

FACTS AND FIGURES

Twice as common in African-Americans

Multiple myeloma accounted for 1% of all malignant neoplasms in whites and 2% in African-Americans in the United States between 1984 and 1988.[13] In whites, the average annual age-adjusted incidence rate is 4.7 and 3.2 per 100 000 in men and women, respectively, while in African-Americans it is nearly double at 10.2 in men and 6.7 in women.[13] Social and economic factors such as household size and family income do not appear to explain the differences in incidence between African-Americans and whites.[14,15] Multiple myeloma accounts for 31% of lymphoproliferative neoplasms among African-Americans and 13% among whites.[13]

Overall prognosis

The overall prognosis in multiple myeloma is poor. In cases diagnosed between 1981 and 1987, African-Americans had a slightly higher 5-year relative survival when compared to whites (28.3% and 26.3%, respectively).[13] The relative survival rates were higher for women than for men regardless of race.[13] In some studies, patients with higher income and education survived longer, regardless of race,[14–16] but other studies did not support this finding.[17,18]

Who is at risk?

Atomic bomb survivors. The strongest evidence linking radiation to myeloma comes from studies of atomic bomb survivors. People who entered Hiroshima city within 3 days after the blast had a nearly

60% greater risk of dying of myeloma than those not exposed.[19,20]

Radiologists. An excess of myeloma deaths among radiologists was observed nearly 30 years ago.[21] In a more recent study, radiologists still had a twofold excess myeloma risk, even though their long-term radiation dose was lower than in the earlier studies.[22]

There is little evidence of an increased risk of multiple myeloma among people who live near nuclear facilities. A recent US nationwide survey found the mortality rate from multiple myeloma among residents of counties with nuclear facilities was similar to that of residents of counties without nuclear facilities.[23] Exposure to diagnostic radiologic procedures has not been clearly linked with multiple myeloma. The effect of therapeutic radiation on risk has been inconsistent in different studies,[24,25] and most authorities believe there is no relationship.

Preexisting medical conditions. Myeloma research has become increasingly focused on the immune system and the role of chronic antigenic stimulation as an etiologic factor.[26] Although several studies have reported a statistically significant association between multiple myeloma and various immune system stimulants such as chronic bacterial infections, diabetes mellitus, medical implants, allergies, and related disorders,[27–33] others have found no such relationships.[27,28,32,34,35]

Occupational exposure. The effect of occupational exposures on risk of multiple myeloma remains unclear. Most occupational associations with multiple myeloma have been in farming.[36] No specific associations with occupations in the metal, benzene, wood, rubber, leather, textile, or petroleum industries have been reported. One recent case-control study did report some elevation in myeloma risk in certain jobs,[37] but workers in many of the occupations were exposed to a wide variety of substances, and causal associations with specific chemicals or types of work are lacking.

Medications. Prescription and over-the-counter medications have been suggested as myeloma risk factors in several case-controlled studies. One study found an association with propoxyphene use,[38] and another found possible associations with previous use of phenytoin, phenobarbital, diazepam, propranolol, ibuprofen, diet drugs, stimulants, and laxatives.[39] Another study found a significant elevation in myeloma risk with previous use of erythromycin, chlorpheniramine, gentamicin, sulfamethoxazole, and terpin hydrate.[40] These studies have variables unaccounted for that make them difficult to interpret.

Family history. Studies to date have yielded only minimal information about the genetic markers for the gammopathies. Human lymphocyte antigens of the 4C group appear slightly more frequent in myeloma.[41–44] First-degree relatives of myeloma patients appear to have a higher incidence, and familial myeloma has been the subject of case reports.

Of etiologic relevance is the 14q+ abnormality, first noted by Wurster-Hill et al in 1973.[45] Gould et al[46] examined 115 myeloma patients for karyotypic abnormalities and found that the translocation t(8;14)(q24;q32) was statistically associated with the IgA myeloma protein. The same translocation has been associated with 80% of all Burkitt's lymphoma cases. Another translocation, t(11;14)(q13;q32), has been observed in various B-cell abnormalities, including multiple myeloma, chronic lymphocytic leukemia, and plasma cell leukemia.[47,48]

WHEN TO PERFORM ELECTROPHORESIS

The diagnosis of multiple myeloma often begins when a monoclonal protein is found in the serum or urine or both. Serum and urine protein electrophoresis, supplemented by immune electrophoresis and immune fixation, should be performed when multiple myeloma, macroglobulinemia, amyloidosis, or other related disorders are suspected. The test should be performed in any patient with unexplained weakness or fatigue, anemia, elevation of the erythrocyte sedimentation rate, back pain, osteoporosis, osteolytic lesions or fractures, immunoglobulin deficiency, hyperglobulinemia, hypercalcemia, Bence Jones proteinuria, renal insufficiency, or recurrent infections. It should also be performed in adults with sensory or motor peripheral neuropathy, carpal tunnel syndrome, refractory congestive heart failure, nephrotic syndrome, orthostatic hypotension, or malabsorption.

SPECTRUM OF MONOCLONAL GAMMOPATHIES

In a large series of patients with a serum monoclonal protein, IgG accounted for 61%, IgM for 18%, IgA for 11%, IgD for 0.5%, and 6% of the patients had only a monoclonal light chain. A biclonal gammopathy was found in 3.5%.[49] The fifth class of immunoglobulins, IgE, has been purified from the sera of allergic patients and subsequently

identified in multiple myeloma, where more than 20 cases of IgE myeloma or monoclonal gammopathy have been reported.[50,51]

Plasma cell dyscrasia is a collection of diseases ranging from benign monoclonal gammopathy ("monoclonal gammopathy of undetermined significance") and smoldering multiple myeloma to very aggressive multiple myeloma. The hallmark of plasma cell disorders is a monoclonal immunoglobulin in the serum or urine or both that occurs in approximately 99% of cases.[52–56] The survival of patients with multiple myeloma ranges from less than 1 year to more than 10 years.[52] Survival is determined by the tumor burden and by intrinsic features such as myeloma cell kinetics at the time of diagnosis.[57–60]

What is the significance of a monoclonal protein?

All patients who present with monoclonal protein in the serum or urine do not necessarily have multiple myeloma[54]; monoclonal proteins occur in association with a variety of nonmyelomatous diseases. One must distinguish between monoclonal gammopathy of unknown significance (MGUS), indolent myeloma, and active multiple myeloma requiring therapy.[54,61,62]

In a long-term follow-up at the Mayo Clinic, of 241 patients with an apparently benign monoclonal gammopathy, 25.4% acquired multiple myeloma or related disorders. The concentration of the monoclonal protein initially ranged from 0.3 to 3.2 g/dL (median 1.7 g/dL). The percentage of plasma cells in the bone marrow ranged from 1% to 10%. After 20 to 35 years of follow-up the patients were divided into four groups. In Group I (46 patients, 19%) the monoclonal protein remained stable and the patients could be classified as having benign monoclonal gammopathy. Of these patients, seven had monoclonal light chains in the urine. In Group II (23 patients, 9.5%), the monoclonal protein concentration increased to more than 3 g/dL, and the patients did not develop symptomatic multiple myeloma, macroglobulinemia, amyloidosis, or other related diseases and have not been treated. Patients in Group III (113 patients, 47%) died without developing myeloma, macroglobulinemia, amyloidosis, or related diseases.

The remaining 59 patients (24.5%) (Group IV) developed multiple myeloma, macroglobulinemia, amyloidosis, or related diseases. Of these 59 patients, 39 (66%) had multiple myeloma. The interval from recognition of the monoclonal gammopathy to diagnosis of multiple myeloma ranged from 2 to 20 years (median 10 years). The median duration of survival after diagnosis of multiple myeloma was 34 months. Waldenström's macroglobulinemia developed in seven patients 4 to 20 years after recognition of the monoclonal protein. Systemic amyloidosis was found in eight patients 6 to 19 years after the diagnosis of serum monoclonal protein. Five patients acquired a malignant lymphoproliferative process 6 to 22 years after recognition of monoclonal protein.[49]

MGUS vs multiple myeloma

No single test differentiates benign from malignant plasma cell proliferation. The most dependable method involves serial measurements of the monoclonal protein in the serum and urine and periodic evaluation of pertinent clinical and laboratory features to determine whether multiple myeloma, systemic amyloidosis, macroglobulinemia, or another plasma cell proliferative disease has developed. The diagnostic features of monoclonal gammopathy of unknown significance, smoldering myeloma, indolent myeloma, and multiple myeloma are detailed in the *Table*. The multiplicity of criteria reflects the lack of a single reliable diagnostic test to distinguish among the entities.[55,61–63]

ASSESSING MULTIPLE MYELOMA

Clinical staging

The staging system of Durie and Salmon[64] is based on the presenting clinical features, response to treatment, and survival duration in a group of patients who underwent direct measurement of total body myeloma cell number. Cases are assigned to one of three stages based on hemoglobin, serum calcium, and monoclonal protein concentrations and on the characteristics of the bone survey. These stages are subclassified on the basis of renal function. There is a clear relationship between stage, renal function, and survival duration.

Cell kinetics and prognosis

Although clinical staging provides important prognostic information, other factors such as intrinsic drug sensitivity of the predominant myeloma cell clone and cell kinetics must also be considered.[65] At diagnosis, most patients with multiple myeloma are in a stage of indolent tumor growth. However, a

subgroup presents with more rapidly progressive disease as determined from changes in monoclonal component level and in [^{3}H] thymidine turnover and incorporation.[59,66,67] The kinetic features of the predominant clone in these patients has proved very important. By multiplying the [^{3}H] thymidine labeling index (the percentage of myeloma cells incorporating [^{3}H] thymidine during a 1-hour flash label) by the total myeloma cell mass, one can calculate the total number of DNA-synthesizing myeloma cells (S cells) in the body. Patients with both a high cell mass and a high labeling index (> 3%) have a median survival of only 5.3 months.[59] Interestingly, involvement of the central nervous system is common in the subgroup with high tumor burden and high labeling index, although it is rare in most myeloma patients.[59] It must be emphasized that the [^{3}H] thymidine labeling index of myeloma cells is only a reflection of the biologically important subset of proliferating tumor cells.

A plateau effect with chemotherapy

Multiple myeloma regresses with induction chemotherapy in a characteristic way. In responsive cases, tumor regression occurs rapidly at first and then slows as the tumor reaches a plateau stage, defined as a stable state with minimal change in the serum or urine monoclonal component level or measured myeloma cell mass for at least 4 to 6 months. This state can persist for several months to years, in spite of ongoing treatment.[68]

The incidence and significance of the plateau phase was investigated in an analysis of 127 patients receiving standard chemotherapy who had serial measurements of myeloma cell mass.[68] A plateau phase occurred in 44% where tumor cells were cytokinetically stable, and 38% had an unstable course with significant ongoing cell turnover despite therapy. Another 9% had steady regression continuing beyond 1 year of therapy. This study was based on findings after the first 6 months of treatment. Reports concerning the initial 6 months indicate that many more patients have high [^{3}H] thymidine labeling indices and evidence of possible cell recruitment.[66,69]

Clinical features of patients whose disease enters a stable plateau phase include a predominance of IgG or IgA monoclonal component and low, intermediate, or high cell mass in patients with normal renal function. This group has a better survival duration than the unstable group.

TABLE
DIAGNOSTIC CRITERIA FOR MULTIPLE MYELOMA, MYELOMA VARIANTS, AND MONOCLONAL GAMMOPATHY OF UNKNOWN SIGNIFICANCE*

- Multiple myeloma†
  - Major criteria
    - Plasmacytoma on tissue biopsy
    - Bone marrow plasmacytosis with > 30% plasma cells
    - Monoclonal globulin spike on serum electrophoresis exceeding 3.5 g/dL for G peaks or 2.0 g/dL for A peaks, Bence Jones protein excretion ≥ 1.0 g/24 hours, or light chain excretion on urine electrophoresis in the presence of amyloidosis
  - Minor criteria
    - Bone marrow plasmacytosis with 10% to 30% plasma cells
    - Monoclonal globulin spike present, but less than the level defined above
    - Lytic bone lesions
    - Residual normal IgM < 50 mg/dL, IgA < 100 mg/dL, or IgG < 600 mg/dL
- Smoldering myeloma
  - Minimal criteria to diagnose multiple myeloma
    - No bone lesions
    - Bone marrow plasma cells ≤ 30%
    - Monoclonal component level:
      - IgG < 7.0 g/dL or
      - IgA < 5.0 g/dL
    - No symptoms or associated features, ie, performance status > 70%, hemoglobin > 10 g/dL, serum calcium normal, serum creatinine < 2.0 mg/dL, no infections
- Indolent myeloma
  - Minimal criteria to diagnose multiple myeloma
    - No bone lesions or only limited bone lesions (lytic lesions); no compression fractures
    - Monoclonal component level:
      - IgG < 7.0 g/dL or
      - IgA < 5.0 g/dL
    - No symptoms or associated disease features
- Monoclonal gammopathy of unknown significance
  - Monoclonal gammopathy
  - Monoclonal component level:
    - IgG ≤ 3.5 g/dL or
    - IgA ≤ 2.0 g/dL
  - Bence Jones protein excretion ≤ 1.0 g/24 hours
  - Bone marrow plasma cells < 10%
  - No bone lesions
  - No symptoms

*Summarized from references 55, 61-63
†Diagnosis of multiple myeloma in symptomatic patients with clearly progressive disease requires a minimum of one major and one minor criterion (bone marrow plasmacytosis is not sufficient with plasmacytoma), or three minor criteria that must include bone marrow plasmacytosis and monoclonal globulin spike

PROGNOSTIC FACTORS

Clinical and laboratory parameters provide important prognostic information that is extremely valuable in evaluating different treatment regimens.

With refining these parameters treatment decisions might be influenced by them in the future.

Serum beta-2-microglobulin

More than 15 years ago, serum beta-2-microglobulin (B2M) levels were found to be elevated in patients with active multiple myeloma,[70] and human myeloma cell lines were shown to produce free B2M. A close relationship was noted between serum B2M (uncorrected for serum creatine) and measured myeloma cell mass.[71] Large perspective studies subsequently revealed that serum B2M levels predict survival remarkably well in multiple myeloma.[70–74] Patients can be assigned to low-risk, medium-risk, and high-risk groups on the basis of serum B2M, albumin levels, and age.[71]

Serum interleukin-6 and C-reactive protein

Interleukin-6 (IL-6) promotes growth of fresh human multiple myeloma cells in vitro, making it possible to obtain myeloma cell lines whose proliferation completely depends on exogenous IL-6.[75–79] Patients with terminal myeloma, especially with plasma cell leukemia, have higher serum IL-6 levels than patients with stable myeloma.[80] An overproduction of IL-6 in multiple myeloma patients is directly evidenced by increased production of C-reactive protein. Indeed, IL-6 is a potent inducer of acute-phase proteins; the production of C-reactive protein by human hepatocytes in primary culture is controlled only by IL-6.[81]

In multiple myeloma patients, treatment with anti-IL-6 monoclonal antibody blocks C-reactive protein production, but production resumes at the end of the treatment.[82] These results clearly show that C-reactive protein production is controlled by IL-6 in vivo and is a convenient and direct indicator of IL-6 production. Increased plasma C-reactive protein levels were found in 97% of patients with progressive multiple myeloma and were associated with severe disease, hypercalcemia, and death.[83]

Karyotype

In a recent study of 104 patients with multiple myeloma and six patients with plasma cell leukemia, abnormal karyotypes were noted in bone marrow cells of 33 patients (30%). Numeric anomalies occurred most often in chromosome 11, and structural aberrations occurred most often in chromosomes 1, 11, and 14. Irrespective of the treatment status, patients with an abnormal karyotype had a significantly shorter median survival than those with a normal karyotype.[84]

Serum interleukin-2

Serum interleukin-2 (IL-2) levels in 61 patients with multiple myeloma were found to be significantly higher than in normal controls. Moreover, higher serum IL-2 levels were associated with a prolonged actuarial survival: 87% of patients with IL-2 levels of 10 U/mL or greater remained alive at 5 years, while only 13% of the patients with lower IL-2 levels survived this long.[85]

The plasma cell labeling index

The plasma cell labeling index (PCLI) powerfully and independently predicts survival.[86–89] Recently, Greipp and colleagues[89] followed up 107 patients who had newly diagnosed myeloma to determine whether thymidine kinase and C-reactive protein values added prognostic information not already available using the PCLI and serum B2M level. Univariate survival analysis revealed prognostic significance for the PCLI and for thymidine kinase, serum B2M, age, serum albumin, and C-reactive protein levels. However, multivariate analysis showed that only the PCLI and the B2M level had independent prognostic significance.

COMPLICATIONS OF MULTIPLE MYELOMA

The clinical features of multiple myeloma develop from tissue damage from multiple bone tumors, complications from the monoclonal component, and an increased vulnerability to infection due to depressed normal immunoglobulin levels. The wide range of abnormalities leads to varied complications and treatment requirements among different patients. These complications provide the first clues to the diagnosis and form the basis for defining the stage and prognosis. Because some are life-threatening, they must be managed expeditiously while combination chemotherapy is being given.

Bone destruction

Bone pain, the most common symptom, results from pathologic fractures, usually compression fractures of thoracic and lumbar vertebral bodies infiltrated by plasma cell tumors. Multiple compression fractures may culminate in painless dorsal kyphosis and loss of as much as 6 inches of height. Pleuritic pain from pathologic rib and clavicle fractures is also

common and is associated with marked local tenderness. Destruction of the proximal bones of the extremities is less frequent, and distal bones of the extremities are rarely affected.

Approximately 20% of patients have bone demineralization only. Radiographs of the axial skeleton, which must include both femurs, will support the diagnosis of myeloma in approximately 70% of the patients. Punched-out lesions are best seen on lateral skull radiographs. Ten percent of patients will have a normal skeletal survey, presumably because at least 30% of bone calcium must be lost before radiographic changes are evident.

Computed tomography and magnetic resonance imaging (MRI) detect bone destruction more sensitively and are especially useful in detecting the extent of extramedullary soft-tissue lesions.[90] MRI of the lumbar spine and pelvis may detect more advanced disease that may require chemotherapy, primarily in patients with an apparently localized plasmacytoma or with asymptomatic indolent multiple myeloma.[91] Bone scans are less sensitive and are rarely useful except to detect rib disease in some patients with ambiguous chest pains.[92]

In rare circumstances, pleural effusions may develop from plasmacytomas, and plasmacytosis will often be present in the pleural fluid.[93] Soft tissue masses may be observed without bone destruction in the pleura, mediastinum, and abdomen and are often associated with an elevated serum lactate dehydrogenase concentration.[94]

In approximately 15% of patients, firm plasma cell tumors arise from areas of underlying bone destruction and may be palpated on the skull, sternum, clavicles, and ribs, where the affected bone is close to the skin. Percutaneous or surgical biopsy is sometimes necessary when other diagnostic features are in doubt because lytic bone lesions may result from other metastatic tumors, eosinophilic granulomas, or benign processes. Rarely (in 1.4%), an osteoplastic reaction is present, such as with peripheral neuropathy or the POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes).

The physician should encourage physical activity and supervise its progress regularly, especially in disabled, hospitalized patients. For most patients with mild or moderate back pain due to vertebral compression fractures, rational use of analgesics, corsets with plastic stays, and walkers is sufficient. Back braces are tolerated poorly but are sometimes necessary in selected patients with severe disability. Carefully fitted thoracic jackets may help some patients who have disabling thoracic compression fractures.

Radiotherapy (approximately 2500 cGy given over 7 to 10 days) may be necessary to relieve severe localized pain but should be delayed in patients with newly diagnosed myeloma until the benefit from the first course of chemotherapy has been assessed. Prophylactic radiotherapy should be given to areas of the femur or the entire femur when bone destruction is severe and the risk of pathologic fracture is high. Radiotherapy is usually unnecessary for pleuritic rib pain.

Preventing paraplegia

Spinal cord compression and paraplegia may result from extradural plasma cell tumors. This serious complication represents an emergency requiring immediate diagnosis and treatment. In patients with known myeloma, one can almost always eliminate the need for decompressive laminectomy by performing emergency radiographic studies (myelography, computed tomography, or MRI) to locate the area of cord compression and giving radiotherapy and steroids immediately afterward. When the diagnosis is uncertain, emergency surgery is mandatory unless the patient is in the terminal phase.

Hypercalcemia

At diagnosis, one fourth of patients have serum calcium concentrations greater than 11.5 mg/dL after correction for serum albumin. Some hypercalcemic patients may not show bone destruction on radiographs. Nausea, confusion, polyuria, and constipation are common symptoms. Hydration, diuresis, and an increased activity level usually relieve hypercalcemia, but such measures must not delay the use of corticosteroids, especially in previously untreated patients, who should receive combination chemotherapy without delay. Bedridden patients with pathologic fractures from advanced myeloma refractory to all available therapies may have increased pain and need more narcotic analgesics when hypercalcemia is controlled; therefore, control of hypercalcemia in this setting may be unjustified.

Cytopenias

Anemia, present in most patients, provides a major diagnostic clue. Severe anemia with hemoglobin values of less than 8.5 g/dL may cause easy fatigability or dyspnea on exertion. Several factors account

for anemia, such as bone marrow infiltration by plasma cells, renal failure, and chronic disease. Low serum levels of vitamin B12 may occur without signs of functional vitamin B12 deficiency; supplementation is usually not required. Secondary myelofibrosis has been attributed to the proliferation of plasma cells in some patients.[95]

High levels of IgA or IgG frequently increase the plasma volume: the hematocrit may be six percentage points less than the value expected from the measured red cell volume.[96] One should consider this before ordering red cell transfusions; anemic patients at risk for pulmonary edema should be considered for plasmapheresis simultaneously with red cell transfusion.

Thrombocytopenia is uncommon at diagnosis and usually reflects a marked degree of bone marrow replacement by plasma cells.

Mild granulocytopenia occurs frequently for reasons that are unclear and usually persists throughout the clinical course. Plasma cell leukemia with more than 2×10^9 plasma cells per liter usually signifies extensive bone marrow infiltration and is seen primarily during the late phase of the disease. Even when the differential count shows no abnormalities, sensitive flow cytometry techniques reveal monoclonal B lymphocytes of the same clone present in the bone marrow of most newly diagnosed patients.[97] In a clinical pattern that resembles macroglobulinemic lymphoma, some patients have splenomegaly, large IgG or IgA peaks, and no bone marrow destruction.[98]

Effects of immunoglobulins

When present at concentrations greater than 5.0 g/dL, some IgG or IgA myeloma globulins can produce features of the hyperviscosity syndrome. Symptoms and signs of this condition are generally not seen unless the relative serum viscosity is greater than 4.0 units (normal range 1.4 to 1.8 units), and the full-blown classic syndrome is usually not observed unless the viscosity is greater than 5.0 units. The signs and symptoms include lassitude, confusion, segmental dilatation of retinal veins with retinal hemorrhages, and increased bleeding tendency. Myeloma proteins of the IgA or IgG3 type are more likely than the other myeloma proteins to produce hyperviscosity because of their greater tendency to polymerize. Tumor control with chemotherapy will reduce myeloma globulin levels and the risk of hyperviscosity. If a remission is not achieved, regular plasmapheresis with an automatic blood cell separator is necessary to prevent and control serum hyperviscosity.

An increased bleeding tendency may occur in myeloma, usually manifesting itself as easy bruising. When not due to severe thrombocytopenia, this effect may result from a myeloma globulin that interferes with platelet function, prolonging the bleeding time and reducing platelet adhesiveness. Clotting factors may be reduced by interactions between myeloma globulin and various clotting proteins.[99] Rare patients, especially those with plasma cell leukemia, show evidence of heparin-like anticoagulant.

Neurologic effects

Occasionally, patients with multiple myeloma experience peripheral neuropathy, which may be severe. Electromyelographic studies suggest this complication occurs more frequently than clinically recognized.[100] Electromyelography and nerve biopsy can show demyelination or axon degeneration or both. Although the pathogenesis is unclear, the neuropathy may be caused by associated amyloidosis in some patients. Severe motor neuropathy occurs more frequently in younger patients with localized or osteosclerotic myeloma. Some of these patients also demonstrate hyperpigmentation, gynecomastia, and hypogonadism (POEMS syndrome).[101] Although some patients describe and exhibit clinical improvement with cytotoxic therapy or plasmapheresis, no patients with neuropathy and myeloma have shown consistent neurologic improvement with such treatments.

Cerebellar involvement has been described; rarely, large plasmacytomas growing internally from the calvarium produce intracranial pressure. Meningeal involvement is also rare; it may occur without evidence of extension from skull lesions and can produce mental confusion or cranial nerve palsies. Plasma cells and increased myeloma protein concentrations will usually be evident in the cerebrospinal fluid.[102,103] Plasma cell leukemia, high lactate dehydrogenase levels, and lymphoma-like clinical features are more frequent in patients with meningeal myeloma. Intrathecal therapy with various drugs should be attempted, although the prognosis is poor.

Renal failure

Renal failure occurs in approximately 25% of patients, more frequently in patients with more extensive myeloma. Most patients with mild azotemia

have no symptoms; however, easy fatigability, nausea, vomiting, and confusion occur with severe renal insufficiency. As with anemia, the pathogenesis is multifactorial, but more than 90% of patients with renal failure have Bence Jones proteinuria or hypercalcemia or both.[104] With myeloma-induced kidney damage, the distal and occasionally the proximal convoluted tubules become obstructed by laminated casts composed of precipitated Bence Jones and other proteins. Severe renal failure may be induced by episodes of dehydration, which may occur in preparation for certain radiologic procedures. Thus, adequate hydration is necessary to reduce the risk of this complication, especially in patients with Bence Jones proteinuria.

The combination of increased hydration, glucocorticoids for hypercalcemia, allopurinol for hyperuricemia, and chemotherapy will rapidly reverse mild renal failure in approximately half of patients. Irreversible acidemia is more likely in patients who have only Bence Jones protein, who presumably have more frequent and severe cast nephropathy. Hemodialysis may be necessary in patients with newly diagnosed myeloma and severe renal failure to provide an opportunity for control of the myeloma. For patients with a comparable extent of myeloma, the presence and degree of renal failure do not adversely affect prognosis.[105]

Infections

Recurrent bacterial infections are a major cause of illness and are the most frequent cause of death in patients with advanced myeloma. Infections result primarily from the marked depression of production of normal immunoglobulins that occurs in more than 75% of patients. Cell-mediated immunity does not appear to become impaired until after the institution of chemotherapy. Advanced myeloma stage and renal failure are also associated with more frequent infections.

Streptococcus pneumoniae and *Hemophilus influenzae* are the most common pathogens in previously untreated myeloma patients and in nonneutropenic patients who respond to chemotherapy. However, in neutropenic patients and in those with refractory disease, *Staphylococcus aureus* and gram-negative bacteria are the predominant organisms.[106,107] Patients with fever, productive cough, and other symptoms of bacterial infection should undergo bacterial cultures and appropriate radiographic studies as quickly as possible and start antibiotic therapy.

Patients who have repeated episodes and signs of pulmonary infections often benefit from keeping a supply of a suitable oral cephalosporin or the amoxicillin-clavulanate combination to begin treatment when symptoms first appear. For patients who have difficulties with compliance, prophylactic treatment with benzathine penicillin G should be considered if there has been a history of recent or previous pneumococcal or meningococcal infection. Pneumococcal vaccination may be worth trying; however, most myeloma patients respond poorly to bacterial antigenic stimulation.[108] Vaccines containing live organisms are contraindicated in patients with myeloma because their immune deficiencies permit infection to disseminate. The role of prophylactic use of intravenous immunoglobulin is not clear. A recent randomised trial using intravenous immunoglobulin as prophylaxis against infections in plateau-phase myeloma has shown a significant benefit in reducing the risk of recurrent infections, especially in the group of patients that had a poor IgG antibody response to pneumococcal vaccine.[109]

Amyloidosis

Systemic amyloidosis occurs in approximately 15% of patients with multiple myeloma. Differentiating between amyloid associated with myeloma and primary amyloidosis is artificial because the amyloid in both entities is of similar genesis and tissue distribution. Thus, they are more appropriately considered to be part of the spectrum of the same disease process. Although kappa light chains are more frequent than lambda light chains on monoclonal component or Bence Jones proteins, amyloidogenic lambda light chains are significantly more frequent than kappa chains.[110]

The presenting symptoms of amyloidosis with or without myeloma include weakness, weight loss, ankle edema, dyspnea, paresthesia, lightheadedness, or syncope.[101] Aching in the hands, particularly at night, can signify median nerve compression associated with carpal tunnel syndrome caused by amyloid infiltration of the transverse carpal ligament. Physical findings include enlargement of the tongue and liver, purpura, and ankle edema (usually due to heart failure or nephrotic syndrome).

A rectal biopsy has been the classic method of diagnosing amyloidosis, and it is positive in more than 60% of patients.[111] A more recent study, however, has shown that abdominal fat aspiration using

a 19-gauge needle can yield positive results in over 70% of patients. This procedure can be done at the bedside and is probably the simplest way to diagnosis amyloidosis.[112]

Treatment of myeloma usually does not have as great an impact in resolving amyloid deposits as it does in causing tumor regression. However, treatment may stop or slow further amyloid deposition. This could be important for patients with early cardiac involvement.[113]

Secondary malignant neoplasms

Secondary acute leukemia develops in approximately 2% of patients who survive 2 years,[114] which is 50 to 100 times more frequently than in normal individuals. The first sign is usually either increasing anemia or thrombocytopenia unrelated to the relapse of myeloma. Cytogenetic studies almost always confirm loss or deletion of the long arm of chromosome 5 or 7 or both. These karyotypic patterns are similar to those of patients with acute myeloid leukemia treated previously with radiation or chemotherapy or both for other malignant and nonmalignant diseases, as well as to those of 5% of new patients with acute nonlymphocytic leukemia. Fewer than 5% of patients with myeloma have acute leukemia at diagnosis or acquire it within several months after starting chemotherapy. The frequency of solid tumors in myeloma patients is no higher than in persons of similar age or sex.

TREATING MULTIPLE MYELOMA

Melphalan and prednisone still standard

Chemotherapy at standard doses is the mainstay of treatment of multiple myeloma. An aggressive approach is hampered by age and clinical condition at presentation, as about 50% of patients are over age 65 and many have intercurrent diseases. However, improved supportive care and development of different growth factors may permit more aggressive therapy in the future. The melphalan-prednisone regimen, introduced over 20 years ago and not significantly modified since,[115] improves median survival from 7 months to 3 years and induces a response in 50% to 60% of patients. Cure is exceedingly rare; the monoclonal component disappears on electrophoresis in approximately 3% of patients.[116,117] In the remaining patients, the monoclonal component remains stable or increases during treatment.

Measuring response to treatment

The kinetics of monoclonal protein following chemotherapy have been carefully evaluated.[118] Bence Jones protein excretion in the urine declines more quickly than the concentration of monoclonal component in the blood (a 50% reduction in less than 2 months vs 3 months, respectively). A careful evaluation at 3 months helps to plan the future treatment strategy. If the monoclonal component does not decrease and Bence Jones proteinuria persists, then therapeutic resistance is present and salvage treatment should be contemplated.

In most responding patients, the tumor burden tends to reach a plateau after an initial fall despite continued treatment.[119] The plateau phase lasts approximately 20 months, after which the tumor resumes growing.[120] The plateau phase is usually achieved within the first year of treatment; afterward, maintenance chemotherapy offers no survival advantage. In the plateau phase, neoplastic cells proliferate very slowly but have an inherited resistance to further chemotherapy.[121,122]

Combination therapy controversial

Combination chemotherapy was introduced in the early 1970s on the strength of theoretic and experimental evidence. Despite strong arguments in its favor, combination chemotherapy has not led to a significantly longer survival than with melphalan and prednisone in most randomized trials,[115,120,123] although there is no complete agreement regarding this point.[124,125]

Salvage therapy: vincristine, doxorubicin, dexamethasone

A common and challenging clinical problem, resistance to treatment can be primary or secondary. In primary resistance, myeloma either progresses during initial therapy (an increase of 25% or more in monoclonal protein or an increase in the size or number of lytic lesions) or remains stable and then progresses. In secondary resistance, patients have an initial response and subsequently have a relapse either during or after therapy.

For truly resistant myeloma, which clearly progresses during initial therapy, high-dose or pulsed glucocorticoids appears to be the best treatment, with an expected response rate of 40% (defined as a reduction in the monoclonal protein concentration of 50% or more). For patients who have a relapse during therapy or within 6 months afterward, the

combination of vincristine, doxorubicin, and dexamethasone is one of the most effective salvage therapies, resulting in approximately a 75% response rate (a reduction in the monoclonal protein concentration of 50% or more). For patients who have a relapse more than 6 months after stopping therapy (an unmaintained remission), restarting the initial therapy leads to recontrol 60% to 70% of the time. If progression is observed or if there is response and then relapse in this setting, vincristine, doxorubicin, and dexamethasone chemotherapy can be administered. Patients for whom second-line salvage chemotherapy fails can enter well-designed clinical trials to evaluate new treatments.[126]

Allogenic bone marrow transplantation

The use of high-dose chemotherapy with allogenic hematopoietic stem-cell support started approximately a decade ago. This approach appears to produce a complete remission in at least 50% and even higher if applied as consolidation treatment in the remission phase. The mortality rate in allogenic bone marrow transplantation can reach 50%. Approximately 40% of patients achieve a long-term survival plateau; however, a recent update demonstrated that this plateau is lost.[126,127]

Retrospective analyses of relatively large series of patients have recently provided information on the factors influencing the outcome of allogenic bone marrow transplantation for multiple myeloma. Favorable pretransplantation variables include sensitive disease, one line of treatment before bone marrow transplantation, and a low myeloma cell mass. Favorable posttransplantation variables include the achievement of a complete remission following transplantation and the development of grade I graft-versus-host disease.[127,128] These promising results and the incurability of multiple myeloma with conventional chemotherapy have encouraged further application of allogenic bone marrow transplantation in a research setting to selected patients with unfavorable prognostic features.[128]

Autologous bone marrow transplantation

There is considerably less information regarding the role of autologous bone marrow transplantation. Available data are insufficient to make specific recommendations as to which patients are most likely to benefit from high-dose chemotherapy. Several prognostic factor analyses have defined the parameters most significantly associated with early death, complete remission, relapse-free survival, and overall survival following high-intensity therapy. The mortality rate within the first 2 months after transplantation is highest among patients with a poor performance status. A low B2M level ($\leq$ 3.0 mg/L) was the single most favorable parameter of achieving complete remission as well as extended relapse-free and overall survival. A low lactate dehydrogenase level ($\leq$ 250 U/L) was an additional independent feature associated with longer durations of relapse-free and overall survival.[129]

Interferon alpha: a biologic modifier

Data suggest that interferon alpha is useful in managing multiple myeloma. However, in view of recent data suggesting that interferon alpha can stimulate the growth of IL-6-dependent myeloma cell lines and that interferon alpha-dependent myeloma cells can be obtained, caution should be exercised before generalising interferon alpha treatment for patients with multiple myeloma. Conceivably, injection of interferon alpha early in a relapse might allow the rapid emergence of autocrine IL-6-producing myeloma subpopulations and thus aggravate the disease.[130–133]

Interleukin-2: preliminary data promising

Preliminary data with IL-2 after transplantation in chronic myelocytic leukemia appear promising.[134] IL-2 administration might further enhance the known increased natural killer cell population in the bone marrow of myeloma patients after bone marrow transplantation.[135] This agent might also have a role in maintenance therapy.

FUTURE TRENDS

There has been substantial advancement in our understanding of multiple myeloma and related plasma cell neoplasms over the past two decades. We can reasonably hope that improvements in treatment will follow our increased knowledge of this fascinating malignant neoplasm.

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