Introduction

This disease site includes the following three malignancies: multiple myeloma, amyloidosis, and waldenstrom's macroglobulinemia. See pages 4 and 5 for descriptions of the latter two diseases.

Disease Information - Multiple Myeloma

Physiology

Multiple myeloma is a neoplastic disorder of the plasma cells, which are located in the bone marrow and circulate also to the spleen and lymph nodes. Plasma cells secrete antibody-immunoglobulins; these immunoglobulins are proteins associated with the body's immune mechanism. There are five types of immunoglobulins in human serum: IgG, IgA, IgD, IgM, and IgE. Each plasma cell and its daughter cells (a clone) produces a unique immunoglobulin. In myeloma, a single-cell clone becomes malignant and outgrows the other normal clones, producing large amounts of its unique immunoglobulin and also inhibiting the other clones from producing their immunoglobulins. The large amount of highly specific and homogeneous immunoglobulin secreted by the malignant cell is called the M protein (also called the myeloma protein, para-protein, or protein spike), referring to its malignant, or monoclonal, characteristics. The M protein is diagnostic of the disease and can usually be measured in the blood or urine.

Symptoms

Presenting symptoms may include bone pain due to osteolytic lesions, resulting from abnormal plasma cells proliferating and accumulating in the bone marrow; weakness; and fatigue. On laboratory exam there may also be signs of anemia, hypercalcemia and hyperuricemia, and elevated serum and/or urine protein level. The protein excreted in the urine is called the Bence-Jones protein, a protein not found in normal urine. The Bence-Jones protein is a fragment of the immunoglobulin molecule called the light chain that the malignant plasma cell produces. Excretion of excess protein by the kidneys may result in renal problems causing the BUN and creatinine to rise.

Prognostic Factors and Treatment

Prognostic factors in myeloma include age, ISS stage (based on serum β2-microglobulin and serum albumin), and chromosome abnormalities, with younger patients, lower stage, or patients without chromosome abnormalities surviving longer than those with, older age, high stage or cytogenetic abnormalities. Treatment options for newly diagnosed myeloma include combination chemotherapy regimens and high-dose chemotherapy with stem cell transplant. Radiation therapy may also be given for palliation and healing of bone lesions. There is no standard treatment for relapsed or refractory disease; patients frequently are treated with Phase II agents.
Diagnosis

Diagnosis is based on major and/or minor criteria as illustrated below.

Criteria for Diagnosis of Multiple Myeloma

Major Criteria

I. Plasmacytomas on tissue biopsy.
II. Bone marrow plasmacytosis with > 30% plasma cells.
III. Monoclonal globulin spike on serum electrophoresis exceeding 3.5 gm% for G peaks or 2.0 gms for A peaks. Greater than or equal to 1.0 g/24 hours of kappa or lambda light chain excretion on urine electrophoresis in the absence of amyloidosis.

Minor Criteria

a. Bone marrow plasmacytosis 10-30%.
b. Monoclonal globulin spike present, but less than the levels defined above.
c. Lytic bone lesions.
d. Normal IgM less than 50 mg%, IgA less than 100 mg%, or IgG less than 600 mg%.

Diagnosis will be confirmed when any of the following features are documented in symptomatic patients with clearly progressive disease. The diagnosis of myeloma requires a minimum of 1 MAJOR + 1 MINOR CRITERION or 3 MINOR CRITERIA which include a+b, i.e.:

1. I+b, I+c, I+d (I+a not sufficient).
2. II+b, II+c, II+d.
3. III+a, III+c, III+d.
4. a+b+c, a+b+d.

The presence of certain non-specific disease features will support the diagnosis, particularly if of recent onset.

1. Anemia.
2. Hypercalcemia.
3. Azotemia.
4. Demineralization and compression fractures.
5. Hypoalbuminemia.

Criteria for Monoclonal Gammopathy of Undetermined Significance (MGUS), Indolent Myeloma, and Smoldering Myeloma (Stage I or IIA)

MGUS

I. Monoclonal gammopathy.
II. M-component level.
   IgG ≤ 3.5 G%.
   IgA ≤ 2.0 G%.
   BJ ≤ 1.0 G/24 hours.
III. Bone marrow plasma cells < 10%.
IV. No bone lesions.
V. No symptoms.
**Indolent Myeloma**
Criteria as for myeloma (please refer to Criteria for Diagnosis of Multiple Myeloma on Page 2) except (all of the following):

I. No or only limited bone lesions (≤ 3 lytic lesions); no compression fractures.
II. M-component levels.
   - IgG < 7 gm%.
   - IgA < 5 gm%.
III. No symptoms or associated disease features, i.e.:
    - Performance status > 50%.
    - Hemoglobin > 10 gm%.
    - Serum calcium normal.
    - Serum creatinine < 2.0 mg%.
    - No infections.

**Smoldering Myeloma**
Criteria as for indolent myeloma except:

I. No bone lesions.
II. Bone marrow plasma cells ≤ 30%.

**Staging**
Staging of myeloma is based on serum β2 microglobulin and serum albumin and is divided into three stages. See Greipp PR, Miguel JS, et al. International Staging System for Multiple Myeloma, Journal of Clinical Oncology 23(15):3412-3420.

Stage I: Serum β2 microglobulin <3.5 mg/L AND serum albumin ≥ 3.5 g/dL
Stage II: Serum β2 microglobulin <3.5 mg/L AND serum albumin <3.5 g/dL OR serum β2 microglobulin 3.5-5.5 mg/L
Stage III: Serum β2 microglobulin ≥ 5.5 mg/L
Disease Information - Amyloidosis (AL)

Physiology
AL amyloidosis is an uncommon plasma cell dyscrasia characterized by deposition of amyloid fibrils derived from immunoglobulin light chains, known as AL (amyloid light chain) proteins. The amyloid fibril is a congophilic beta pleated protein distributed extracellularly, most often appearing as accumulations proximal to the basement membrane. They have a predilection for tissues of mesodermal origin. The organs most often involved include the heart, kidneys, nervous system, and gastrointestinal tract. The precise mechanism of immunoglobulin deposition and resultant organ damage is undetermined. However, amyloigenic properties of the light chains as well as tissue specific factors likely determine the extent of organ deposition and damage.

Signs and Symptoms
The signs and symptoms depend on which tissue have deposits of amyloid protein. The most common features are shortness of breath, fatigue, edema (swelling of ankles and legs), dizziness upon standing, a feeling of fullness in the stomach, diarrhea, weight loss, enlarged tongue, numbness of the legs and arms, and protein in the urine.

Diagnosis
Diagnosis depends on the demonstration of amyloid deposits in a tissue biopsy. The tissue can usually be obtained by using a fine needle. If the organ is inaccessible, for example the heart, diagnosis can often be made by simply taking a small sample from the pad of fat on the abdomen or from within the rectum.

Treatment
Drug treatment is aimed at reducing the level of amyloid protein and thus the symptoms. It is not a cure and will not eliminate the underlying disease. The main drugs used in treatment of amyloidosis are melphalan and prednisone. Response rates are 20-25%, and the median time to response is 12 months. Patients with severe heart or kidney disease, whose amyloidosis has been brought under control, may require a transplant.

Prognosis
The median survival of all patients is short, ranging from 12-22 months (5-year survival 19%). A major prognostic determinant is the clinical syndrome at presentation, with heart failure associated with the worst diagnosis. Elevated beta 2 microglobulin and plasma cell labeling index have also been linked to a poor prognosis. In a multivariate analysis, the presence of CHF, hepatomegaly, urinary light chains, and associated myeloma were associated with a poor survival for the first year, while orthostatic hypotension, elevated creatinine, and serum M protein predicted poor survival beyond one year.
Disease Information - Waldenstrom's Macroglobulinemia (WM)

**Physiology**
Recent studies suggest that WM bears close resemblance to small cell lymphocytic lymphoma or diffuse well-differentiated lymphocytic lymphoma (DWDL) and chronic lymphocytic leukemia (CLL), in that patients present with similar histology in lymph nodes and bone marrow as well as visceral organs such as liver and spleen. Transitional forms exist where DWDL or CLL are associated with low level IgM monoclonal gammopathy.

**Symptoms**
With increasing serum viscosity, a condition of hypervolemia develops, accounting in part for a dilutional anemia and may contribute to the development of increased vascular resistance and congestive heart failure. Fatigue, dizziness, and visual inacuity may also develop. Hemostatic abnormalities increase with increasing levels of IgM and viscosity. Symptoms develop related to anemia, hemorrhagic diathesis, organomegaly, or hyperviscosity. Bone marrow failure, infection, hemorrhage, thromboembolism, and cardiac insufficiency are common terminal events.

**Diagnosis**
Diagnostic criteria of WM include demonstration of IgM monoclonal gammopathy with monoclonal light chain components in serum and/or urine, presence of monoclonal lymphocytic infiltration in bone marrow, lymph nodes, spleen and/or liver.

**Staging**
Staging criteria are under development.

**Prognostic Factors and Treatment**
Median survival in symptomatic patients is around five years. Prognostic factors for overall survival include: age, serum β2 microglobulin, IgM level, albumin, and hemoglobin. Prognostic models are currently being developed, with β2-M, IgM, and hemoglobin the important prognostic factors in multivariate models.

The mainstay of therapy in WM has been low-dose chlorambucil, other alkylating agents, and glucocorticoids. Purine analogs, such as Fludarabine phosphate and 2-CDA have shown remarkable activity in low-grade lymphoproliferative disorders and are currently under evaluation in WM in a SWOG protocol (S9003).