

Plasma Cell Disorders



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KEYWORDS

- MGUS • Multiple myeloma • Waldenström macroglobulinemia • Amyloidosis
- POEMS

KEY POINTS

- Monoclonal gammopathy of undetermined significance is a premalignant condition with an incidence of 3% in the general population and a rate of progression to myeloma of 1% per year.
- Myeloma patients can present with anemia, bone lesions, renal dysfunction, and/or hypercalcemia. There are now multiple treatment options for myeloma, which have improved survival.
- Waldenström macroglobulinemia can present with anemia, hyperviscosity, and/or neuropathy. The US Food and Drug Administration has approved ibrutinib to treat Waldenström macroglobulinemia.
- Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes syndrome is a rare disease with a prolonged survival but high rates of disability due to progressive neuropathy.

INTRODUCTION

Plasma cell disorders are a heterogeneous group of blood disorders characterized by the detection of a monoclonal paraprotein in the serum or urine and/or the presence of monoclonal plasma cells in the bone marrow space or, rarely, in other tissues. Plasma cell diseases include monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma (MM), lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM), amyloidosis, and POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, and Skin changes).

MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

MGUS is a clinically asymptomatic premalignant clonal plasma cell, and in some cases, lymphoplasmacytic disorder that is typically identified incidentally while patients are being worked up for other reasons, such as anemia, neuropathy, or hypercalcemia, among others.

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MGUS has been identified in 1% to 2% of individuals in studies from the United States and Europe.¹⁻³ The incidence and prevalence of MGUS increase with age, are higher in men than women, and are higher in individuals of African descent.^{4,5} Limited data suggest the incidence of MGUS in Asians and Hispanics is lower than in Caucasians.^{6,7} First-degree relatives of patients with MGUS have a higher risk of developing other plasma cell disorders.^{8,9}

Current population-based data support that about half of individuals diagnosed with MGUS at age 70 had had a monoclonal paraprotein for 10 years.¹⁰ Patients are typically diagnosed due to the presence of a monoclonal paraprotein in serum or urine protein electrophoresis (SPEP and UPEP, respectively). Immunoglobulin G (IgG) MGUS is the most common type (70% of the cases), followed by IgM (15%) and IgA (12%).¹¹ IgD, IgE, and light chain-only MGUS have been reported.

The diagnosis of MGUS is made when a monoclonal paraprotein less than 3 g/dL is found in an asymptomatic patient. The minimum initial evaluation for patients with MGUS should include the following:

- Complete blood count (CBC)
- Serum calcium and creatinine levels
- SPEP/UPEP with immunofixation
- Serum free light chain (FLC) levels and ratio
- Quantitation of immunoglobulins
- Skeletal survey (radiographs)

A bone marrow biopsy is indicated in patients with an IgG monoclonal paraprotein greater than or equal to 1.5 g/dL, patients with non-IgG (IgM, IgA, IgD, light chain-only) monoclonal paraprotein of any size, patients with an abnormal FLC ratio, and in patients with abnormalities of the CBC, creatinine, calcium, or radiographs. Therefore, a bone marrow biopsy can be deferred in patients with IgG MGUS with monoclonal protein less than 1.5 g/dL, normal FLC ratio, and with no clinical concerns for myeloma. In patients with IgM MGUS, computed tomography (CT) scans should be considered to evaluate for the presence of lymphadenopathy and/or hepatosplenomegaly.

The diagnostic criteria for MGUS are as follows¹²:

Diagnostic criteria for non-IgM MGUS

- Presence of a serum monoclonal protein (IgG, IgA, or IgD) less than 3 g/dL
- Fewer than 10% clonal plasma cells in the bone marrow
- Absence of lytic bone lesions, anemia, hypercalcemia, and renal insufficiency related to the plasma cell disorder.

Diagnostic criteria for IgM MGUS

- Presence of a serum IgM monoclonal protein less than 3 g/dL.
- Fewer than 10% clonal plasma cells in the bone marrow
- Absence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, hepatomegaly, or splenomegaly related to the plasma cell disorder

Diagnostic criteria for light chain MGUS

- Abnormal FLC ratio (ie, kappa to lambda ratio <0.26 or >1.65)
- Increased level of the appropriate involved light chain
- No monoclonal immunoglobulin heavy chain (IgG, IgA, IgD, or IgM)
- Fewer than 10% clonal plasma cells in the bone marrow
- Absence of lytic bone lesions, anemia, hypercalcemia, and renal insufficiency related to the plasma cell disorder

Each of the clinical types of MGUS carries a risk of progressing to a malignant plasma cell or lymphoplasmacytic disorder of about 1% per year. It is impossible, however, to know with certainty which patient will have a benign course and which patient will eventually progress. Therefore, patients with MGUS should be monitored for progression and potential complications.

Patients with non-IgM MGUS might progress into MM, and in smaller proportion into AL amyloidosis, light chain deposition disease, and other lymphoproliferative disorders.¹¹ Patients with IgM MGUS can progress into WM, and rarely, into AL amyloidosis or IgM MM.¹³ Light chain MGUS can progress into light chain MM, AL amyloidosis, or light chain deposition disease.¹⁴

Three risk factors are currently used for evaluating the risk of progression from MGUS to symptomatic plasma cell or lymphoplasmacytic disorder^{15,16}:

- Serum monoclonal paraprotein level greater than or equal to 1.5 g/dL
- Non-IgG MGUS
- Abnormal serum FLC ratio

The 20-year risk of progression is as follows¹⁷:

- 3 risk factors (high risk): 58%
- 2 risk factors (high-intermediate risk): 37%
- 1 risk factor (low-intermediate risk): 21%
- 0 risk factors (low risk): 5%

Patients with low-risk MGUS can be followed with history and physical and routine laboratory studies on a yearly basis. All other patients should be followed with at least an annual examination, CBC, calcium and creatinine levels, SPEP/UPEP, and serum FLC ratio. Additional investigation should be undertaken if any of the following develop:

- Bone pain
- Fatigue or generalized weakness
- Constitutional symptoms (unintentional weight loss, fever, night sweats)
- Neurologic symptoms (neuropathy, headache, dizziness)
- Bleeding
- Symptoms suggestive of amyloidosis (macroglossia, nephrotic syndrome, restrictive cardiomyopathy)
- Lymphadenopathy, hepatomegaly, or splenomegaly
- Abnormal laboratory findings (anemia, elevated creatinine, hypercalcemia)

The survival of patients with MGUS approximates the survival of the general population.¹⁸ Patients with MGUS, however, have a higher risk of fractures, thromboembolic episodes, and secondary myeloid malignancies.^{19–24} Patients with MGUS should undergo bone densitometry studies and receive bisphosphonates if there is evidence of osteopenia or osteoporosis.

MULTIPLE MYELOMA

MM is a plasma cell neoplasm characterized by the accumulation of malignant plasma cells in the bone marrow producing a monoclonal paraprotein. A diagnosis of MM should be suspected in these following scenarios:

- Unexplained anemia
- Hypercalcemia
- Acute renal failure or nephrotic syndrome

- Bone fractures or presence of bone lytic lesions on imaging studies
- Increased serum protein or presence of monoclonal paraprotein in serum or urine

MM accounts for 10% of all hematologic malignancies with an incidence that has remained stable for the last 5 decades.^{25,26} The median age at diagnosis is 66 years with 10% of patients being younger than 50 years, and a slight male predominance.²⁷ The risk of MM is higher in blacks than in whites, and lower in Asians and Mexicans.^{28,29} Individuals with a first-degree family member with MM have a 4-fold increased risk of developing MM.³⁰

The most common presenting signs and symptoms of MM include the following:

- Anemia (75%), typically normochromic and normocytic
- Bone pain (60%), particularly back and chest
- Elevated creatinine (50%), typically associated with light chain cast nephropathy (myeloma kidney), amyloid kidney, or light chain deposition disease
- Hypercalcemia (30%), which should be treated emergently if calcium greater than or equal to 11 mg/dL
- Fatigue (30%)
- Weight loss (25%)

Less common signs or symptoms of MM include neuropathy (5%), hepatosplenomegaly (5%), lymphadenopathy (1%), and fever (1%).

Cord compression due to plasmacytoma or vertebral fracture may be seen in 5% of patients with MM and is considered an emergency. Patients present with severe back pain, weakness of the lower extremities, and bladder or bowel incontinence. MRI should be performed immediately and treatment instituted with chemotherapy, radiotherapy, or neurosurgery to avoid permanent neurologic deficit.

SPEP detects a monoclonal protein in approximately 80% of patients with MM. The rate of detection increases to 90% with immunofixation and to more than 95% with serum FLC ratio. The distribution of types of monoclonal protein is as follows:

- IgG: 50% to 55%
- IgA: 20% to 25%
- Kappa or lambda light chain only: 15% to 20%
- IgD: 1% to 2%
- IgM 0.5% to 1%
- Biclonal: 1% to 2%
- Nonsecretory: 3% to 5%

A bone marrow aspirate and biopsy are key components to the diagnosis of MM. The percentage of involvement should be quantified from a core biopsy. Clonality is established by identifying light chain restriction by flow cytometry or immunohistochemistry.

DIAGNOSTIC CRITERIA FOR MULTIPLE MYELOMA ACCORDING TO THE REVISED INTERNATIONAL MYELOMA WORKING GROUP

Definition of Multiple Myeloma

Clonal bone marrow plasma cells greater than or equal to 10% OR biopsy-proven bone or soft tissue plasmacytoma, AND one or more of the following³¹:

- Hypercalcemia: serum calcium greater than 11 mg/dL
- Renal insufficiency: creatinine clearance less than 40 mL/min or serum creatinine greater than 2 mg/dL

- Anemia: hemoglobin less than 10 g/dL
- Bone lesions: osteolytic lesions on radiographs, CT, or PET/CT

The following represent an 80% risk of developing active MM within 2 years and should be considered active MM:

- Clonal bone marrow plasma cell involvement greater than or equal to 60%
- Serum FLC ratio greater than or equal to 100; kappa:lambda in kappa-restricted myeloma or lambda:kappa in lambda-restricted myeloma
- Greater than 1 focal lesion on MRI

Once the diagnosis of MM is made, the patients should undergo staging for prognostic purposes. The International Staging System (ISS) has become the preferred staging system given its simplicity.³²

- ISS I: serum β -2-microglobulin less than 3.5 mg/L and serum albumin greater than 3.5 g/dL
- ISS II: neither stage I nor stage III
- ISS III: serum β -2-microglobulin greater than or equal to 5.5 mg/L

The median survival of MM patients with ISS stage I, II, and III is 62, 44, and 29 months, respectively.

The revised ISS (R-ISS) incorporates serum lactate dehydrogenase (LDH) and high-risk chromosomal abnormalities detected by fluorescence in situ hybridization (FISH).³³ The latter includes del(17p), t(4;14), and t(14;16).

- R-ISS stage I: ISS stage I AND normal serum LDH AND no high-risk FISH abnormalities
- R-ISS stage II: neither R-ISS stage I nor stage III
- R-ISS stage III: ISS stage III AND serum LDH above normal limits AND/OR detection of one of the high-risk FISH abnormalities.

The 5-year survival rates for R-ISS stages I, II, and III were 82%, 62%, and 40%, respectively.

Patient-related factors associated with worse prognosis include older age, poor performance status, higher serum creatinine and calcium, lower hemoglobin and platelet count, and higher bone marrow involvement. Also, non-IgG MM, circulating plasma cells, and abnormal FLC ratio have been associated with worse outcomes.

Before initiation of therapy, eligibility for autologous stem cell transplantation (ASCT) should be determined. Patients who are eligible for ASCT should not receive stem cell toxic drugs (eg, melphalan) as part of the induction treatment. The combination of the proteasome inhibitor bortezomib, the immunomodulator lenalidomide, and dexamethasone (RVD) is commonly used in ASCT-eligible and -ineligible patients with MM. RVD is associated with a response rate of 100% with a reasonable toxicity profile.³⁴ Lenalidomide needs adjustment for renal insufficiency. The combination of the alkylator cyclophosphamide, bortezomib, and dexamethasone has also shown efficacy with a response rate of 80% and does not need adjusted for renal dysfunction.³⁵ Other treatment options include but are not limited to bortezomib, thalidomide, and dexamethasone, bortezomib and dexamethasone, and lenalidomide and dexamethasone (RD). Bortezomib can be given weekly and subcutaneously to decrease risk of neurotoxicity. Patients on proteasome inhibitor therapy should receive prophylaxis against herpes zoster. In elderly patients, 2-drug combinations are safe and effective; however, lenalidomide and dexamethasone might need to be dose-reduced to minimize toxicity. In eligible patients, once induction therapy is completed, the standard

approach is to proceed with high-dose chemotherapy followed by ASCT. ASCT-ineligible patients can receive regimens containing stem cell toxic agents, such as melphalan. The duration of induction varies depending on the regimen. Patients on melphalan or bortezomib-containing regimens continue therapy until a response plateau is reached (usually at 12–18 months). Patients on RD typically continue therapy until progression or unacceptable toxicity.

Response to therapy is assessed using serum monoclonal protein, immunofixation, serum FLC ratio, flow cytometry, and molecular studies.

INTERNATIONAL MYELOMA WORKING GROUP RESPONSE CRITERIA FOR MULTIPLE MYELOMA

- Molecular complete response: Stringent complete response AND no identifiable oligonucleotides on polymerase chain reaction³⁶
- Immunophenotypic complete response: Stringent complete response AND no detectable aberrant clonal plasma cells by flow cytometry analysis of the bone marrow
- Stringent complete response: Complete response AND normal FLC ratio AND no clonal cells in the bone marrow by immunohistochemistry
- Complete response: No monoclonal protein in serum and urine by immunofixation AND no evidence of plasmacytoma AND bone marrow showing less than 5% plasma cells
- Very good partial response: monoclonal protein detectable by immunofixation but not electrophoresis or at least 90% reduction in serum monoclonal protein
- Partial response: At least 50% reduction in serum monoclonal protein AND at least 50% reduction in size of plasmacytomas
- Stable disease: Does not meet criteria for complete, very good partial or partial response, or progressive disease
- Progressive disease: At least 25% increase from lowest response value in serum or urine monoclonal protein, bone marrow plasma cell percentage, or difference in the serum FLC levels OR increase in size or new bone lesions or plasmacytomas

Almost all patients with MM who survive initial treatment will eventually experience relapse requiring therapy. Treatment options for relapsed disease include ASCT, use of the previous regimen, or a new regimen, including clinical trials. The novel proteasome inhibitors carfilzomib and ixazomib, the novel immunomodulatory drug pomalidomide, the histone deacetylase inhibitor panobinostat, and the monoclonal antibodies daratumumab (anti-CD38) and elotuzumab (anti-SMF7) have recently gained US Food and Drug Administration (FDA) approval for the treatment of patients with MM. Overall, the 5-year overall survival rate in patients with MM has increased from 40% before 2000 to higher than 60% after 2010, with larger survival benefits observed in patients older than 65 years.³⁷

Smoldering Multiple Myeloma

Patients with smoldering MM meet all the criteria for active MM with exception of end-organ damage. The definition of smoldering MM includes serum monoclonal protein greater than or equal to 30 g/L OR urinary protein greater than or equal to 500 mg per 24 hours AND/OR clonal bone marrow plasma cells 10% to 60% AND absence of myeloma-defining events or amyloidosis. The rate of progression to active MM or AL amyloidosis occurs at a rate of 10% per year for the first 5 years, 3% per year for the next 5 years, and 1% to 2% per year for the following 10 years.³⁸ Three factors have been associated with progression from smoldering to active MM: abnormal

serum FLC ratio, bone marrow plasma cells greater than or equal to 10%, and serum monoclonal protein greater than or equal to 3 g/dL. The rate of progression at 5 years was 25%, 51% and 76% for patients with 1, 2, or 3 risk factors, respectively.^{38,39} After initial diagnosis, follow-up visit can span from every 3 to every 12 months depending on stability of the values. Similar to patients with MGUS, patients with smoldering MM have higher risk of fractures, thromboembolic disease, and secondary cancers. A group of patients with high-risk smoldering MM might benefit from early intervention with lenalidomide and dexamethasone.⁴⁰ However, additional studies are needed to standardize the treatment of patients with high-risk smoldering MM.

WALDENSTRÖM MACROGLOBULINEMIA

LPL/WM is a B-cell disorder characterized by the malignant accumulation of clonally related B cells, lymphoplasmacytic cells, and plasma cells in the bone marrow and other tissues.⁴¹ LPL/WM is a rare disease with an incidence of 1000 new cases per year in the United States. The median age at diagnosis is 70 years, and less than 10% of patients are younger than 50 years.⁴² More than 80% of patients are white, and about 20% are of Ashkenazi Jewish descent. About 20% of patients have a positive family history of hematologic malignancy in first-degree relatives.

The most common presenting symptoms in patients with LPL/WM are as follows:

- Fatigue/tiredness 40% to 50%, due to anemia
- Constitutional symptoms 25% to 30%
- Neurologic symptoms 20% to 25%, usually symmetric sensory neuropathy in lower extremities with evidence of demyelination in electromyography
- Symptoms of hyperviscosity 10% to 20%, such as nosebleeds, blurred vision, and headaches. A funduscopic examination should be performed in patients with typical symptoms, and if signs of hyperviscosity are seen (eg, increased tortuosity and sausageing of retinal vessels, retinal hemorrhages), plasmapheresis should be instituted urgently.
- Lymphadenopathy 10% to 15%
- Hepatosplenomegaly 10% to 15%

Other rare symptoms can be associated with cryoglobulinemia (vasculitic rash, non-healing ulcers in lower extremities), cold agglutininemia (hemolysis, hemoglobinuria), and amyloidosis. Renal involvement and bone lytic lesions in LPL/WM are rare.

The diagnosis of LPL/WM is made based on findings in the bone marrow biopsy, SPEP, and the clinical scenario. The following criteria must be met⁴³:

- A serum IgM monoclonal protein of any size
- Involvement of the bone marrow by an intertrabecular infiltrate of any size of small lymphocytes, lymphoplasmacytoid forms, and plasma cells
- The lymphocytic cells typically express surface IgM, CD19, CD20, and CD22. The plasmacytic cells express CD38 and CD138.

More than 90% of patients with LPL/WM carry the recurrent MYD88 L265P gene mutation, which can help secure the diagnosis.⁴⁴ The MYD88 L265P mutation can be identified in about 50% of patients with IgM MGUS.

Initial evaluation of patients with LPL/WM should include the following:

- Laboratory studies: CBC, liver and kidney function, LDH, SPEP, and immunofixation, quantitative immunoglobulins, β -2-microglobulin, and serum FLC. In special cases, workup can include cryoglobulins, cold agglutinins, and von Willebrand disease screening

- Bone marrow aspiration and biopsy
- CT scans of the chest, abdomen, and pelvis with intravenous contrast
- Patients with neuropathy should undergo electromyograph (EMG) studies, and if demyelination is identified, then be tested for anti-myelin-associated glycoprotein antibodies.
- Amyloidosis should be evaluated by means of a fat pad biopsy stained with Congo red.

Approximately 25% to 35% of patients with LPL/WM do not meet criteria for initiation of therapy at diagnosis. Immediate treatment is not needed in all LPL/WM given its incurability and also prolonged survival. Criteria for initiation of therapy include the following⁴⁵:

- Recurrent fever, night sweats, weight loss, and fatigue
- Hyperviscosity
- Symptomatic lymphadenopathy
- Symptomatic hepatomegaly and/or splenomegaly
- Symptomatic organomegaly and/or organ or tissue infiltration
- Peripheral neuropathy due to LPL/WM
- Hemoglobin less than or equal to 10 g/dL
- Platelet count less than $100 \times 10^9/L$
- Symptomatic cryoglobulinemia
- Symptomatic cold agglutinin anemia
- Autoimmune cytopenias
- Systemic amyloidosis

Primary therapy for LPL/WM should be reserved for patients with symptomatic disease. There is no clear advantage for early therapy. Patients who are eligible for ASCT should not receive stem cell toxic drugs. In patients with symptomatic hyperviscosity, plasmapheresis should be instituted urgently and followed by definitive therapy directed at LPL/WM. Most primary treatment regimens for LPL/WM are recommended based on single-arm prospective studies. The Bruton tyrosine kinase inhibitor ibrutinib is the only FDA-approved agent in the frontline and relapsed settings for patients with LPL/WM.⁴⁶ Commonly used regimens include alkylators (bendamustine or cyclophosphamide) or proteasome inhibitors (bortezomib or carfilzomib) in combination with the anti-CD20 monoclonal antibody rituximab.^{47–49} Rituximab can also be used as a single agent. Rituximab should be used with caution in patients with LPL/WM with serum IgM levels greater than 4000 mg/dL as, in up to 40% of patients, rituximab therapy can be associated with an IgM flare that can be symptomatic. Such an IgM flare does not represent progression of disease. About 7% of LPL/WM patients exposed to rituximab can become intolerant to it, and ofatumumab can be used in such cases.⁵⁰

Response to therapy is assessed using serum IgM levels, SPEP, and immunofixation, bone marrow biopsy, and CT scans.

INTERNATIONAL WORKING GROUP ON WALDENSTRÖM MACROGLOBULINEMIA RESPONSE CRITERIA

- Complete response: normal serum IgM level, disappearance of monoclonal protein on immunofixation, resolution of extramedullary disease, and resolution of signs and symptoms attributed to WM.⁵¹
- Very good partial response: At least 90% reduction in serum IgM, resolution of extramedullary disease, and resolution of signs and symptoms attributed to WM.
- Partial response: At least 50% but less than 90% decrease in serum IgM level AND at least 50% decrease in extramedullary disease.

- Minor response: At least 25% but less than 50% reduction in serum IgM level.
- Stable disease: Neither minor response or progressive disease.
- Progressive disease: Two measurements showing at least 25% increase in serum IgM level or progression of clinically significant cytopenias, extramedullary disease or constitutional symptoms, hyperviscosity, neuropathy, cryoglobulinemia, or amyloidosis.

All patients with LPL/MM will eventually relapse after primary therapy. Treatment options for relapsed disease include the same regimen used for primary therapy, another frontline regimen, including clinical trials and, in exceptional cases, ASCT. Other agents used in the relapsed setting include thalidomide, lenalidomide, everolimus, fludarabine, cladribine, and chlorambucil.

A commonly used prognostic tool is the International Prognostic Scoring System for WM, which includes age greater than 65 years, hemoglobin less than or equal to 11.5 g/dL, platelet count less than or equal to $100 \times 10^9/L$, β -2-microglobulin greater than 3 mg/dL, and serum IgM greater than 7000 mg/dL. Patients are stratified in low-, intermediate-, and high-risk categories with 5-year survival rates of 87%, 68%, and 36%, respectively.⁵² However, the patients included in such a study were not treated with novel regimens. High von Willebrand antigen level has been associated with a worse outcome.⁵³ Overall, the median survival on patients with LPL/MM has improved from 6 years in the 1990s to higher than 8 years in the 2000s.⁴²

LIGHT CHAIN AMYLOIDOSIS

Light chain amyloidosis (AL amyloidosis) refers to the extracellular tissue deposition of monoclonal light chain fibrils. Patients can have AL amyloidosis alone or in association with other plasma cell disorders such as MGUS, MM, and LPL/MM. The incidence of AL amyloidosis is unknown. The median age at presentation is 64 years with men accounting for 70% of the cases.

The clinical presentation depends on the organs affected. Common organs affected include the following:

- Kidney (70%): asymptomatic proteinuria or nephrotic syndrome
- Heart (60%): restrictive cardiomyopathy or arrhythmias
- Nervous system, peripheral (20%) or autonomic (15%), characterized as numbness, paresthesias, carpal tunnel syndrome, orthostatic hypotension
- Gastrointestinal tract and liver: bleeding, gastroparesis, malabsorption, liver enzyme elevation
- Soft tissue: macroglossia, shoulder pad
- Skin: purpura, easy bruisability, subcutaneous nodules
- Bleeding: associated with factor X deficiency

Once the diagnosis is suspected, demonstration of amyloid fibrils should be pursued by biopsy of less invasive sites such as fat pad, rectal area, or bone marrow or, if negative, the affected organ. The diagnosis of AL amyloidosis requires all the following³¹:

- Presence of an amyloid-related systemic syndrome
- Positive staining by Congo red in any tissue
- Evidence the amyloid is light chain-related using spectrometry or electron microscopy
- Evidence of monoclonal plasma cell disorder

Initial evaluation of patients with AL amyloidosis should include the following:

- Laboratory studies: CBC, chemistries with liver and renal function, international normalized ratio, partial thromboplastin time, SPEP, and UPEP with immunofixation, serum FLC ratio, 24-hour urine protein, troponin, NT-proBNP, thyrotropin, and cortisol level. Factor X levels should be checked in special situations.
- Bone marrow aspirate and biopsy with Congo red staining
- Cardiac involvement should be evaluated with 12-lead electrocardiogram and echocardiogram. Cardiac MRI should be done in special situations
- Patients with neuropathy should undergo EMG studies
- Gastrointestinal involvement can be evaluated with stool guaiac studies, liver ultrasound, and/or gastric-emptying studies

In patients eligible for ASCT, high-dose melphalan followed by ASCT can be used as initial therapy.⁵⁴ If delays in ASCT are expected, induction with bortezomib-based regimen is preferred. In patients who are ineligible for ASCT, which account for approximately 75% of the cases, melphalan or bortezomib-based regimens have shown efficacy.⁵⁵ In the relapsed setting, combination regimens with agents such as melphalan, cyclophosphamide, bendamustine, bortezomib, thalidomide, lenalidomide, and pomalidomide have been investigated in prospective studies.^{56–60}

Response to treatment can be assessed with SPEP, UPEP, serum and urine immunofixation, serum FLC levels, and markers specific to the organs affected.

ROUNDTABLE ON CLINICAL RESEARCH IN LIGHT-CHAIN AMYLOIDOSIS RESPONSE CRITERIA

Hematologic Response

- Complete response: Normalization of FLC levels and ratio, negative urine, and serum immunofixation⁶¹
- Very good partial response: Reduction in the difference between involved and uninvolved FLC (dFLC) to less than 40 mg/L
- Partial response: A greater than 50% reduction in the dFLC
- No response: Less than partial response
- Progression: FLC increase of 50% to greater than 100 mg/L; if patient achieved complete remission, any detectable monoclonal protein, or abnormal FLC ratio. If patient achieved partial response, 50% increase in monoclonal protein to greater than 0.5 g/dL or 50% increase in urine monoclonal protein to greater than 200 mg/d

Specific criteria for organ response and progression have been published.

The prognosis of AL amyloidosis varies greatly. Poor survival has been consistently reported in patients with cardiac or liver failure and is typically measured in a few months.⁶² On the other hand, patients with limited organ disease can have survival times more than 5 years. Patients with concurrent AL amyloidosis and myeloma tend to have a worse prognosis than AL amyloidosis alone.⁶³ Other adverse prognostic factors are elevated NT-proBNP, elevated troponin, elevated uric acid, and dFLC.

POLYNEUROPATHY, ORGANOMEGALY, ENDOCRINOPATHY, MONOCLONAL PROTEIN, AND SKIN CHANGES SYNDROME

POEMS syndrome is a rare disorder that affects patients in the fifth to sixth decade of life. The clinical manifestations are highly variable. According to the IMWG, the

diagnosis of POEMS syndrome is made by the presence of 2 mandatory criteria in addition to one major and one minor criterion.³¹

Mandatory Criteria

- Peripheral neuropathy, clinically sensorimotor with evidence of axonal and demyelinating damage in EMG studies
- Monoclonal plasma cell disorder, characterized by serum or urine monoclonal protein, typically lambda restricted. Bone marrow biopsy might be unrevealing.

Major Criteria

- Osteosclerotic bone lesions, which can be detected by plain radiographs or CT scans. Biopsy of these lesions show light chain–restricted plasma cells.
- Increased vascular endothelial growth factor (VEGF) levels, of at least 3 to 4 times the upper limit of normal
- Castleman disease, observed in lymph node biopsy

Minor Criteria

- Endocrine abnormalities, such as hypogonadism, high follicle stimulating hormone levels, adrenal insufficiency, hypothyroidism, and diabetes mellitus
- Skin changes, such as hyperpigmentation, hemangiomas, or hypertrichosis
- Organomegaly, such as hepatomegaly, splenomegaly, or lymphadenopathy
- Extravascular volume overload, such as ascites, peripheral edema, or pleural effusion
- Hematologic abnormalities, such as leukocytosis, thrombocytosis, or polycythemia
- Papilledema

There is no standard treatment for POEMS syndrome. Radiotherapy can be used for the management of localized disease (eg, 1–3 isolated bone lesions). For more widespread disease, similar treatment to MM is recommended. In young patients with widespread disease or severe neuropathy, high-dose chemotherapy followed by ASCT can be considered. Formal response criteria have not been published. However, CBC, serum monoclonal protein, SPEP and immunofixation, VEGF levels, and PET/CT can be used for response assessment. The median survival is longer than patients with myeloma at about 14 years.⁶⁴ Neuropathy is typically progressive, reaching disability in most cases. Most common causes of death are infections and cardiopulmonary failure.

SUMMARY

Plasma cell disorders are benign, premalignant, and malignant processes characterized by the presence of a monoclonal protein in the serum or urine. Clinically and biologically, these disorders are heterogeneous. However, there have been substantial advances in the understanding of the biology of these diseases that have prompted improvements in treatment, which are translating into better survival rates and quality of life. Additional research should focus on improving the efficacy as well as the short- and long-term toxicity profile of our interventions.

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