Clinical Diagnosis of the Monoclonal Gammopathies

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ABSTRACT
The clinical and laboratory bases for the diagnosis of a monoclonal gammopathy are presented and are related to recent information about plasmacytoma growth kinetics. The variant forms of monoclonal lesions are reviewed and the criteria for diagnosis of benign monoclonal gammopathy are delineated.

Introduction
A diagnosis is the ascription to an individual of a set of manifestations that describes a state of health or illness. If the state of illness corresponds to a codified biological entity that has been observed in a sufficient number of individuals, it is called a disease and given an appropriate name. The conceptualization of diseases into etiology and pathogenesis is valuable for interpreting manifestations, designing therapy and forming a prognosis. The entity, multiple myeloma or multifocal plasmacytoma, is a disease. It is regarded as malignant since it exhibits: multiple proliferative sites, invasiveness (tissue destruction), systemic side effects, cellular de-differentiation and lethality. Even though lethality is characteristic of multiple myeloma and emotionally evokes the adjective malignant, it is no more an exclusive characteristic of malignancy than any of the other attributes, and each of these may be encountered in benign inflammatory plasmacytic responses.

The key manifestation of multiple myeloma is the relentless "uncontrolled" (and presumably purposeless) proliferation of a single cell type appearing to have arisen from a single progenitor (clonal origin). Whether or not all malignant tumor cells are members of a single clone or whether or not identical or similar cells have been revolutionarily recruited by biochemical mobilization from orderly uncommitted bystanders is not established for most malignancies. At present, however, multiple myeloma is regarded as a prime example of a monoclonal malignancy. The hallmark of its origin is the uniformity of the committed secretory product of the multiplying clone,—a single form of a single species of immunoglobulin.

Characteristics
The morphologic and cellular characteristics of multiple myeloma are based upon the recognition of the plasma cell as a distinct replicating cell type. Controlled proliferation of plasma cells is difficult and often impossible to distinguish from uncontrolled proliferation since both may exhibit focal and diffuse forms and variable degrees of hyperplasia. Thus, relative and
absolute numbers of plasma cells in a mar­row specimen can, at best, provide pre­sumptive evidence for a diagnosis of my­eloma. Even the presence of immature cells (so called plasmablasts) is only a pre­sumptive finding of malignancy. Associated evidence of bone catabolism: (excessive hydroxyproline excretion, hypercalcemia, bone pain, X-ray evidence of lytic lesions and osteoporosis or fractures) or bone anabolism: (elevation of serum alkaline phosphatase, osteosclerosis) imply uncontrol­led proliferation if plasmacellular re­ponses to other rare diffuse systemic dis­eases can be excluded.

In some cases of multiple myeloma, plasma cells are consistently found in the peripheral blood at levels above 500 per mm³. Even rarer are spontaneous leukemoid reactions, a tendency that may be related to recent reports in which pro­longed melphalan treatment appears to be leukemogenic in multiple myeloma. When the disease has progressed to a total proliferating tissue mass above a critical size, the characteristic plasmatic findings occur and the diagnosis of multiple my­eloma is relatively easy to establish. Early diagnosis is rarely possible solely on the basis of bone lesions or cellular findings.

Since the plasma cell is accepted to be a modified lymphocyte, it is not surprising that other lymphoproliferative disorders may display morphologic, cytologic, ultra­structural and biochemical parallels to multiple myeloma. Thus Waldenström's macroglobulinemia has a distinctive modified lymphocyte and immunoglobulin se­cretory pattern, and other rarer lympho­sarcomas have exhibited similar features leading to the designation of new disease names such as the H-chain diseases: α, γ and μ.

Multiple myeloma may present initially as a single discrete tumor of soft tissue, usually in the respiratory passages or bone marrow. Ultimately, most of these les­sions develop into disseminated processes that are indistinguishable from cases ini­tially presenting with multiple erosive tu­mor masses in the marrow or diffuse plasmacytic marrow involvement. A small number of extramedullary plasmacytomas progress with lymphoid and soft tissue spread similar to reticulum cell sarcoma. The existence of isolated plasmacytoma as a benign tumor entity is open to question.

Immunoglobulins

At least 20 species of immunoglobulins are produced at all times in any normal adult and, since numerous antigen-oriented amino acid variants of these species are also secreted by innumerable committed plasma cell clones, these serum immuno­globulins at pH 8.6 exhibit varying electro­phoretic migration rates overlapping one another from α₂ through the entire γ region. If a single variant of an immuno­globulin species is produced in significant amounts, it reveals itself by a confined localization in the electrophoretic field, on the stained strip and in the densitometric scan of this preparation (the "M-spike"). The correlation of protein manifestation and clonal theory has led to the coining of the term monoclonal gammopathy for multiple myeloma and other conditions having similar biochemical findings. This concept embodies certain diagnostic neces­sities and possible conclusions.

Immunoprotein

An "M-spike" on electrophoresis is val­i­dated as a monoclonal immunoprotein when it has been established that it is indeed a single species of immunoglobulin. This requires at least the demonstration that it possesses antigen characteristics of one light chain (either κ or λ) or of one heavy chain (α, δ, ε, γ or μ) and probably of both. The future state of the art may demand IgA or IgG subgrouping or even amino acid sequencing as further validation. Electrophoresis alone is only a
presumptive identification, since interpret-
tational errors may be made of other elec-
trophoretically homogeneous proteins that
may be present in increased amounts in the
specimen (fibrin split products, fibrinogen,
hemoglobin, macroglobulins, etc.).

The diagnosis of multiple myeloma in
the absence of a "M-spike" must be justi-
ﬁed on clear classical grounds or explained
by other appropriate characteristics. The
majority of myelomas develop a greater
increase in the production of light chains
than of heavy chains resulting in the secre-
tion of free light chain dimers. These
dimers (MW about 44,000) are rapidly
cleared by normal kidneys and appear in
the urine as Bence Jones protein. A com-
mon variant form (up to 20 percent of
cases) of multiple myeloma is "Bence
Jones" or light-chain myeloma. In this
condition, there is production of a light
chain dimer but not of a complete single
immunoprotein. Since the dimer is rapidly
cleared in the urine, a serum "M-spike"
may be absent, weak or overlooked. Care-
ful study of urine specimens for Bence
Jones protein is mandatory in these cases.

A few cases of nonsecreting myeloma
have been reported. An ultramicroscopic
defect has not been found, but the intra-
cellular presence of a specific immuno-
globulin has been demonstrated by immu-
nofluorescence in some patients. In these
cases it is hypothesized that the clone has
defect in either its synthetic or secretory
mechanism. Cases with two "M-spikes"
have been seen. Most represent only
the presence of the involved monoclonal
species and a large amount of the appropri-
ate free light chain dimer, while a few have
been due to two electrophoretic migration
rates for the same molecule due to forma-
tion of aggregates with itself or another
plasma protein. An increasing number of
"two spike" cases are being reported.
A few involve IgG and IgM species with
the same light chain specificity. If, in
normal immunity, production of a specific
IgM antibody is antecedent to the produc-
tion of a specific IgG antibody, then such
an ambivalent transitional state can be hy-
pothesized in a single proliferating clone.
Monoclonal explanations for all of the "two
spike" cases are not yet available.

Although the "M-spike" is morphologi-
cally distinctive, by definition it is merely
a special case of the general normal re-
response, and immunologic specificities are
being reported for some monoclonal pro-
teins. Since there is always an undefined
amount of each immunoglobulin in a nor-
mal serum, a quantitative discriminative
level must be placed upon the "M-spike"
which diagnostically places it in the set of
criteria expected in the diagnosis of mul-
tiple myeloma. This level is accepted as 1.0
gm per dl for IgA and 2.0 gm per dl for
IgG.

The presence of Bence Jones protein in
urine in minute amounts has been noted
in several disease states associated with
hyperglobulinemia, but these conditions do
not have associated serum "M-spikes." The
ready detection of Bence Jones protein in
a urine specimen is thus by itself a pre-
sumptive indicator of multiple myeloma.
It is often necessary to concentrate the
urine specimen as much as 300-fold to
demonstrate the light-chain dimer by elec-
trophoresis and then to identify it as a
single light-chain species by immunologic
means. It has been stated that urinary
Bence Jones protein levels above 200 mg
per dl only occur in multiple myeloma.

From studies of cell kinetics, it has been
determined that it requires about 20 gm of
plasma cells to produce a detectable (0.2
gm per dl) "M-spike" protein. Extrapo-
lating backward using Gompertzian growth
equations suggests that the origin of the
clon e occurs about five years before the
cell mass reaches diagnostic size. Most
cases of multiple myeloma have an esti-
estimated 300 grams of active plasmacytic tissue at diagnosis with three kilograms or more present in "untreated" terminal cases. The immunoglobulin production rate from all tumors is not identical but, reasoning from these criteria, patients presenting with over 100 grams of active tissue should be diagnosable as having myeloma. Patients with between 20 and 100 grams of plasmacytic tissue should be suspected of having the disease and patients with less than 20 grams probably would not be diagnosed by present methods. While some asymptomatic cases are first encountered fortuitously, most patients are studied because of related symptomatology. Since the growth from 20 to 100 grams of proliferating plasmacytic tissue should take about one year without treatment, in these cases time will often become the diagnostician.

Complications of Multiple Myeloma

The complications of multiple myeloma are frequently the aspects of the disease that bring the patient to the physician and may in themselves readily lead to the diagnosis. Bone marrow failure, anemia, infection, hemorrhagic tendencies, hypercalcemia, bone pain, fracture and renal failure are often encountered. Although this wide array of problems may suggest the diagnosis to the alert clinician, it has been found in our laboratory that a side effect of hyperglobulinemia, known as hyperviscosity, usually gives the laboratory the first opportunity to make the diagnosis. Rouleaux formation, unexplained rapid erythrocyte sedimentation rates and obstruction of continuous flow analyzers lead to the unsolicited diagnosis in many patients each year. The physical manifestations of hyperviscosity in the patient are as varied as they are in the laboratory.

A small percentage of multiple myeloma cases may present initially with widespread amyloidosis having the pattern of primary amyloidosis. These patients are most often first considered as a nephrotic syndrome. The presence of pronounced marrow plasmacytosis in most cases of nephrosis plus universal proteinuria with immunoglobulinuria do not simplify this problem of differential diagnosis. Immunoelectrophoresis using a complete battery of antisera may be needed to establish the diagnosis of multiple myeloma, other forms of nephrosis being diagnosed by exclusion. As a further point of differentiation, most cases of multiple myeloma will exhibit subnormal levels of the uninvolved immunoglobulin classes when these are quantitated. This is not so in non-myeloma nephrosis.

With the widespread use of biochemical profiles in health care, early cases of multiple myeloma are being detected, including some that may not easily fulfill the diagnostic criteria for the disease. Among the suspects are individuals with serum protein electrophoretic patterns indistinguishable from those found with multiple myeloma or macroglobulinemia. They may be apparently healthy persons or patients with diseases that may or may not have immunologic correlates. Long term follow-up of these patients has disclosed examples of each of three theoretically predictable courses: disappearance of the monoclonal pattern without evidence of residual disease, progression to diagnosable malignancy, or stability of the process. Waldenström has named the stable cases benign monoclonal gammopathy. The condition is diagnosed by exclusion: (1) the monoclonal protein level does not exceed 3 gm per dl, (2) it does not progressively increase from its initial level on serial examination, (3) levels of the uninvolved immunoglobulins are not decreased below normal, (4) Bence Jones protein is rarely detected in the urine even with concentration of the specimen, (5) there is no evidence of abnormal bone destruction or new bone formation, (6) marrow plasmacytosis is diffuse or focal but never tumorous and (7) there is no evidence of
infiltrative or destructive lesions in the kidney or other organs at risk in multiple myeloma.

A recent report describes two cases of idiopathic Bence Jones proteinuria at levels near 100 mg per dl and with associated monoclonal IgG serum protein levels between 2 and 3 gm per dl. Each case had been stable for over seven years without other evidence of disease. Since the amount of monoclonal immunoprotein is directly proportional to the number of grams of specific protein producing plasma cells, benign gammopathies with prominent “M-spikes” exhibit greater marrow plasmacytosis and are harder to distinguish from multiple myeloma. The decision to diagnose malignancy and to place the patient on a chemotherapy regimen depends upon the cautious assessment of bone marrow specimens, careful evaluation of Bence Jones proteinuria (if present) and the detection of systemic manifestations of multiple myeloma.

Each of the malignant monoclonal gammopathies has subtle characteristics of its own related to the chemical or biological properties of the unique immunoprotein. Thus, IgA has a high carbohydrate content, and IgA producing plasma cells have a reddish (“flaming”) tint when examined with good Romanowsky stains. In addition, in IgA myeloma PAS-positive intranuclear inclusions and thesaurocytes are prominent. IgE myeloma patients show a pronounced peripheral blood plasmacytosis. Hyperviscosity is common with IgM immunoglobulinemia and is sometimes seen with IgA or IgG₃ myeloma. These molecules easily tend to form aggregates and complexes. Cryoimmunoglobulins may also have distinctive molecular associations. The role of the newly detected J-chain (“joining” chain) in this problem is yet to be elucidated. As our knowledge of immunology expands, the information and insights gained will further extend the clinical diagnostic approach to the monoclonal gammopathies and lead to improved therapy.

References


