Differential Diagnosis of Monoclonal Gammopathies

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• **Several disorders are associated with a monoclonal immunoglobulin detected by serum or urine electrophoresis, the most common being a monoclonal gammopathy of undetermined significance, multiple myeloma, Waldenström's macroglobulinemia, and amyloidosis. The clinical features of these conditions, as well as other similar entities, are described in this review. The objective is to demonstrate the importance of electrophoretic studies in the differential diagnosis of plasma cell dyscrasias and in guiding the decision for rational therapies.**

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Monoclonal gammopathies represent a group of related disorders characterized by a clone of plasma cells or lymphocytes with the capacity to secrete a homogeneous immunoglobulin or its components, which may be recognized as a peak on serum or urine protein electrophoresis. The presence, level, and type of immunoglobulin have important implications in the diagnosis, staging, and treatment of these diseases. The levels of uninvolved immunoglobulin classes are also useful in the differential diagnosis. This review describes the clinical features of the most common plasma cell dyscrasias and focuses on the role of serum and urine electrophoreses in distinguishing these entities. The most important disorders to be considered (summarized in Table 1) may be grouped separately as plasmacytic, lymphocytic, protein infiltrative, or miscellaneous disorders.

PLASMA CELL DISORDERS

Solitary Plasmacytoma

Most solitary plasmacytomas are recognized as a single area of bone destruction with no evidence of clonal disease elsewhere (eg, marrow plasmacytosis or bone defects on radiographic studies that include magnetic resonance imaging of the spine). In one recent series, a monoclonal protein was present in serum or urine of one half of the patients but was always detected at a low level (serum monoclonal protein, <2.5 g/dL; Bence Jones protein, <500 mg/d).[1] Even when high-resolution electrophoreses of serum and urine are negative, immunofixation is indicated to detect a low level of monoclonal protein. Uninvolved immunoglobulins were preserved. After radiotherapy to the solitary lesion with curative intent (45 Gy), approximately 30% of the patients included in the series have remained free of disease for more than 10 years. Retrospective studies have indicated that patients with disappearance of monoclonal protein by immunofixation were most likely to live for a long period and had a high likelihood of cure. The remaining patients developed multiple myeloma after a median of 3 years, and the median survival of all patients was approximately 10 years. Even with careful staging procedures that include magnetic resonance imaging of the spine, this disorder will rarely be diagnosed.

Some solitary plasmacytomas are extramedullary, and they most frequently involve the sinuses and nasopharynx. This entity occurs at a frequency approximately one-third that of solitary plasmacytoma of bone and should be distinguished from a clonal lymphocytic growth by phenotypic studies that confirm CD38 expression. Approximately 20% of patients have a low-level monoclonal immunoglobulin other than immunoglobulin M (IgM) in serum or urine. In recent series, local radiotherapy with curative intent (45 Gy) was associated with long-term stability in approximately 60% of patients.[2]

Multiple Myeloma

Multiple myeloma is a generalized disease of malignant plasma cells that affects approximately 13 000 Americans each year (Table 2). Among symptomatic patients, marrow plasma cells usually exceed 10%, or sheets of plasma cells are present in a lytic bone lesion or contiguous soft tissue mass. More than 95% of patients have a monoclonal protein in serum, urine, or both, and approximately 70% have a lytic bone lesion. Malignant plasma cells usually express CD38 and CD56 antigen, but usually do not express other B-cell antigens, such as CD19, CD20, and CD23.[3] Major clinical features include severe localized pain from a pathologic fracture (such as of a vertebra or rib); easy fatigability caused by severe anemia; nausea, confusion, and polyuria due to hypercalcemia; nausea and fatigue from severe renal failure; and recurrent infections due to multiple factors, including a marked depression of uninvolved immunoglobulins. Renal failure has been attributed primarily to hypercalcemia or Bence Jones proteinuria in patients with advanced disease; concurrent amyloidosis (AL) or immunoglobulin deposition disease are less common factors.[4] With spinal cord pressure arising from an affected vertebra, paraplegia may develop. Hyperviscosity syndrome with fatigue, confusion, and blurred vision is rare in myeloma but may occur with very high serum myeloma protein values (>6.0 g/dL). Far advanced disease may be associated with bleeding from severe thrombocytope-

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Table 1. Monoclonal Gammopathies

Myeloma
Solitary plasmacytoma
Bone
Extramedullary
Asymptomatic myeloma
Multiple myeloma
POEMS syndrome
Waldenström's macroglobulinemia
Overt disease
Asymptomatic disease
Heavy-chain diseases
Protein infiltrative or deposition diseases
Amyloidosis (AL)
Immunoglobulin deposition disease
Monoclonal gammopathy of undetermined significance
Chronic
Transient (after myeloablative therapy)

Table 2. Approximate Annual Incidence of Common Monoclonal Gammopathies in the United States

	No. of Cases/y	Median Survival, y
Multiple myeloma	13 000	3
Waldenstrom's disease	3000	5
Amyloidosis (AL)*	2000	1†
Monoclonal gammopathy of undetermined significance	750 000	12‡

* Approximately 20% of patients have myeloma or Waldenström's disease.
† Involvement of 2 or more organ systems.
‡ Most deaths due to unrelated diseases.

nia, skin nodules from plasma cell tumors, plasma cell leukemia, and meningeal disease.

The median age at diagnosis is 65 years, and only 15% of patients are younger than 50 years. The median survival is 3 years, but approximately 10% of patients live more than 10 years. Standard therapies have included various alkylating agent–glucocorticoid combinations; high-dose dexamethasone, either alone or with vincristine-doxorubicin by continuous infusion (VAD); and more intensive treatments supported by granulocyte colony-stimulating factor, autologous blood progenitor cell transplantation, or both. Ancillary therapies have included radiotherapy for painful fractures or spinal cord pressure, bisphosphonates to enhance bone mineralization, erythropoietin for anemia, and hemodialysis for severe renal failure.

Asymptomatic Multiple Myeloma

Approximately 15% of patients with multiple myeloma are free of symptoms when their diagnosis is made by chance after the detection of an elevated serum protein or erythrocyte sedimentation rate on screening studies. Various terms, including smoldering myeloma, indolent myeloma, and asymptomatic myeloma, have been used to describe disease with marrow plasmacytosis greater than 10% and serum monoclonal protein greater than 2.5 g/dL, which cannot be classified as monoclonal gammopathy of undetermined significance (MGUS), but which may remain stable for a long period without treatment. Chemotherapy is indicated primarily when features occur that portend a serious complication, such as rising serum myeloma protein (>5.0 g/dL), increasing anemia (hemoglobin, <10.5 g/dL), or the appearance of a lytic bone lesion.

Table 3. Comparisons of Asymptomatic Myeloma and Monoclonal Gammopathy of Undetermined Significance (MGUS)

	Asymptomatic Myeloma	MGUS
Serum peak	>2.0 g/dL in 85%	<2.5 g/dL†
Bence Jones protein	Any level	<50 mg/d
Uninvolved immunoglobulin	Low in 75%	Preserved in 75%
Marrow plasma cells	>10%*	<10%‡
Magnetic resonance imaging of spine	Abnormal in 50%	Normal
Median survival, y	7	12§

* May be <10% with blood dilution or unrepresentative sample.
† Some laboratories use a higher threshold level.
‡ May be 10% to 20% in focal areas.
§ Most patients die of unrelated diseases.

Recent studies have indicated that the presence of a lytic bone lesion, serum myeloma protein levels greater than 3.0 g/dL, IgA myeloma protein, Bence Jones protein levels greater than 50 mg/d, or abnormalities on magnetic resonance imaging of the spine represent harmful factors associated with earlier progression than that observed in patients without these features.[5] The laboratory features that distinguish asymptomatic myeloma from MGUS may not be clear in some patients, but follow-up without treatment is appropriate for both entities (Table 3).

POEMS Syndrome

POEMS syndrome refers to a rare disorder with peripheral neuropathy, organomegaly, endocrine deficiency, monoclonal gammopathy (of IgAL or IgGL types in 75% of patients), and skin pigmentation; osteosclerotic bone lesions have also been described in most patients. Many patients have only a monoclonal gammopathy and a sensorimotor peripheral neuropathy with leg pain, weakness, or both. The clinical course is more indolent than that of multiple myeloma, with a median survival of approximately 5 years. In addition, some patients have a monoclonal gammopathy and peripheral neuropathy that appear to be coincidental.[6]

LYMPHOCYTIC DISORDERS

Waldenström's Macroglobulinemia

Waldenström's macroglobulinemia is a generalized clonal malignancy of well-differentiated lymphocytes with plasmacytoid features that produce a monoclonal IgM globulin. The malignant cells usually express the same antigens that are present in chronic lymphocytic leukemia, such as CD5, CD19, CD20, and CD23, but expression of cytoplasmic immunoglobulin is more evident. Approximately 3000 Americans are afflicted with Waldenström's macroglobulinemia each year. The median age at diagnosis is 65 years, and the median survival is 5 years. Clinical features are usually related to tumor growth with lymphadenopathy, splenomegaly, and marrow infiltration to a degree that may cause severe anemia. Some patients may have complications from the IgM, such as hyperviscosity syndrome, cryoglobulinemia with Raynaud's syndrome and vasculitis, cold agglutinin hemolytic anemia, bleeding, or peripheral neuropathy with symmetric sensorimotor defects of the lower extremities (Table 4). Some patients may even express complications from a pathologic monoclonal IgM without evidence of clonal tu-

Table 4. Clinical Features Due to Monoclonal IgM
Impaired blood flow
Hyperviscosity
Hypervolemia
Cryoglobulinemia
Anemia*
Cold agglutinin
Bleeding
Anti-von Willebrand factor
Platelet dysfunction
Abnormal fibrin clot
Neuropathy
Anti–myelin-associated glycoprotein
Amyloidosis (AL)

* Coombs' test may be positive as an artifact of monoclonal IgM or may explain severe hemolysis due to warm antibodies unrelated to monoclonal IgM.

mor cells, and we have regarded such patients to have Waldenström's macroglobulinemia.[7]

Early diagnosis of this disease requires the demonstration of monoclonal immunoglobulin of IgM type in a patient with symptoms attributable to lymphoma growth, complications from IgM, or both. Patients with symptoms that may be due to a cryoglobulin should be screened for this abnormality, which sometimes requires serum to be collected and transported at 37°C. Recommended therapies for Waldenström's disease have usually consisted of alkylating agent–steroid combinations, but recent studies show that primary therapy with a nucleoside analog (2-chlorodeoxyadenoside, fludarabine) may be superior.[7] As with asymptomatic myeloma, some patients are diagnosed by chance while free of symptoms, but with a low level of monoclonal IgM, and should be monitored without chemotherapy. The laboratory features that distinguish asymptomatic Waldenström's disease from MGUS of IgM type remain to be defined.

The level of abnormal protein on standard electrophoresis has major implications for the diagnosis of myeloma or Waldenström's disease. For example, a serum monoclonal globulin level of at least 3.0 g/dL has always signified a generalized malignant disorder, whether of IgG or IgA type from myeloma or of IgM type from Waldenström's disease. Patients have also been described with low-grade lymphocytic lymphoma or chronic lymphocytic leukemia with a high level of monoclonal IgG or IgA immunoglobulin.[8] Even though the disease may be asymptomatic in some patients, progression to overt disease is inevitable unless death results from another disorder. The presence of easily detectable Bence Jones protein (ie, >50 mg/d) also signifies a potentially serious disorder, namely myeloma, amyloidosis (AL), or Waldenström's disease.

Heavy-Chain Diseases

Heavy-chain diseases refer to a family of rare, lymphoma-like clinical disorders that produce a monoclonal immunoglobulin component devoid of light chains. Heavy-chain diseases may produce monoclonal IgG with features that resemble Hodgkin's disease, monoclonal IgA with a small bowel infiltrate of lymphocytes that may cause malabsorption, or monoclonal IgM with features similar to chronic lymphocytic leukemia. Immunofixation and/or immunoselection studies are necessary to confirm the presence of an immunoglobulin heavy-chain fragment, which may also be present in urine, but which does not have a corresponding light chain.

Table 5. Clinical Features of Amyloidosis (AL)
Nephrosis
Cardiomyopathy
Autonomic insufficiency
Pulmonary failure with interstitial infiltrate
Malabsorption/macroglossia
Peripheral neuropathy
Skin purpura, fragility
Carpal tunnel syndrome

PROTEIN INFILTRATIVE AND DEPOSITION DISEASES

Amyloidosis (AL)

Amyloidosis (AL) refers to a clonal disorder of plasma cells or lymphocytes that produce a monoclonal immunoglobulin that leads to a fibrillar protein deposition in multiple organs (Table 5). Amyloidogenic λ light chains of the VI subgroup have been implicated most frequently.[9] Approximately 20% of patients also have overt evidence of multiple myeloma or Waldenström's disease, but 80% of the remainder show a small monoclonal immunoglobulin on serum or urine electrophoresis similar to that observed in either malignant disease.[10] In the absence of myeloma or Waldenström's disease, the marrow contains a low percentage of monoclonal plasma cells, as in MGUS. Approximately 2000 Americans are affected by amyloidosis (AL) each year. The median age at diagnosis is 60 years, the diagnosis is often difficult to reach since tissue biopsy is necessary, and the survival time varies markedly depending on the organs affected and the presence of overt myeloma or Waldenström's disease. Certain clinical features and a high index of suspicion are necessary to pursue the diagnosis, which involves electrophoretic studies and an aspirate of subcutaneous fat stained with Congo red. Table 6 illustrates that the symptoms and findings are often vague and are less specific than those of multiple myeloma or Waldenström's disease.

Immunoglobulin Deposition Disease

This disease affects fewer than 100 Americans each year and results from the deposition of crystals of a monoclonal immunoglobulin or its components in certain tissues.[11] As with amyloidosis (AL), patients usually do not have underlying myeloma. The major complications in immunoglobulin deposition disease are nephrotic syndrome and renal failure from extensive deposition of monoclonal immunoglobulin in glomeruli, but other organs affected include the heart, the liver, and the lens. Renal transplantation has reversed the major morbidity of some patients, but there are few data on the natural history and survival time.[12]

MISCELLANEOUS DISORDERS

Monoclonal Gammopathy of Undetermined Significance

A monoclonal globulin of low level is present in approximately 1% of otherwise healthy persons over the age of 50 years, and the frequency is 3% among those over 70.[13] Criteria for diagnosis include no other symptoms or findings that indicate a specific clonal dyscrasia, such as myeloma, Waldenström's disease, or amyloidosis. Criteria have usually required a low monoclonal peak (≤2.5 g/dL) of IgG, IgA, or IgM type; marrow plasma cells ≤10%;

Table 6. Common Abnormalities in Plasma Cell Dyscrasias

	Multiple Myeloma	Waldenström's Disease	Amyloidosis (AL)	MGUS*
Symptoms and signs	Bone pain Fatigue Infections Nausea	Fatigue Drowsiness Enlarged nodes, spleen Raynaud's syndrome Neuropathy	Fatigue Weight loss Edema Neuropathy Postural syncope Macroglossia Periorbital purpura	None
Laboratory findings	Elevated serum protein Anemia Hypercalcemia Azotemia Proteinuria Bone lesions or fracture None of above	Elevated serum protein Anemia Hyperviscosity Cryoprecipitate Lymphocytic leukemia or lymphoma None of above	Occasionally elevated serum protein Proteinuria Neither of above	Occasionally elevated serum protein
Monoclonal globulin	IgG, IgA, IgD, IgE, κ or λ light chains May be nonsecretory	IgM	IgG, IgA, IgD, IgM, κ or λ light chains May be nonsecretory in amyloid	IgG, IgA, IgD, IgM, κ or λ light chains

* MGUS indicates monoclonal gammopathy of undetermined significance.

Table 7. Features of Monoclonal Gammopathy of Undetermined Significance

Asymptomatic, older persons (2% of individuals >60 y)
Serum monoclonal peak, <2.5 g/dL
Marrow plasma cells, <10%
No bone lesions
Bence Jones protein, absent or <50 mg/d
Usually preserved uninvolved immunoglobulins
Progression to myeloma, Waldenström's disease, or amyloidosis in 1.5% of patients per year

no bone lesions; and no Bence Jones protein (ie, <10 mg/d) (Table 7). The level of 1 or more uninvolved immunoglobulins may be low in approximately 25% of patients. The distinction between MGUS and asymptomatic multiple myeloma may be difficult in some patients, especially when the abnormal serum protein ranges between 2.0 and 3.0 g/dL, Bence Jones protein ranges from 10 to 50 mg/d, marrow plasmacytosis ranges between 5% and 15%, or there is bone demineralization with or without nonpathologic vertebral compression fractures (Table 3). Thus, the laboratory criteria for diagnosis vary in accordance with the precision of the electrophoretic, bone marrow, and radiographic data, and the physician's experience in integrating the findings. Yet, long-term follow-up without treatment is appropriate for both MGUS and asymptomatic myeloma. Approximately 1.5% of patients with MGUS progress each year to multiple myeloma, Waldenström's disease, or amyloidosis, unless the patient dies of an unrelated disease, which has been the outcome for most individuals.[13]

Transplant-Related Monoclonal Gammopathy

Following allogeneic or autologous progenitor cell transplantation in support of intensive therapy for any disorder, a transient monoclonal gammopathy has developed in approximately 50% of patients.[14,15] Most commonly, a low-level monoclonal IgG peak develops between 2 and 6 months after the procedure and persists for a median of 6 months, but may remain for as long as 2 years. The mechanism has been attributed to a clonal plasma cell response to antigen in a regenerating but deficient immune system.

WHO SHOULD BE TESTED?

Electrophoretic studies of serum and urine are necessary for the diagnosis, staging, and serial follow-up of patients with plasma cell dyscrasia. A high index of suspicion is often required when symptoms are vague or inconsistent, overt physical findings are not evident, and standard laboratory data are negative. Patients older than 35 years who have the symptoms or laboratory abnormalities summarized in Table 6 should have a serum protein electrophoresis of high resolution to help identify a plasma cell dyscrasia. If an abnormality is present, follow-up studies include immunofixation to define the abnormal protein type and nephelometry for the quantitation of uninvolved immunoglobulins. Many clinicians are not familiar with the independent, but sometimes overlapping, information provided by these studies and how each feature contributes to the differential diagnosis.

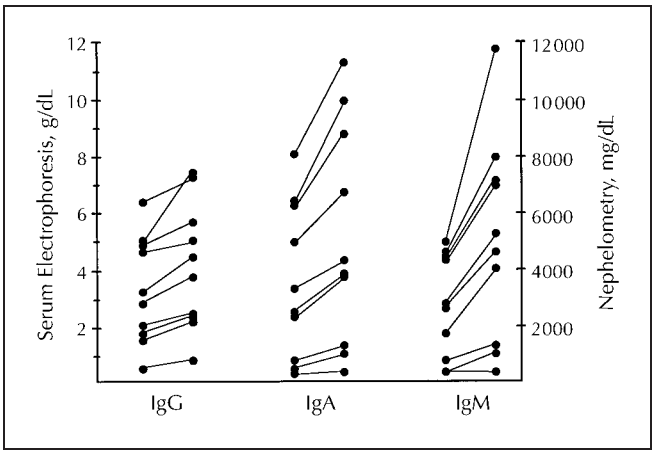
The diagnosis of multiple myeloma is most often reached after severe back or pleuritic pain occurs from a vertebral or rib fracture in a patient who is then found to have an elevated serum protein level, mild anemia, or both. Thus, the presence of any unexplained elevation of serum protein or findings of anemia, hypercalcemia, azotemia, proteinuria, or lytic bone lesions may be due to multiple myeloma. Waldenström's disease has often been recognized when fatigue has resulted from severe anemia or hyperviscosity syndrome, or during the evaluation of patients with small cell lymphocytic lymphoma or blood lymphocytosis (>4000/μL), when a monoclonal IgM may be detected. Unexplained Raynaud's syndrome may be due to a cryoglobulin, chronic anemia may result from a cold agglutinin, and peripheral neuropathy may be due to an antimyelin antibody; each of these features is due to a monoclonal IgM. When unexplained nephrosis, heart failure, macroglossia, carpal tunnel syndrome, or peripheral neuropathy are present, alone or in combination, further evaluation of amyloidosis is indicated. Amyloidosis has often been recognized after many months of unexplained fatigability, weight loss, or peripheral edema.

WHAT SHOULD BE TESTED?

After a monoclonal abnormality has been detected on serum electrophoresis, immunofixation is necessary to confirm heavy-chain and light-chain types. For patients with lymphoma and monoclonal IgM, the light-chain type should be the same as that of the malignant cells; in patients with myeloma after hematopoietic cell transplantation, the new immunoglobulin should be compared with any pretreatment monoclonal globulin to distinguish disease recurrence from an idiopathic posttransplant gammopathy. In many patients with plasma cell dyscrasia, the serum protein electrophoresis may be normal because the complete monoclonal immunoglobulin is absent or occurs at a very low level (<0.2 g/dL). Such patients may show monoclonal light chains (Bence Jones protein) in urine, which should be quantified by 24-hour urine protein quantitation and electrophoresis of a concentrated sample. Urine protein studies are indicated in all patients with a suspected plasma cell dyscrasia based on the symptoms and findings outlined in Table 6, since even those initially considered to have MGUS may have evidence of nephrosis due to previously unsuspected amyloidosis or immunoglobulin deposition disease.

When both serum and urine studies are negative on standard electrophoreses, immunofixation of serum is indicated only for those patients with a high likelihood of plasma cell dyscrasia (eg, ''nonsecretory'' myeloma or clinical evidence of amyloidosis [AL]). Such an assessment may detect levels of monoclonal IgG, IgA, IgD, or IgM that are below the threshhold concentration of 0.2 g/dL usually necessary to detect an abnormality on standard electrophoresis. Thus, the presence of monoclonal immunoglobulin in serum, urine, or both provides important laboratory data in support of other clinical data that point to a serious plasma cell dyscrasia, such as myeloma, Waldenström's disease, or amyloidosis. For myeloma or Waldenström's disease, a marrow aspirate is indicated, whereas subcutaneous fat aspirate stained with Congo red is useful in the diagnosis of amyloidosis. Rarely, one of the heavy-chain diseases or immunoglobulin deposition disease will be uncovered, or the presence of MGUS may be identified for future long-term follow-up. Once defined, repeat immunofixation is not justified unless a new clonal abnormality is suspected, such as after a transplant-supported treatment. Following such intensive therapy, the disappearance of abnormal globulin by immunofixation has been a major criterion for confirming ''complete'' remission, which signifies the eradication of visible disease and the likelihood of prolonged remission.[16]

The quantitation of uninvolved immunoglobulins by nephelometry provides supplemental information. A high level for one component coupled with low or normal levels for other components confirms the definition by immunofixation of a specific monoclonal protein elevation. Approximately 2% of patients with multiple myeloma may be classified as ''nonsecretory,'' and, coupled with marrow plasmacytosis and lytic bone lesions, low levels of uninvolved immunoglobulins provide useful supporting data for this diagnosis. Yet, most patients with asymptomatic multiple myeloma and approximately 25% of patients with MGUS also have a low level of one or more uninvolved immunoglobulins, so that values should be interpreted in relation to all other data. Follow-up of uninvolved immunoglobulins at long intervals has sometimes been useful in supporting sustained disease response or early progression in patients with myeloma or Waldenström's disease.



Comparative levels (same sera) of monoclonal immunoglobulin on serum electrophoresis (left) and of total immunoglobulin on nephelometry (right). Levels of monoclonal IgA and IgM are frequently exaggerated on nephelometry.

Even when serum electrophoresis suggests a monoclonal globulin, high levels for all components indicate a polyclonal elevation due to a reactive inflammatory process. Chronic liver disease and collagen vascular diseases are the most frequent causes of chronic polyclonal elevations in this country. Very low levels in myeloma or chronic lymphocytic leukemia (IgG, <400 mg/dL; IgA, <30 mg/dL; IgM, <15 mg/dL) may explain repeated infections and justify immune globulin therapy for selected patients.

There is an important distinction between measurements of abnormal protein level based on serum electrophoresis and those based on total immunoglobulin quantitation. For most occasions, standard electrophoresis of high resolution with precisely cut margins of monoclonal component provides the best indicator of monoclonal immunoglobulin level. In the evaluation of serum with a monoclonal immunoglobulin, assays of total immunoglobulins are always higher because normal globulins of the same class are included. In addition, with high levels of monoclonal component, nephelometry often results in a distorted elevation and should be avoided in the serial assessments of monoclonal globulin change in patients. The Figure compares simultaneous measurements of monoclonal and total IgG, IgA, or IgM immunoglobulins collected from randomly chosen patients. Distortions were most evident for monoclonal IgA and IgM immunoglobulins of high level.

For patients with low levels of monoclonal IgA (<2.0 g/dL), precise densitometry measurements by standard electrophoreses are often difficult because of the blending of low, broad-based elevations into the beta globulin region. Only in this situation are direct serial measurements of monoclonal IgA by nephelometry more reliable, especially when one considers that normal IgA is often less than 50 mg/dL in patients with multiple myeloma.

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