Monoclonal Gammopathy of Undetermined Significance, Waldenström Macroglobulinemia, AL Amyloidosis, and Related Plasma Cell Disorders: Diagnosis and Treatment

S. Vincent Rajkumar, MD; Angela Dispenzieri, MD; and Robert A. Kyle, MD

The spectrum of plasma cell disorders is broad. Monoclonal gammopathy of undetermined significance and smoldering multiple myeloma are asymptomatic disorders characterized by monoclonal plasma cell proliferation in the bone marrow in the absence of end-organ damage. Waldenström macroglobulinemia typically involves an ontogenically less mature lymphoplasmacytic bone marrow cell and is characterized by secretion of a monoclonal IgM protein. Solitary plasmacytoma is the only known potentially curable plasma cell disorder. Finally, AL (immunoglobulin light chain) amyloidosis and POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome are disorders characterized by low tumor burden but profound multisystemic disease. Updated diagnostic criteria for these disorders, risk stratification models to determine prognosis, and the current management of these diverse entities are discussed in this review.


The diagnosis and management of multiple myeloma were reviewed earlier in this Symposium on Oncology Practice: Hematological Malignancies.1 This review focuses on the current diagnosis and management of other related clonal plasma cell disorders (Table 1). This list is diverse and includes the relatively common pre-malignant condition monoclonal gammopathy of undetermined significance (MGUS), as well as uncommon disorders such as POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome.

MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

MGUS is an asymptomatic premalignant disorder characterized by limited monoclonal plasma cell proliferation in the bone marrow and absence of end-organ damage.10,12 It is the most common plasma cell dyscrasia, prevalent in approximately 3% of the general population aged 50 years and older.13 The prevalence increases with age: 1.7% in those 50 to 59 years of age and more than 5% in those older than 70 years. Within each age group, prevalence rates are higher in men than in women. The age-adjusted prevalence of MGUS is 3-fold higher in African Americans compared with white persons.14

MGUS is associated with a lifelong risk of progression to multiple myeloma or related disorders. The rate of progression of MGUS to multiple myeloma or related malignancy is 1% per year (Figure 1).4,15 However, the true lifetime probability of progression is substantially lower when competing causes of death are taken into account, approximately 11% at 25 years (Figure 1).16 The risk of progression with MGUS does not diminish with time, making lifelong follow-up necessary in all persons.3,17 In fact, the risk of progression remains constant regardless of duration of known MGUS, strongly suggestive of a random 2-hit model of malignant progression, rather than a cumulative damage model in which case the risk of progression will be expected to rise with the duration of the abnormality.12

MGUS is characterized by evidence of genomic instability on molecular genetic testing: primary chromosomal translocations at the immunoglobulin heavy chain locus 14q32 (50%), hyperdiploidy (40%), or other or unknown (10%).12,18-23 Interleukin 6 is a major growth factor for plasma cells,24 and CD126 (interleukin 6 receptor α-chain) is overexpressed in MGUS compared with normal plasma cells.25,26 A significantly higher proportion of plasma cells express CD45 in the MGUS stage compared with multiple myeloma.27 Recent advances in the pathogenesis and progression of MGUS have been reviewed earlier in this series.1

From the Division of Hematology, Mayo Clinic College of Medicine, Rochester, Minn.

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Address correspondence to S. Vincent Rajkumar, MD, Division of Hematology, Mayo Clinic College of Medicine, 200 First St SW, Rochester, MN 55905 (e-mail: rajkumar.v Vincent@mayo.edu). Individual reprints of this article and a bound booklet of the entire Symposium on Oncology Practice: Hematological Malignancies will be available for purchase from our Web site www.mayoclinicproceedings.com.

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### Table 1. Mayo Clinic Diagnostic Criteria for Selected Clonal Plasma Cell Disorders*

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Disease definition</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGUS</td>
<td>Serum monoclonal protein level &lt;3 g/dL, bone marrow plasma cells &lt;10%, and absence of end-organ damage, such as lytic bone lesions, anemia, hypercalcemia, or renal failure, that can be attributed to a plasma cell proliferative disorder.</td>
<td>2, 3</td>
</tr>
<tr>
<td>SMM (also referred to as asymptomatic multiple myeloma)</td>
<td>Serum monoclonal protein (IgG or IgA) level ≥3 g/dL, and/or bone marrow plasma cells ≥10%, absence of end-organ damage, such as lytic bone lesions, anemia, hypercalcemia, or renal failure, that can be attributed to a plasma cell proliferative disorder.</td>
<td>2, 3</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>Bone marrow plasma cells ≥10%, presence of serum and/or urinary monoclonal protein (except in patients with true nonsecretory multiple myeloma), plus evidence of lytic bone lesions, anemia, hypercalcemia, or renal failure that can be attributed to the underlying plasma cell proliferative disorder.</td>
<td>1-3</td>
</tr>
<tr>
<td>Waldenström macroglobulinemia</td>
<td>IgM monoclonal gammopathy (regardless of the size of the M protein) with &gt;10% bone marrow lymphoplasmacytic infiltration (usually intertrabecular) by small lymphocytes that exhibit plasmacytoid or plasma cell differentiation and a typical immunophenotype (eg, surface IgM, CD5⁺, CD10⁺, CD19⁺, CD20⁺, CD23⁺) that satisfactorily excludes other lymphoproliferative disorders, including chronic lymphocytic leukemia and mantle cell lymphoma. Note: IgM MGUS is defined as serum IgM monoclonal protein level ≥3 g/dL, bone marrow lymphoplasmacytic infiltration &lt;10%, and no evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly. Smoldering Waldenström macroglobulinemia (also referred to as indolent or asymptomatic Waldenström macroglobulinemia) is defined as serum IgM monoclonal protein level ≥3 g/dL and/or bone marrow lymphoplasmacytic infiltration ≥10% and no evidence of end-organ damage, such as anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly, that can be attributed to a plasma cell proliferative disorder.</td>
<td>4-8</td>
</tr>
<tr>
<td>Solitary plasmacytoma</td>
<td>Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells, normal bone marrow with no evidence of clonal plasma cells, normal skeletal survey and MRI of spine and pelvis, and absence of end-organ damage, such as anemia, hypercalcemia, renal failure or additional lytic bone lesions, that can be attributed to a plasma cell proliferative disorder.</td>
<td>2, 9</td>
</tr>
<tr>
<td>Systemic AL amyloidosis</td>
<td>Presence of an amyloid-related systemic syndrome (such as renal, liver, heart, gastrointestinal tract, or peripheral nerve involvement) with positive amyloid staining by Congo red in any tissue (eg, fat aspirate, bone marrow, or organ biopsy), plus evidence that amyloid is light chain related established by direct examination of the amyloid (immunoperoxidase staining, direct sequencing, etc), plus evidence of a monoclonal plasma cell proliferative disorder (serum or urine M protein, abnormal free light chain ratio, or clonal plasma cells in the bone marrow) Note: Approximately 2%-3% of patients with AL amyloidosis will not meet the requirement for evidence of a monoclonal plasma cell disorder; the diagnosis of AL amyloidosis must be made with caution in these patients.</td>
<td>10</td>
</tr>
<tr>
<td>POEMS syndrome</td>
<td>Presence of a monoclonal plasma cell disorder, peripheral neuropathy, and at least 1 of the following 7 features: osteosclerotic myeloma, Castlemam disease, organomegaly, endocrinopathy (excluding diabetes mellitus or hypothyroidism), edema, typical skin changes, and papilledema. Note: Not every patient who meets these criteria will have POEMS syndrome; the features should have a temporal relationship to each other and no other attributable cause. The absence of either osteosclerotic myeloma or Castlemam disease should make the diagnosis suspect. Elevations in plasma or serum levels of vascular endothelial growth factor and thrombocytosis are common features of the syndrome and are helpful when the diagnosis is difficult.</td>
<td>11</td>
</tr>
</tbody>
</table>

*MGUS = monoclonal gammopathy of undetermined significance; MRI = magnetic resonance imaging; SMM = smoldering multiple myeloma.

### Diagnosis

The diagnostic criteria for MGUS are listed in Table 1.³ MGUS is differentiated from multiple myeloma and related disorders based on the presence or absence of end-organ damage that can be attributed to the plasma cell disorder. The differentiation of MGUS from multiple myeloma or other related disorders can be difficult at the time of initial presentation because MGUS is relatively common in the general population older than 50 years, and a number of clinical and laboratory abnormalities may be coincidental. The typical laboratory investigations necessary to differentiate MGUS from other related plasma cell disorders are a complete blood cell count, serum creatinine measurement, serum calcium measurement, and a complete radiographic bone survey. If abnormalities are detected on these tests, additional tests to determine the cause of these abnormalities are required; only patients in whom abnormalities are believed to be related to the plasma cell proliferative disorder can be considered to have myeloma or related malignancy. A bone marrow aspirate and biopsy are indicated when the M protein level is greater than or equal to 1.5 g/dL and when abnormalities are noted in the complete blood cell count, serum creatinine level, serum calcium level, or radiographic bone survey. Bone marrow aspirate and biopsy should also be considered in patients with non-IgG MGUS, patients with an abnormal serum free light chain (FLC) ratio, and any other patient with presumed MGUS in whom there is doubt about the diagnosis.
**ATYPICAL PLASMA CELL DISORDERS**

**PROGNOSIS**

In a large population-based study of MGUS that involved 1384 patients, only the size and type of M protein (IgM and IgA subtypes) were predictive of progression to myeloma or related malignancy.\(^4\) In another study, a bone marrow plasma cell percentage of 6% to 9% carried twice the risk of progression compared with marrow involvement of 5% or lower.\(^28\) The presence of circulating plasma cells detected using a sensitive slide-based immunofluorescent assay is also a risk factor for progression,\(^29\) but the test is not widely available in clinical practice.

An abnormal serum FLC ratio using the serum FLC assay is an important risk factor for progression of MGUS. In a study of 1148 patients, the risk of progression with an abnormal FLC ratio at the time of diagnosis of MGUS was significantly higher compared with a normal ratio (hazard ratio, 3.5; 95% confidence interval, 2.3-5.5; \(P<.001\)) and was independent of the size and type of the serum M protein.\(^16\) The risk of progression to myeloma or related malignancy at 10 years was 17% with an abnormal ratio compared with 5% with a normal ratio.

A risk stratification system can be used to predict the risk of progression of MGUS based on 3 factors: size of the serum M protein, the type of immunoglobulin, and the serum FLC ratio (Table 2).\(^16\) Patients with 3 adverse risk factors, namely, an abnormal serum FLC ratio, non-IgG MGUS, and a high serum M protein level (\(\geq 15\) g/L), had a risk of progression at 20 years of 58% (high-risk MGUS) compared with 37% in patients with any 2 of these risk factors present (high- to intermediate-risk MGUS), 21% with 1 risk factor present (low- to intermediate-risk MGUS), and 5% when none of the risk factors were present (low-risk MGUS). In fact, the low-risk MGUS subset (constituting almost 40% of the cohort) had a lifetime risk of only 2% when competing causes of death were taken into account.

**TREATMENT**

The current standard of care for MGUS is observation alone, without therapy.\(^30,31\) Patients with MGUS may benefit from risk stratification to guide follow-up. Patients with low-risk MGUS can be reassessed in 6 months and then once every 2 years or only at the time of symptoms for evidence of progression.\(^16\) All other subsets of patients need to be reassessed in 6 months and then yearly thereafter.

**SMOLDERING MULTIPLE MYELOMA**

Smoldering multiple myeloma (SMM) accounts for approximately 15% of all cases with newly diagnosed multiple myeloma.\(^9,10\) The prevalence estimates for SMM are unreliable since some studies include asymptomatic patients with small lytic bone lesions on skeletal survey and/or abnormalities on magnetic resonance imaging (MRI).

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**TABLE 2. Risk Stratification Model to Predict Progression of Monoclonal Gammopathy of Undetermined Significance to Myeloma or Related Disorders**

<table>
<thead>
<tr>
<th>Risk group</th>
<th>No. of patients</th>
<th>Relative risk</th>
<th>Absolute risk of progression at 20 y (%)</th>
<th>Absolute risk of progression at 20 y accounting for death as a competing risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk (serum M protein level &lt;1.5 g/dL, IgG subtype, normal free light chain ratio [0.26-1.65])</td>
<td>449</td>
<td>1.0</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Low to intermediate risk (any 1 factor abnormal)</td>
<td>420</td>
<td>5.4</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>High to intermediate risk (any 2 factors abnormal)</td>
<td>226</td>
<td>10.1</td>
<td>37</td>
<td>18</td>
</tr>
<tr>
<td>High risk (all 3 factors abnormal)</td>
<td>53</td>
<td>20.8</td>
<td>58</td>
<td>27</td>
</tr>
</tbody>
</table>

Similar to MGUS, SMM is an asymptomatic condition. However, the risk of progression to myeloma or related malignancy is much higher in SMM compared with MGUS: 1% per year vs 10% to 20% per year, respectively.\textsuperscript{4,15,32,33} This difference in the risk of progression means that patients with SMM and MGUS should be managed differently in terms of frequency of follow-up, development of chemopreventive strategies, and enrollment into clinical trials. Similar to patients with MGUS and active myeloma, almost all patients with SMM appear to have evidence of genomic instability manifested as IgH translocations or hyperdiploidy on molecular genetic testing.\textsuperscript{34}

Most patients with SMM eventually experience progression to symptomatic disease\textsuperscript{6}; however, some patients can remain free of progression for a number of years.\textsuperscript{35} The time to progression (TTP) to symptomatic disease is approximately 3 to 4 years but differs greatly depending on the definition used for SMM.\textsuperscript{35} In the subset of SMM patients with 10% or more bone marrow plasma cells, the median TTP is approximately 2 to 3 years.\textsuperscript{36} Preliminary data from a large study by Kyle et al\textsuperscript{37} using the current criteria for SMM estimate the risk of progression at approximately 10% per year for the first 5 years, a rate much higher than that observed with MGUS.

**Diagnosis**

Smoldering multiple myeloma is asymptomatic. The diagnosis requires the presence of a serum IgG or IgA M protein level of 3 g/dL or higher and/or 10% or more bone marrow plasma cells, plus absence of anemia, hypercalcemia, lytic bone lesions, or renal failure that can be attributed to the plasma cell proliferative disorder (Table 1).\textsuperscript{1,3} Testing to differentiate SMM from multiple myeloma is the same as that described for MGUS.

**Prognosis**

Similar to results in MGUS, abnormal peripheral blood monoclonal plasma cell studies, defined as an increase in the number or proliferative rate of circulating plasma cells by slide-based immunofluorescent assays, have been shown to indicate a higher risk of progression in SMM.\textsuperscript{36} However, this test is not widely available in clinical practice. Weber et al\textsuperscript{32} have shown that, similar to MGUS, the size and type of immunoglobulin are important predictors of progression in SMM (Table 3).

The presence of occult bone lesions on MRI increases the risk of progression in patients otherwise defined as having SMM.\textsuperscript{7} In a recent study, Wang et al\textsuperscript{33} estimated the risk of progression in 72 patients with SMM in whom an MRI of the spine was also performed. The median TTP was significantly shorter with an abnormal MRI result compared with a normal MRI result (1.5 years vs 5 years, respectively).

**Treatment**

The standard of care is observation alone until evidence of progression to myeloma.\textsuperscript{30} Patients with SMM need more frequent follow-up than those with MGUS (at least every 3 to 4 months).\textsuperscript{12} Two small randomized trials have shown no benefit with early therapy compared with therapy at the time of symptomatic progression.\textsuperscript{38,39} Preliminary data indicate that thalidomide may delay TTP,\textsuperscript{40,41} but data are needed from randomized trials before such therapy can be recommended, particularly given the adverse effects associated with the drug. With the increasing availability of novel targeted therapies for myeloma,\textsuperscript{42-44} clinical trials are ongoing to determine whether the early use of new agents or bisphosphonates can delay progression in SMM.

**WALDENSTRÖM MACROGLOBULINEMIA**

Waldenström macroglobulinemia is a clonal IgM monoclonal protein–secreting lymphoid and plasma cell disorder, which currently also includes the entity referred to previously as lymphoplasmacytic lymphoma. The median age at diagnosis is approximately 65 years, with a slight male predisposition. The typical symptoms at presentation are weakness and fatigue due to anemia. Other clinical manifestations may include constitutional symptoms (fever, night sweats, and weight loss), hepatosplenomegaly, lymphadenopathy, hyperviscosity, cryoglobulinemia, and sensorimotor peripheral neuropathy.\textsuperscript{15} Unlike multiple myeloma, primary IgH translocations are not seen in Waldenström macroglobulinemia.\textsuperscript{46}

**Diagnosis**

The diagnostic criteria for Waldenström macroglobulinemia are listed in Table 1. The Second International Consensus Panel did not assign a specific level of bone marrow infiltration that would be required to differentiate IgM MGUS from Waldenström macroglobulinemia.\textsuperscript{3} The diag-

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### TABLE 3. Risk Stratification Model to Predict Progression of Smoldering Multiple Myeloma\textsuperscript{32}

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Approximate percentage of patients in category</th>
<th>Median time to progression (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (serum M protein ≤ 3 g/dL and IgG type)</td>
<td>45</td>
<td>&gt;48</td>
</tr>
<tr>
<td>Intermediate (serum M protein &gt;3 g/dL or IgA type)</td>
<td>45</td>
<td>24</td>
</tr>
<tr>
<td>High (serum M protein &gt;3 g/dL and IgA type)</td>
<td>10</td>
<td>9</td>
</tr>
</tbody>
</table>
nostic criteria given in Table 1 have been updated in an evidence-based manner such that the diagnosis of Waldenström macroglobulinemia requires 10% or greater lymphoplasmacytic infiltration.54-56 Presence of less than 10% lymphoplasmacytic infiltration in the absence of end-organ damage represents IgM MGUS and not Waldenström macroglobulinemia; such patients have a risk of progression to symptomatic disease at a rate of only 1.5% per year.57 In fact, patients with IgM MGUS and smoldering Waldenström macroglobulinemia, as defined using the criteria in Table 1, have an overall survival rate similar to (perhaps even better than in the case of IgM MGUS) the general population and should not be considered to have malignant disease.7

Historically, patients with an IgM M protein level less than 3 g/dL, who met the criteria for Waldenström macroglobulinemia have been classified as having “lymphoplasmacytic lymphoma with an IgM M protein.” However, except for hyperviscosity, the clinical picture, therapy, and prognosis in these patients are no different than in those patients classified as having Waldenström macroglobulinemia who have an IgM M protein level of 3 g/dL or higher.58 By the current definition, patients are considered to have Waldenström macroglobulinemia regardless of the size of the serum M protein.

PROGNOSIS
The median survival is approximately 5 years.45 Adverse prognostic factors include age older than 70 years, hemoglobin level less than 9 g/dL, weight loss, and cryoglobulinemia.48 Morel et al49 have constructed a risk stratification model based on a set of 3 adverse prognostic factors: age 65 years or older, albumin level less than 4.0 g/dL, and cytopenias (Table 4).

TREATMENT
As with SMM, patients who meet the diagnostic criteria for Waldenström macroglobulinemia who are asymptomatic may also be considered to have smoldering Waldenström macroglobulinemia and have no need of immediate therapy. The indications for therapy are anemia (hemoglobin level <10 g/dL) or thrombocytopenia (platelet count <100 × 10^9/L) believed to be related to Waldenström macroglobulinemia; constitutional symptoms such as weakness, fatigue, night sweats, or weight loss; hyperviscosity; symptomatic cryoglobulinemia; and significant hepatosplenomegaly or lymphadenopathy.45,50,51

INITIAL THERAPY
There are 4 options for initial therapy: rituximab, purine nucleoside analogues, alkylators, and combination chemotherapy. Unfortunately, no randomized data exist to deter-

TABLE 4. Risk Stratification Model to Predict Survival in Patients With Waldenström Macroglobulinemia49

<table>
<thead>
<tr>
<th>Risk group*</th>
<th>5-year survival rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (0-1 risk factors)</td>
<td>87</td>
</tr>
<tr>
<td>Intermediate (2 risk factors)</td>
<td>62</td>
</tr>
<tr>
<td>High (3-4 risk factors)</td>
<td>25</td>
</tr>
</tbody>
</table>

*Risk factors: age ≥65 years, albumin <4.0 g/dL, and cytopenias; cytopenia restricted to 1 hematopoietic lineage was scored as 1 risk factor, whereas ≥2 cytopenias were scored as 2 risk factors.

mine the best option; therapy is typically decided based on the age of the patient and the aggressiveness of the presentation. Patients should preferably be treated in clinical trials as much as possible.

Single-agent therapy with rituximab, a chimeric anti-CD20 monoclonal antibody, produces a response in approximately 50% of untreated patients.52,53 Response to rituximab may be affected by polymorphisms in the Fc-γ RIIIA (CD16) receptor gene.54 Responses to rituximab can be delayed and may occur months after initial therapy. An initial increase in IgM levels (flare) has been reported.55 The usual dose is 375 mg/m² administered intravenously weekly for 4 weeks,53 with consideration given to further doses or maintenance, depending on response.

Purine nucleoside analogues, fludarabine or cladribine, are also effective as initial therapy.56-61 Reported response rates vary widely from 40% to 90% and likely reflect patient selection and the stringency and timing of the response assessment. Both agents are likely equally effective; randomized comparisons have not been conducted. We prefer a cladribine dosage of 5 mg/m² intravenously over 2 hours for 5 days, repeated once after 28 days if needed. The need for further cycles is determined by the extent of response to the first 2 cycles and observed toxic effects.

Alkylators such as chlorambucil are an option, especially for elderly patients, as initial therapy. Chlorambucil is administered orally at a dosage of 6 to 8 mg/d with dose adjustments based on blood cell counts. Patients are treated until the disease has reached a plateau state; treatment can then be discontinued and patients observed closely.

Preliminary results of several combination chemotherapeutic approaches have been reported, with response rates of more than 75%.50 Examples of active combinations include fludarabine plus rituximab, fludarabine plus cyclophosphamide, cladribine plus cyclophosphamide plus rituximab, and R-CHOP (rituximab, cyclophosphamide, hydroxydaunomycin (doxorubicin), vincristine (Oncovin), prednisone).51,62 Our preferred approach outside a clinical
ATYPICAL PLASMA CELL DISORDERS

The trial setting is to use single-agent therapy in most patients, reserving combination therapy for aggressive disease.

**Relapsed Disease and Supportive Care**

The options for initial therapy can be tried at the time of relapse. In fact, the same initial therapy can be tried again at relapse if there was an adequate interval between cessation of therapy and relapse. A response rate of 25% has been reported with single-agent thalidomide. Other options for relapsed, refractory disease include stem cell transplantation, interferon alfa, and bortezomib. Novel agents are also being investigated. A small subset of chemotherapy-resistant patients may respond to splenectomy. Patients with refractory anemia or anemia during chemotherapy will benefit from erythropoietin and/or red blood cell transfusions. Plasmapheresis is indicated for the treatment of hyperviscosity syndrome. Plasmapheresis may need to be continued intermittently until a therapeutic response is achieved with one of the treatment options discussed herein.

**Systemic AL (Immunoglobulin Light Chain) Amyloidosis**

Amyloid is a fibrillar proteinaceous material that can be deposited in various tissues and detected with Congo red staining based on a characteristic apple-green birefringence under polarized light. It consists of rigid, linear, non-branching fibrils, 7.5 to 10 nm in width, aggregated in a β-pleated sheet conformation. Several distinct types of amyloidosis have been classified based on the protein composition of the amyloid material (Table 5).

<table>
<thead>
<tr>
<th>Type of amyloidosis</th>
<th>Precursor protein component</th>
<th>Clinical presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL amyloidosis*</td>
<td>κ or λ immunoglobulin light chain</td>
<td>Primary or localized; see text for syndromes</td>
</tr>
<tr>
<td>AA amyloidosis</td>
<td>Serum amyloid A protein</td>
<td>Associated with chronic inflammatory conditions; typically acquired, but hereditary in case of familial Mediterranean fever; renal presentation most common</td>
</tr>
<tr>
<td>ATTR amyloidosis</td>
<td>Mutated transthyretin</td>
<td>Hereditary; peripheral neuropathy and/or cardiomyopathy</td>
</tr>
<tr>
<td></td>
<td>Normal transthyretin</td>
<td>Restrictive cardiomyopathy; carpal tunnel syndrome</td>
</tr>
<tr>
<td>β₂-microglobulin</td>
<td>β₂-microglobulin</td>
<td>Carpal tunnel syndrome</td>
</tr>
<tr>
<td>Aβ amyloidosis</td>
<td>Aβ protein precursor</td>
<td>Alzheimer syndrome</td>
</tr>
<tr>
<td>Other hereditary amyloidosis</td>
<td>Fibrinogen α-chain</td>
<td>Renal presentation</td>
</tr>
<tr>
<td>Lysozyme</td>
<td>Lysozyme</td>
<td>Renal presentation most common</td>
</tr>
<tr>
<td>Apolipoprotein A-I</td>
<td>Apolipoprotein A-I</td>
<td>Renal presentation most common</td>
</tr>
</tbody>
</table>

*A AL amyloidosis is the only form of amyloidosis that is secondary to a clonal plasma cell disorder. AL amyloidosis can be associated with multiple myeloma in approximately 10% of patients.

†TTR refers to transthyretin, which is commonly referred to as prealbumin.

**Table 5. Classification of Amyloidosis**

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<th>Type of amyloidosis</th>
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</tr>
<tr>
<td>β₂-microglobulin</td>
<td>β₂-microglobulin</td>
<td>Carpal tunnel syndrome</td>
</tr>
<tr>
<td>Aβ amyloidosis</td>
<td>Aβ protein precursor</td>
<td>Alzheimer syndrome</td>
</tr>
<tr>
<td>Other hereditary amyloidosis</td>
<td>Fibrinogen α-chain</td>
<td>Renal presentation</td>
</tr>
<tr>
<td>Lysozyme</td>
<td>Lysozyme</td>
<td>Renal presentation most common</td>
</tr>
<tr>
<td>Apolipoprotein A-I</td>
<td>Apolipoprotein A-I</td>
<td>Renal presentation most common</td>
</tr>
</tbody>
</table>

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†TTR refers to transthyretin, which is commonly referred to as prealbumin.

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Systemic AL amyloidosis should be differentiated from localized amyloidosis, which can be derived from immunoglobulin light chains in many patients (localized AL amyloidosis). Localized amyloidosis is typically benign and can manifest as isolated carpal tunnel syndrome; isolated lesions in the ureter, urethra, bladder, lung, bronchus, or trachea; or nonpurpuric cutaneous lesions. Localized amyloidosis, regardless of whether the source of the amyloid is immunoglobulin light chain or some other protein, is treated primarily for symptom relief as needed and should not be treated with systemic therapy.

The median age at diagnosis of systemic AL amyloidosis is 65 years. The clinical manifestations vary greatly and depend on the dominant organ involved. Nephrotic syndrome, restrictive cardiomyopathy, and peripheral or autonomic neuropathy are common presenting syndromes. Patients may also have associated macroglossia, carpal tunnel syndrome, and purpura that involve the neck, face, and eyes. Immunofixation reveals an M protein in the serum or urine in approximately 90% of patients at diagnosis. The FLC ratio is abnormal in most of the patients with a negative immunofixation. Regardless of the number of plasma cells in the bone marrow, the syndrome is referred to as AL or primary as long as the amyloid fibrils are composed of immunoglobulin light chain. Systemic AL amyloidosis and symptomatic multiple myeloma can coexist in the same patient, but usually 1 of the 2 disorders dominates the clinical picture.

**Prognosis**
Survival varies greatly, depending on the dominant organ involved (with cardiac amyloid having the worst outcome) and the number of affected major organs. Patients ineligible for stem cell transplantation have an estimated median survival of 18 months compared with more than 40 months for those eligible for transplantation. Elevated levels of cardiac troponin T carry an adverse prognosis. Median survival for patients with detectable cardiac troponin T (≥1 µg/L) is significantly shorter than for those with undetectable levels (6 vs 22 months, respectively). Elevated serum cardiac troponin I and N-terminal pro–brain natriuretic peptide levels are also valuable prognostic markers. A risk stratification model using the cardiac troponin T and N-terminal pro–brain natriuretic peptide levels is given in Table 6.

**Treatment**
Response to therapy in AL amyloidosis can be difficult to assess. Specific response criteria to assess hematologic and organ responses in primary amyloidosis were recently published. Melphalan and prednisone have been the mainstay of treatment for many years, but results are unsatisfactory. Currently, our approach is to stratify patients based on eligibility for stem cell transplantation. Patients ineligible for stem cell transplantation (poor performance status, major comorbidities, 3 or more organs involved, and advanced cardiac amyloidosis) are offered therapy in clinical trials or treatment with melphalan plus high-dose dexamethasone. Melphalan is administered at a dosage of 0.22 mg/kg per day orally on days 1 through 4 with high-dose dexamethasone, 40 mg/d orally, on the same 4 days. Cycles are repeated every 28 days for approximately 9 months. Using this regimen, a hematologic response was noted in 67% of patients in one trial, with 33% achieving complete hematologic remission. Improvement in organ function is seen in approximately 50% of responding patients.
Prolonged and impressive organ remissions can be achieved with autologous stem cell transplantation in approximately 50% of patients treated with such therapy. However, preliminary results of a French randomized trial suggest that overall survival may not be superior with stem cell transplantation compared with melphalan plus high-dose dexamethasone. This trial randomized 100 patients; median actuarial survival was 57 months with melphalan plus high-dose dexamethasone and 49 months with transplantation (P=.20). However, interpretation of this trial is confounded by the relatively short follow-up (29 months) and the very high treatment-related mortality observed in the transplantation arm (24%). It is wise to consider enrollment in ongoing clinical trials that compare the 2 approaches. At Mayo Clinic, a randomized trial is ongoing that compares autologous stem cell transplantation vs melphalan plus high-dose dexamethasone. For selected candidates, autologous stem cell transplantation is appropriate as initial therapy but is better performed at specialized centers since, unlike with transplantations for myeloma, treatment-related mortality is high (approximately 13%). In patients who proceed to early transplantation, there does not appear to be any need for induction therapy. Excessive fluid accumulation during stem cell mobilization (>2% weight gain) is predictive of a higher mortality rate with stem cell transplantation. The typical conditioning regimen used is high-dose intravenous melphalan (100-200 mg/m²) with the exact dose level based on age, presence or absence of cardiac involvement, number of organs involved, and creatinine clearance. Highly selected patients with end-stage amyloid renal disease and end-stage amyloid cardiomyopathy have been considered for sequential kidney stem cell transplantation and sequential cardiac stem cell transplantation, respectively.

A recent study found that thalidomide plus dexamethasone may be a second-line treatment option for patients with systemic AL amyloidosis, with hematologic responses seen in 48% of 31 enrolled patients, including complete responses in 19% and organ responses in 26%. However, thalidomide is less well tolerated in amyloidosis compared with myeloma, and the regimen is associated with significant adverse effects. Lenalidomide, an analogue of thalidomide with lesser toxicity, may have activity in AL amyloidosis, but further studies are needed. Patients with amyloidosis also require significant supportive care based on the nature of organ involvement, such as treatment of nephrotic syndrome, malabsorption, neuropathy, and heart failure.

**SOLITARY PLASMACYTOMA**

Solitary plasmacytomas may be confined to bone (solitary bone plasmacytoma) or occur in extramedullary sites (extramedullary plasmacytoma). Extramedullary plasmacytoma is localized to the upper respiratory tract (nasal cavity and sinuses, nasopharynx, and larynx) in more than 80% of cases but can also occur in the gastrointestinal tract, central nervous system, urinary bladder, thyroid, breast, testes, parotid gland, or lymph nodes. Patients with solitary plasmacytoma are at risk of progression to multiple myeloma. Increased microvessel density detected in the initial diagnostic tissue specimen has been associated with an increased risk of progression to multiple myeloma, suggesting that the evolution to systemic disease may depend on an angiogenic switch.

**DIAGNOSIS AND PROGNOSIS**

Diagnostic criteria are listed in Table 1. An MRI of the spine and pelvis should be performed in addition to a skeletal survey, since approximately one third of patients may have additional occult lesions that will be missed in the absence of an MRI.

Patients with a baseline serum M protein greater than 1 g/dL have a high risk of persistence of an M protein after radiation therapy to the involved site. Persistence of an M protein 1 year or more after radiation therapy has been associated with an increased probability of progression to multiple myeloma in patients with solitary bone plasmacytoma. The 10-year myeloma-free survival was 29% in patients with a persistent serum or urinary M protein compared with 91% in those in whom the M protein was not detectable after radiation therapy.

**TREATMENT**

Treatment consists of radiation in the range of 40 to 50 Gy to the involved site. Patients who meet criteria for solitary plasmacytoma except for evidence of clonal involvement of the bone marrow can be also treated with radiation therapy to the involved site and then observed until disease progression, similar to MGUS (<10% bone marrow plasma cells) or SMM (≥10% plasma cells).

More than 50% of patients with a solitary bone plasmacytoma are alive at 10 years, and disease-free survival at 10 years ranges from 25% to 50%. Progression to myeloma, when it occurs, usually occurs within 3 years, but patients must be followed up indefinitely. Prognosis may be better in patients with solitary extramedullary plasmacytoma, with 10-year disease-free survival rates of approximately 70% to 80%.

**POEMS SYNDROME**

POEMS syndrome is a rare, atypical plasma cell proliferative disorder. It has been variously referred to in the literature as osteosclerotic myeloma, Crow-Fukase syndrome,
PEP (plasma cell dyscrasia, endocrinopathy, polyneuropathy) syndrome, and Takatsuki syndrome. In almost all cases the immunoglobulin light chain type in POEMS syndrome is \( \lambda \).

**Diagnosis**

The median age at presentation is 51 years. POEMS syndrome is defined by the criteria listed in Table 1.11 Almost all patients with POEMS syndrome have either osteosclerotic lesions or Castleman disease. The major clinical features of POEMS syndrome are a predominantly motor chronic inflammatory demyelinating polyneuropathy, sclerotic bone lesions, and a varying number of associated abnormalities, such as hepatomegaly, hyperpigmentation, hypertrichosis, gynecomastia, testicular atrophy, clubbing, polycythemia, thrombocytosis, and Castleman disease. Patients may have respiratory problems that range from neuromuscular weakness to reduced diffusion capacity of carbon monoxide to pulmonary hypertension. Biopsy of an osteosclerotic lesion may be necessary for the diagnosis. The pathogenesis of the syndrome is unclear but appears to be at least in part cytokine mediated, and elevated vascular endothelial growth factor levels are commonly found.102,103

**Prognosis and Treatment**

POEMS syndrome may have an indolent or a fulminant course. In one study of 99 patients, median survival was 13.8 years.104 If unchecked, the clinical course is characterized by progressive disabling neuropathy, inanition, anasarca, and pulmonary demise. The number of features involved is not predictive of survival, but the presence of fingernail clubbing or extravascular volume overload is predictive.

The clinical features of patients with POEMS syndrome are distinct from those with classic multiple myeloma. In POEMS syndrome, progressive anemia and bone pain are unusual. When renal failure occurs in POEMS syndrome, it is in the context of extravascular overload, and membranoproliferative features and endothelial injury are seen rather than light chain deposition.105,106

Therapy for POEMS syndrome has not been well studied. If the lesions are in a limited area, radiation therapy (40-50 Gy) produces substantial improvement of clinical symptoms and signs in more than 50% of patients. For patients with widespread osteosclerotic lesions, treatment is similar to myeloma and depends on eligibility for stem cell transplantation. In eligible patients, autologous stem cell transplantation has provided significant responses; in one study all 14 evaluable patients achieved improvement or stabilization of neuropathy.107 Supportive care, including aggressive physical and occupational therapy, is an important component of care.

**References**

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The Symposium on Oncology Practice: Hematological Malignancies will continue in the June issue.