

Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group

THE INTERNATIONAL MYELOMA WORKING GROUP*

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Summary. The monoclonal gammopathies are a group of disorders associated with monoclonal proliferation of plasma cells. The characterization of specific entities is an area of difficulty in clinical practice. The International Myeloma Working Group has reviewed the criteria for diagnosis and classification with the aim of producing simple, easily used definitions based on routinely available investigations. In monoclonal gammopathy of undetermined significance (MGUS) or monoclonal gammopathy, unattributed/unassociated (MG[u]), the monoclonal protein is < 30 g/l and the bone marrow clonal cells $< 10\%$ with no evidence of multiple myeloma, other B-cell proliferative disorders or amyloidosis. In asymptomatic (smouldering) myeloma the M-protein is ≥ 30 g/l and/or bone marrow clonal cells $\geq 10\%$ but no related organ or tissue impairment (ROTI)(end-organ damage), which is typically manifested by

increased calcium, renal insufficiency, anaemia, or bone lesions (CRAB) attributed to the plasma cell proliferative process. Symptomatic myeloma requires evidence of ROTI. Non-secretory myeloma is characterized by the absence of an M-protein in the serum and urine, bone marrow plasmacytosis and ROTI. Solitary plasmacytoma of bone, extramedullary plasmacytoma and multiple solitary plasmacytomas (\pm recurrent) are also defined as distinct entities. The use of these criteria will facilitate comparison of therapeutic trial data. Evaluation of currently available prognostic factors may allow better definition of prognosis in multiple myeloma.

Keywords: classification, monoclonal, gammopathies, multiple myeloma.

The monoclonal gammopathies (paraproteinaemias) are a group of disorders associated with monoclonal proliferation of plasma cells. This group of disorders has also been referred to as paraproteinaemias, dysproteinaemias or immunoglobulinopathies. They are characterized by the secretion of electrophoretically and immunologically homogeneous (monoclonal) proteins. Each monoclonal protein (M-protein, myeloma protein or paraprotein) consists of two heavy (H) polypeptide chains of the same class and subclass and two light (L) polypeptide chains of the same type. The heavy polypeptide chains are IgG, IgA, IgM, IgD and IgE (gamma, alpha, mu, delta, epsilon) while the light chain types are kappa (κ) and lambda (λ). The characterization of specific entities continues to be an area of potential difficulty in clinical practice and there is a need to review classification with a view to improving the definition of these disorders.

IDENTIFICATION AND MEASUREMENT OF MONOCLONAL PROTEINS

Both serum and urine should be assessed for monoclonal proteins (M-proteins/paraproteins) when there is a clinical suspicion of B-cell neoplasia such as multiple myeloma, light-chain amyloidosis (AL), Waldenström's macroglobulinaemia or related B-cell lymphoproliferative disorders. Agarose gel electrophoresis is preferred to screen for the presence of M-proteins. Immunofixation is now the gold standard and should be performed to confirm the presence of an M-protein and to distinguish its heavy chain and light chain type. It is essential to differentiate monoclonal gammopathies from polyclonal gammopathies because monoclonal gammopathies are neoplastic or potentially neoplastic, whereas polyclonal gammopathies (with increase in both types of light chain) result from an inflammatory or reactive process such as chronic liver disease, connective tissue disorders, chronic infections, etc. (Dispenzieri *et al.*, 2001).

Serum protein electrophoresis should be performed whenever multiple myeloma or related disorders are suspected or in the presence of unexplained weakness or fatigue, anaemia,

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back pain, osteopenia, osteolytic lesions or spontaneous fractures, elevation of the erythrocyte sedimentation rate or plasma viscosity, hypergammaglobulinaemia, hypercalcaemia, Bence Jones proteinuria, renal insufficiency, immunoglobulin deficiency or recurrent infections. An M-protein is usually seen as a narrow peak in the densitometer tracing or as a dense, discrete band on the agarose gel.

Immunofixation should be performed when a peak or band is seen on protein electrophoresis or when multiple myeloma or related disorders are suspected, despite a normal serum protein electrophoretic pattern. Immunofixation is especially helpful when searching for a small M-protein in patients with AL, solitary plasmacytoma of bone, extramedullary plasmacytoma, heavy chain disease, light chain deposition disease, or after successful treatment of multiple myeloma or macroglobulinaemia. Immunofixation will detect a serum M-protein of 0.2 g/l and a urine M-protein of 0.04 g/l. It must be kept in mind that an M-protein may be present when the total protein concentration, beta and gamma globulin levels, and quantitative immunoglobulin values are all within normal limits. A small M-protein may be concealed in the normal β or γ areas and easily overlooked. Furthermore, the presence of a monoclonal light chain (Bence Jones proteinuria) requires immunofixation because it is rarely seen in the agarose gel pattern. In addition, in the heavy chain diseases a discrete band or spike is often not apparent. IgD and IgE monoclonal proteins are usually small and may be overlooked. Immunofixation should also be performed in patients with unexplained peripheral neuropathy, carpal tunnel syndrome, refractory congestive heart failure, nephrotic syndrome, orthostatic hypotension or malabsorption, because a monoclonal protein strongly suggests the possibility of primary systemic amyloidosis (AL).

Quantification of the M-protein by densitometry gives prognostic information in monoclonal gammopathy of undetermined significance (MGUS) and a baseline for monitoring disease activity in the malignant causes of paraproteinaemia.

Urine analysis is important in the evaluation of multiple myeloma and related disorders. Immunofixation of an aliquot from an adequately concentrated 24-h urine specimen is recommended. Immunofixation can also be performed on the first morning specimen or a random sample. An M-protein appears as a dense, localized band on the agarose gel or a tall, narrow, homogeneous peak in the densitometer tracing. Its amount can be calculated on the basis of the size of the spike and the amount of total protein in the 24-h specimen. It is not uncommon for a patient to have a negative protein reaction and no spike on electrophoresis but for immunofixation of the concentrated urine specimen to show a monoclonal light chain. Immunofixation should be performed in all patients with multiple myeloma, Waldenström's macroglobulinaemia, AL, solitary plasmacytoma or heavy chain disease. It should also be performed in patients with MGUS if the M-spike is greater than 15 g/l (Kyle, 1999). Immunofixation should also be performed on the urine of every adult patient over 40 years of age who develops an unexplained nephrotic syndrome.

The presence of a monoclonal light chain in nephrotic urine is indicative of AL or light chain deposition disease in almost all instances.

Light chains may not be detectable in urine because of reabsorption by the proximal renal tubules. For this reason, variation in glomerular filtration and tubular function, assay of light chains in serum can provide a more sensitive method of detecting and monitoring light chain disease. This is particularly relevant in patients with non-secretory myeloma, solitary plasmacytoma or primary systemic amyloidosis (Drayson *et al*, 2001; Katzmann *et al*, 2002).

RATIONALE FOR AN INTERNATIONAL CLASSIFICATION SYSTEM

It is a challenge to develop fixed criteria for the diagnosis of the monoclonal gammopathies because they often have overlapping features. If one attempts to cover all clinical and laboratory parameters, the definitions are very complex and lengthy. This will result in definitions that will be difficult to accept and follow in everyday practice. The International Myeloma Working Group decided that the criteria should be simple, easy to use and based upon routinely available laboratory tests rather than attempting to cover all diagnostic situations.

A wide variety of diagnostic criteria have been utilized by various groups of investigators such as the Medical Research Council of the United Kingdom, Nordic Myeloma Study Group, Spanish (Pethema) Study Group, Eastern Cooperative Oncology Group, Southwest Oncology Group and Chronic Leukaemia Myeloma Task Force of the National Cancer Institute. A uniform approach would facilitate comparison of therapeutic trial data.

MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE (MGUS)

Since Waldenström's introduction of the term essential hyperglobulinaemia in 1952, many similar terms have been used including benign, idiopathic, asymptomatic, non-myelomatous, discrete, cryptogenic, lanthanic and rudimentary monoclonal gammopathy, dysimmunoglobulinaemia, asymptomatic paraimmunoglobulinaemia and idiopathic paraproteinaemia. The term benign monoclonal gammopathy is misleading because at diagnosis it is not known whether the process will remain stable and asymptomatic or will develop into symptomatic multiple myeloma, macroglobulinaemia, amyloidosis or a related lymphoplasma cell disorder.

The term MGUS denotes the presence of a monoclonal protein in persons without evidence of multiple myeloma, macroglobulinaemia, amyloidosis, or other related plasma cell or lymphoproliferative disorders. It was introduced over a quarter of a century ago (Kyle & Bayrd, 1976; Kyle, 1978). MGUS occurs in 3% of persons over 70 years of age and 1% of persons older than 50 years (Axelsson *et al*, 1966; Kyle *et al*, 1972; Saleun *et al*, 1982). The incidence increases with advancing age and is higher in African-Americans than in Caucasians (Cohen *et al*, 1998).

The original Mayo Clinic series of 241 MGUS patients, diagnosed in 1970 or earlier, was followed for 24–38 years. At the time of analysis, 10% were alive with a stable M-protein while more than half had died of unrelated causes without developing multiple myeloma or a related disorder. Approximately one-quarter of the patients developed multiple myeloma, macroglobulinaemia, amyloidosis or related lymphoproliferative disorders, with an actuarial rate of 16% at 10 years, 33% at 20 years and 40% at 25 years. The interval from the time of recognition of the M-protein to the diagnosis of serious disease ranged from two to 29 years (median, 10 years). In seven patients multiple myeloma was diagnosed more than 20 years after detection of the serum M-protein (Kyle, 1993).

During a 20-year follow-up of 64 Swedish patients from a survey of 6995 persons, Axelsson (1986) reported that three patients had died of multiple myeloma or lymphoma while four of the 19 surviving patients had shown an increase in the serum M-protein or had developed Bence Jones proteinuria. In another group of 128 patients with MGUS, followed for 12–156 months (median 56 months), 13 developed malignant disease. The actuarial probability of developing malignant disease was 8.5% at 5 years and 19.2% at 10 years (Bladé *et al.*, 1992).

Isaksson *et al.* (1996) reported that 15 (26%) of 57 patients developed a malignant plasma cell process during follow-up. In another study, 6.8% of 335 patients with MGUS showed progression during a median follow-up of 70 months (Baldini *et al.*, 1996). In a follow-up of 263 cases of MGUS, the actuarial probability of malignant transformation was 31% at 20 years (Pasqualetti *et al.*, 1997). Cesana *et al.* (2002) reported that in 5.8% of 1104 patients, MGUS evolved to multiple myeloma or related disorders.

In a recent series, 1384 MGUS patients, residing in south-eastern Minnesota, were diagnosed at the Mayo Clinic between 1960 and 1994. During the 11 009 person years of follow-up, 115 of the 1384 patients with MGUS showed progression to multiple myeloma or a related lymphoplasma cell disorder. The relative risk (RR), when compared to the white population of the Surveillance, Epidemiology and End-Results Program (SEER), was as follows: multiple myeloma (RR 25), IgM lymphoma (RR 2.4), primary amyloidosis (RR 8.4), macroglobulinaemia (RR 46), chronic lymphocytic leukaemia (RR 0.9) and plasmacytoma (RR 8.5). The overall relative risk for progression was 7.3 times the expected rate. In 32 additional patients the M-protein level increased to more than 30 g/l or the percentage of plasma cells in the bone marrow increased to more than 10%, but they have not progressed to overt myeloma or a related disorder. The cumulative probability of progression was 12%, 25% and 30% at 10, 20 and 25 years respectively. The risk of progression of MGUS to multiple myeloma or a related disorder was about 1% per year. Patients with IgM and IgA M-proteins showed an increased risk of progression compared with patients who had IgG M-proteins (principally to lymphoproliferative diseases other than multiple myeloma in IgM MGUS). However, concentration of serum M-protein was the most important risk factor for progression. Risk of progression with an M-protein value of 15 g/l was almost

twofold greater than the risk of progression with a value of 5 g/l, while the risk of progression with an M-protein value of 25 g/l was 4.6 times that of the reference value of 5 g/l. Uninvolved (normal or background) immunoglobulins were reduced in 38% of cases, but this reduction did not identify patients in whom progression developed. In addition, the presence of small amounts of monoclonal light chain in the urine did not predict progression (Kyle *et al.*, 2002).

Considerable debate occurred about the designation of a specific serum M-protein level. Many patients with symptomatic multiple myeloma will have a serum M-protein of less than 30 g/l. The size of the M-protein is not a prognostic factor in multiple myeloma. However, most clinicians think of a serum M-protein of 30 g/l as a watershed number and one in which they look closely for the possibility of multiple myeloma. An M-spike of greater than 30 g/l usually indicates the presence of multiple myeloma. While an IgA value of 20–25 g/l might be equivalent to an IgG M-protein of 30 g/l, the use of a single value of 30 g/l, although arbitrary, would make for simplicity and be more likely to be adopted in practice.

The presence of a monoclonal light chain in the urine is generally considered as a finding that suggests the diagnosis of multiple myeloma. However, almost one-third of patients with well-documented MGUS had a small amount of monoclonal light chain in the urine, which is not a risk factor for progression to multiple myeloma (Kyle *et al.*, 2002). Some patients with a large amount of Bence Jones proteinuria (>1 g/24 h) may follow a benign course. Although these patients with idiopathic Bence Jones proteinuria are at high risk for the development of multiple myeloma or primary systemic amyloidosis, they may remain stable for many years and should be observed indefinitely (Kyle & Greipp, 1982).

While the level of M-protein is a major risk factor for progression to multiple myeloma, consideration also needs to be given to changes in the plasma cells even though a bone marrow examination is frequently not performed for small M-proteins. Approximately 5% of patients with symptomatic myeloma will have a plasma cell content <10%, but this is usually due to an inadequate specimen or to the possibility of uneven distribution of plasma cells in the bone marrow. Patients with a plasma cell content >10% may be asymptomatic but they are likely to develop symptomatic multiple myeloma and require treatment. Plasma cells in myeloma are phenotypically distinct from their normal counterparts by virtue of the absence of CD19 expression or expression of CD56. Using flow cytometry, phenotypically 'neoplastic' plasma cells are demonstrable with phenotypically normal plasma cells (Ocqueteau *et al.*, 1998; Rawstron *et al.*, 2000). In the future, the monitoring of such changes may provide additional information with regard to progression. In practice it is usual to use an arbitrary figure of less than 10% plasma cells in the bone marrow aspirate and minimal infiltration in a trephine biopsy.

The term MGUS has been widely adopted but, for patients, 'undetermined significance' can be difficult to understand and accept. An alternative would be to use the term primary monoclonal gammopathy, although this

Table I. Monoclonal gammopathy of undetermined significance (MGUS) or monoclonal gammopathy, unattributed/unassociated (MG[u]).

M-protein in serum < 30 g/l
Bone marrow clonal plasma cells < 10% and low level of plasma cell infiltration in a trephine biopsy (if done)
No evidence of other B-cell proliferative disorders
*No related organ or tissue impairment (no end organ damage, including bone lesions)

*AL amyloid and the IgM paraprotein-related neurological syndromes would be instances of 'MG associated with...'

would be more likely to convey the impression of a disease entity and also requires the introduction of 'secondary monoclonal gammopathy'. Another approach would be to simply delineate monoclonal gammopathy as a biochemical finding and qualify it as unattributed to or unassociated with any disease entity, i.e. monoclonal gammopathy, unattributed/unassociated or MG(u). There is a significant risk of transformation to multiple myeloma or a related disorder and consequently such patients should be monitored throughout their lives for evidence of progression.

The criteria recommended by the International Myeloma Working Group for the diagnosis of MGUS are shown in Table I. Obviously, patients must have no related organ or tissue impairment (end organ damage including bone lesions) in order to be classified as MGUS. Because of the risk of developing a disease requiring therapy, these individuals should be monitored at periodic intervals indefinitely for evidence of progression. The duration of follow-up for assigning the diagnosis is not, however, included in the definition because patients with MGUS are at risk indefinitely, although with a low risk plasma cell proliferative process.

RELATED ORGAN OR TISSUE IMPAIRMENT (ROTI) (END ORGAN DAMAGE)

The effect of end organ damage related to the plasma cell proliferative process is a critical aspect in the diagnosis of these disorders (Table II). A normocytic normochromic

Table II. Myeloma-related organ or tissue impairment (end organ damage) (ROTI) due to the plasma cell proliferative process.

*Calcium levels increased: serum calcium > 0.25 mmol/l above the upper limit of normal or > 2.75 mmol/l
*Renal insufficiency: creatinine > 173 mmol/l
*Anaemia: haemoglobin 2 g/dl below the lower limit of normal or haemoglobin < 10 g/dl
*Bone lesions: lytic lesions or osteoporosis with compression fractures (MRI or CT may clarify)
Other: symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (> 2 episodes in 12 months)

*CRAB (calcium, renal insufficiency, anaemia or bone lesions).

anaemia is present at the time of diagnosis in two-thirds of patients with multiple myeloma but eventually occurs in almost all patients. Anaemia is considered to be present when the haemoglobin is 2 g/dl below the normal level for the laboratory or if the haemoglobin falls to 10 g/dl. Hypercalcaemia, which is present in 15–20% of myeloma patients at presentation, is a major but treatable cause of renal insufficiency. A serum calcium level > 0.25 mmol/l above normal or a value of 2.75 mmol/l is considered as representing hypercalcaemia. The serum creatinine is 173 mmol/l or more in one-fifth of multiple myeloma patients at diagnosis. Conventional radiographs show abnormalities consisting of lytic lesions, osteoporosis or fractures in nearly 80% of patients with multiple myeloma at diagnosis. The vertebrae, skull, thoracic cage, pelvis, and humeri and femori are the most frequent sites of involvement and should be included in the films. Technetium-99m bone scanning is inferior to conventional radiography because it detects only bone formation and should not be used. Computerized tomography (CT) or magnetic resonance imaging (MRI) is helpful in patients who have compression fractures or skeletal pain without abnormalities on the radiographs or a neurological deficit from spinal cord compression. The MRI, if performed, shows no abnormalities in patients with MGUS (Bellaïche *et al.*, 1997).

Additional evidence of end organ damage consists of symptomatic hyperviscosity, primary systemic amyloidosis or recurrent bacterial infections (> 2 episodes in 12 months). Serum viscosity levels do not correlate well with the patient's symptoms or clinical findings. Examination of the fundus reveals dilatation of the veins and haemorrhages. These findings are more important in evaluating the patient than the actual viscosity level. Primary systemic amyloidosis (AL) occurs in almost 10% of patients with multiple myeloma and is an indication for therapy, although the association of only an M-protein with AL amyloid occurs, requiring patient management to be considered individually. The neurological syndromes occurring in association with isolated IgM monoclonal gammopathy also require separate consideration. Susceptibility to recurrent bacterial infections may result from impairment of antibody response due to the reduction of normal uninvolved immunoglobulins and neutropenia or a combination of these factors.

The evidence of myeloma-related organ or tissue damage or functional impairment may frequently not be clear cut and the diagnosis of transition from asymptomatic myeloma to multiple myeloma requiring treatment (symptomatic myeloma) may need to be the subject of multidisciplinary critical assessment.

ASYMPTOMATIC MYELOMA ('SMOULDERING MULTIPLE MYELOMA')

The point of transition from MGUS to myeloma without anaemia, renal insufficiency, or skeletal lesions attributable to the neoplastic plasma cell proliferation is not sharply defined. If the M-protein level is ≥ 30 g/l and/or the bone marrow contains $\geq 10\%$ plasma cells, it would be reasonable to apply the term asymptomatic myeloma (smouldering

Table III. Asymptomatic myeloma (smouldering myeloma).

M-protein in serum ≥ 30 g/l and/or
Bone marrow clonal plasma cells $\geq 10\%$
No related organ or tissue impairment (no end organ damage, including bone lesions) or symptoms

myeloma). These patients may have small amounts of M-protein in the urine and decreased concentration of normal immunoglobulins in the serum, but the plasma cell labelling index is low (Kyle & Greipp, 1980). These patients must have no evidence of related organ or tissue impairment (end organ damage). Biologically, patients with asymptomatic myeloma are similar to MGUS but it is difficult to accept that diagnosis when the serum M-protein level is ≥ 30 g/l, or the bone marrow contains $\geq 10\%$ plasma cells. These patients must be followed up closely because symptomatic myeloma develops in many of them. They should not be treated unless progression occurs. Although the term 'smouldering myeloma' has been frequently used to describe this state, the term can be difficult for patients to understand and accept. The use of asymptomatic to describe a stage of disease of which there are no symptoms and no related organ or tissue impairment is preferred. Patients categorized as having Durie-Salmon stage I disease would be included in this category, as would asymptomatic patients with an apparently solitary plasmacytoma of bone who have abnormalities detected by an MRI. The criteria agreed upon by the International Myeloma Working Group are presented in Table III.

SYMPTOMATIC MULTIPLE MYELOMA

Multiple myeloma (Kahler's disease, myelomatosis) is characterized by the neoplastic proliferation of a single clone of plasma cells producing an M-protein. The clone of plasma cells proliferates in the bone marrow and frequently invades the adjacent bone, producing skeletal destruction that results in bone pain and pathological fractures. Anaemia, hypercalcaemia and renal insufficiency are other concomitant features. Bone pain, particularly in the spine or chest and less often in the extremities, is present at the time of diagnosis in two-thirds of patients. Weakness and fatigue are common and are often due to anaemia. Anaemia is present initially in more than two-thirds of patients, while renal insufficiency (creatinine greater than 173 mmol/l) is present in one-fifth of patients at diagnosis. A serum M-spike is seen in 80% of patients at diagnosis, while immunofixation reveals an M-protein in over 90%. An IgG M-protein is found in about one-half of patients, while one-fifth have an IgA M-protein, and monoclonal light chain only (light chain myeloma) is found in almost 20% of cases. The urine contains an M-protein in approximately 75% of patients. Ninety-seven per cent of patients with multiple myeloma have an M-protein in the serum or urine at the time of diagnosis. Hypercalcaemia is present in nearly 20% of patients initially and is a major but treatable cause of

Table IV. Laboratory tests for multiple myeloma.

History and physical examination
Complete blood count and differential peripheral blood smear
Chemistry screen including calcium and creatinine
Serum protein electrophoresis, immunofixation
Nephelometric quantification of immunoglobulins
Routine urinalysis, 24 h urine collection for electrophoresis and immunofixation
Bone marrow aspirate and trephine biopsy (cytogenetics, immunophenotyping and plasma cell labelling index if available)
Radiological skeletal bone survey including spine, pelvis, skull, humeri and femurs. An MRI may be helpful
$\beta 2$ microglobulin, C-reactive protein, and lactate dehydrogenase
Measurement of free monoclonal light chains if available

Table V. Symptomatic multiple myeloma.

M-protein in serum and/or urine
Bone marrow (clonal) plasma cells* or plasmacytoma
Related organ or tissue impairment (end organ damage, including bone lesions)

*If flow cytometry is performed, most plasma cells (> 90%) will show a 'neoplastic' phenotype.

Some patients may have no symptoms but have related organ or tissue impairment.

renal insufficiency. Monoclonal plasma cells usually account for 10% or more of all nucleated cells but they may range from less than 5% to almost 100%. Bone marrow involvement may be focal rather than diffuse, requiring repeated bone marrow examinations for diagnosis. Identification of a monoclonal immunoglobulin in the cytoplasm of plasma cells by immunoperoxidase staining or immunofluorescence is helpful for differentiating monoclonal plasma cell proliferation from reactive plasmacytosis due to connective tissue disorders, chronic liver disease, chronic infections or metastatic carcinoma. Conventional radiographs reveal abnormalities consisting of lytic lesions, osteoporosis or fractures in nearly 80% of patients at diagnosis. The suggested laboratory tests for the diagnosis of multiple myeloma are shown in Table IV.

The criteria agreed upon by the International Myeloma Working Group for the diagnosis of symptomatic multiple myeloma are shown in Table V. No level of serum M-protein or urine M-protein was included in the proposed diagnostic criteria. Approximately 40% of patients with symptomatic multiple myeloma have an M-protein less than 30 g/l. However, 97% of patients with multiple myeloma will have an M-protein in the serum or in the urine. No minimal level of clonal bone marrow plasma cells was designated because 5% of patients with symptomatic myeloma have fewer than 10% plasma cells in the bone marrow. The most critical criterion for symptomatic or treatable disease is the evidence of organ or tissue impairment (end organ damage) manifested by anaemia, hypercalcaemia, lytic bone lesions, renal insufficiency, hyperviscosity, amyloidosis or recurrent infections.

Definitions of multiple myeloma and criteria for treatment adopted by study groups in various countries have differed. Agreement to adopt a uniform approach would be advantageous in collating data internationally and carrying out treatment overviews and meta-analyses. An agreed-upon definition of symptomatic multiple myeloma requiring treatment would also remove the need for the use of older staging systems. Inevitably, the newer prognostic indicators such as cytogenetic changes will result in more accurate stratification of risk groups. The International Myeloma Working Group has now initiated a major investigation of prognostic features with a view to producing an international prognostic index (IPI) for multiple myeloma. Response criteria have been adopted by the International Myeloma Working Group (Bladé *et al*, 1998). These criteria are currently undergoing review and some modification.

NON-SECRETORY MYELOMA

Patients with non-secretory myeloma have no monoclonal protein in either the serum or the urine with immunofixation (Table VI) (Cavo *et al*, 1985). This occurs in only 3% of patients with symptomatic multiple myeloma. The monoclonal protein should be identified in the plasma cells by immunoperoxidase or immunofluorescence. More than a dozen patients in whom no M-protein was found in the plasma cells have been described. These patients apparently do not synthesize an M-protein. Renal insufficiency is less common than in patients with secretory multiple myeloma. The more carefully the serum and urine are examined for evidence of an M-protein, the fewer cases of non-secretory myeloma will be found. The advent of accurate light-chain assays is likely to result in further definition of diagnosis; in fact, two-thirds of patients with non-secretory multiple myeloma based upon immunofixation had an elevation of free monoclonal light chains in the serum (Drayson *et al*, 2001). Treatment for non-secretory myeloma is the same as for multiple myeloma. Response to therapy and survival of patients with non-secretory myeloma are similar to those in patients with a serum or urinary M-component.

SOLITARY PLASMACYTOMA OF BONE

Solitary plasmacytoma of bone is uncommon and occurs in 3–5% of patients with plasma cell neoplasms. It occurs more commonly in men than in women (65% vs. 35%) and the median age is about a decade younger than that of patients with multiple myeloma (55 vs. 65 years). The most common symptom at presentation is pain at the site of the skeletal lesion. Severe back pain or spinal cord compression

Table VI. Non-secretory myeloma.

No M-protein in serum and/or urine with immunofixation
Bone marrow clonal plasmacytosis $\geq 10\%$ or plasmacytoma
Related organ or tissue impairment (end organ damage, including bone lesions)

Table VII. Solitary plasmacytoma of bone.

No M-protein in serum and/or urine*
Single area of bone destruction due to clonal plasma cells
Bone marrow not consistent with multiple myeloma
Normal skeletal survey (and MRI of spine and pelvis if done)
No related organ or tissue impairment (no end organ damage other than solitary bone lesion)*

*A small M-component may sometimes be present.

may be the presenting feature; a pathological fracture may be the first symptom. Soft tissue extension of a plasmacytoma, as in a rib, may result in a palpable mass. The axial skeleton is more commonly involved than the appendicular skeleton. Thoracic vertebrae are more commonly involved than lumbar or cervical vertebrae. Involvement of the distal appendicular skeleton below the knees or elbows is rare. The diagnosis of solitary plasmacytoma of bone is based on histological evidence of a tumour consisting of monoclonal plasma cells identical to those seen in multiple myeloma (Table VII). In addition, complete skeletal radiographs must show no other lesions of multiple myeloma, but the bone marrow aspirate may contain a few plasma cells. A MRI of the spine and pelvis may show unsuspected and asymptomatic skeletal lesions. This finding would place the patient in the asymptomatic or smouldering myeloma category. The presence of marrow involvement on the MRI is associated with a higher rate of relapse. In a group of 23 patients with solitary plasmacytoma of the thoracolumbar spine, multiple myeloma developed in seven of eight patients with a solitary lesion on plain roentgenographs alone but in only one of seven patients who also had negative results on MRI (Liebross *et al*, 1998). Typically, immunofixation of the serum and concentrated urine should show no M-protein, but approximately 50% of patients do have a small M-protein in the serum or urine. Most patients with solitary plasmacytoma of bone have normal uninvolved immunoglobulin levels (Dimopoulos *et al*, 2000). There should be no evidence of anaemia, hypercalcaemia or renal insufficiency related to the plasmacytoma. Treatment consists of radiation in the range of 40 Gy to 50 Gy. Radiotherapy of the solitary lesion usually results in disappearance of the M-protein. However, some patients may remain stable for long periods despite the persistence of an M-protein after tumoricidal radiation. The persistence of an M-protein following tumoricidal radiation to an apparent solitary plasmacytoma is associated with an increased risk of progression (Wilder *et al*, 2002). Solitary plasmacytomas > 5 cm have a greater incidence of progression (Tsang *et al*, 2001). There is no convincing evidence that prophylactic chemotherapy affects the incidence of conversion to multiple myeloma. Progression, when it occurs, usually does so within 3–4 years, but the most uncertain criterion for diagnosis is the duration of observation necessary before deciding that the disease will not become generalized. Almost 50% of patients with solitary plasmacytoma are alive at 10 years; 25–40% are surviving disease-free at 10

years. Overt multiple myeloma occurs in almost 50% of patients with solitary plasmacytoma of bone. However, progression may occur as long as 15 years later. Multiple solitary plasmacytomas without evidence of multiple myeloma occur in up to 5% of patients.

EXTRAMEDULLARY PLASMACYTOMA

Extramedullary plasmacytoma is a plasma cell tumour that arises outside the bone marrow (Table VIII). The upper respiratory tract, including the nasal cavity and sinuses, nasopharynx and larynx, is the most frequent location of lesions. Epistaxis, rhinorrhoea and nasal obstruction are the most frequent symptoms. Extramedullary plasmacytomas may also occur in virtually any organ including the gastrointestinal tract, central nervous system, urinary bladder, thyroid, breasts, testes, parotid gland or lymph nodes. There is a predominance of IgA monoclonal protein. The diagnosis is made on the basis of finding a monoclonal plasma cell tumour in an extramedullary site and the absence of multiple myeloma on the basis of bone marrow, radiography, and appropriate studies of blood and urine. Treatment consists of tumoricidal radiation (40–50 Gy) and is often curative. The plasmacytoma may occur locally or metastasize to regional nodes. In contrast to solitary plasmacytoma of bone, symptomatic multiple myeloma occurs in only 15% of patients (Alexiou *et al*, 1999).

MULTIPLE SOLITARY PLASMACYTOMAS (± RECURRENT)

Multiple solitary plasmacytomas, which may be recurrent and without evidence of multiple myeloma, occur in up to

Table VIII. Extramedullary plasmacytoma.

No M-protein in serum and/or urine*
Extramedullary tumour of clonal plasma cells
Normal bone marrow
Normal skeletal survey
No related organ or tissue impairment (end organ damage including bone lesions)

*A small M-component may sometimes be present.

Table IX. Multiple solitary plasmacytomas (± recurrent).

No M-protein in serum and/or urine*
More than one localized area of bone destruction or extramedullary tumour of clonal plasma cells which may be recurrent
Normal bone marrow
Normal skeletal survey and MRI of spine and pelvis if done
No related organ or tissue impairment (no end organ damage other than the localized bone lesions)

*A small M-component may sometimes be present.

5% of patients with an apparently solitary plasmacytoma (Table IX). Lesions may be in soft tissue (extramedullary) or bone (osseous). There is no evidence of bone marrow involvement or other skeletal lesions. Multiple plasmacytomas may be treated by tumoricidal radiation when recurrent if there is no evidence of multiple myeloma. Large numbers of solitary plasmacytomas or recurrent lesions at short intervals are an indication for systemic therapy such as autologous stem cell transplantation.

PLASMA CELL LEUKAEMIA

Plasma cell leukaemia has been previously delineated by the finding of a peripheral blood absolute plasma cell count of at least $2.0 \times 10^9/l$ and more than 20% plasma cells in the peripheral blood differential white cell count. Plasma cell leukaemia may be classified as primary when it presents in the leukaemic phase or as secondary when there is leukaemic transformation of a previously recognized multiple myeloma. Approximately 60% of patients with plasma cell leukaemia have the primary type. Patients with primary plasma cell leukaemia are younger and have a higher incidence of hepatosplenomegaly and lymphadenopathy, a higher platelet count, fewer lytic bone lesions, a smaller serum M-protein level, and longer survival than do patients with secondary plasma cell leukaemia (Noel & Kyle, 1987; Garcia-Sanz *et al*, 1999). If looked for, plasma cells may frequently be detected in the peripheral blood. An alternative would be to use the term multiple myeloma with peripheral blood involvement, recognizing that appreciable numbers of circulating plasma cells would be regarded as a poor prognostic feature, particularly when seen later in the course of disease.

CONCLUSIONS

This review has considered the laboratory investigatory and clinical features that are used to characterize the monoclonal gammopathies. Criteria to define individual disorders are suggested with specific tabulated recommendations for the following: monoclonal gammopathy of undetermined significance (MGUS) for which the alternative term monoclonal gammopathy, unassociated/unattributed (MG[u]) is suggested; asymptomatic myeloma (to replace 'smouldering myeloma'); symptomatic multiple myeloma; non-secretory myeloma; solitary plasmacytoma of bone; extramedullary plasmacytoma; and multiple solitary plasmacytomas (± recurrent). Additional systems of staging are not necessarily required but it is anticipated that prognostic groupings may be better defined as a result of the evaluation of prognostic factors that is currently underway.

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