Should Bone Marrow Examination be Routinely Performed for the Diagnosis of Monoclonal Gammopathy of Undetermined Significance?

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Abstract

Background: Monoclonal gammopathy of undetermined significance is defined by the presence of: low serum and/or urine monoclonal protein level; less than 10% plasma cells in bone marrow; normal serum calcium, creatinine and hemoglobin levels; and no bone lesions on full skeletal X-ray survey.

Objectives: To study the necessity of bone marrow examination for the diagnosis and clinical course of MGUS.

Methods: We retrospectively screened the medical records of all patients in whom monoclonal protein was found in the serum during 2001–2002 in the medical laboratories of Meir Medical Center. Asymptomatic patients who had serum monoclonal immunoglobulin G < 3.0 g/dl or IgA < 2.0 g/dl or IgM < 1.0 g/dl without anemia, renal failure, hypercalcemia or any bone lesions on skeletal survey were eligible. Full records of patients who were evaluated in the hematology clinic were available (group 1). The remaining patients were followed by their family physicians; thus we had access only to their electronic files including laboratory results and new diagnoses (group 2). Demographic and clinical parameters as well as clinical course were evaluated.

Results: Both groups (57 and 255 patients, respectively) had similar demographic, laboratory and clinical characteristics. Bone marrow examination was performed in 30 of 57 patients (group 1): 16 were normal, 8 had an excess of normal plasma cells, and 6 had excess of pathologic plasma cells. However, only in two of the latter six could a diagnosis of multiple myeloma be established. All group 1 patients were followed for 22 ± 11 months and only two developed overt multiple myeloma. During the same period, 6 of 255 patients (group 2) were diagnosed as multiple myeloma and 3 as MGUS in other hospitals. The rest had a stable course with no change in their laboratory values.

Conclusions: Our findings suggest that bone marrow examination should not be performed routinely in patients who fulfill strict clinical and laboratory criteria of MGUS.

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The term Monoclonal Gammopathy of Undetermined Significance indicates the presence of a monoclonal protein in patients with no features consistent with multiple myeloma, Waldenström macroglobulinemia or primary amyloidosis. MGUS is defined by the presence of all three diagnostic criteria: a) low serum and/or urine M protein level (serum immunoglobulin G < 3.0 g/dl, serum IgA < 2.0 g/dl, urine monoclonal kappa or lambda < 1.0 g/24 hours); b) less than 10% bone marrow plasma cells; and c) normal serum calcium, creatinine and hemoglobin levels, no bone lesions on full skeletal X-ray survey, and no clinical or laboratory features of amyloidosis or light-chain deposition disease [1].

The short and long-term prognosis of patients with MGUS is good. Their median survival rate is only slightly less than the survival of a comparable population, while the risk of progression to multiple myeloma or related disorder is about 1% per year [2,3].

The main purpose of bone marrow examination in patients with MGUS is to differentiate it from multiple myeloma, the malignant spectrum of plasma cell disorders, or to estimate the risk of its progression to multiple myeloma. Most textbooks and guidelines indicate that bone marrow examination should be included in the initial workup of patients who otherwise comply with the diagnostic criteria of MGUS [1,4,5]. In contrast, Kyle et al. [3] suggested that bone marrow examination is unnecessary in cases of a low concentration of M protein, unless other features suggest the possibility of multiple myeloma. The aim of the present study was to evaluate the necessity of bone marrow examination for the diagnosis and clinical course of MGUS.

Patients and Methods

The medical laboratories of Meir Medical Center, Kfar Saba, serve Meir Hospital as well as the primary care clinics of Clalit Health Services in the Sharon area, with more than 450,000 members. (Clalit is the largest health management organization in Israel.)

We retrospectively screened the medical records of all patients in whom M protein was found in the serum during 2001–2002 in Meir Medical Center. Asymptomatic patients older than 18 years who fulfilled the following criteria were included: low serum M protein level (IgG < 3.0 g/dl, IgA < 2.0 g/dl, IgM < 1.0 g/dl); normal levels of hemoglobin (> 10.0 g/dl), creatinine (< 1.5 mg/dl) and calcium (< 10.0 mg/dl), and normal skeletal X-ray survey.

The patients were followed either in the hematology clinic of Meir Hospital (group 1) or by their family physicians (group 2). For group 1 patients, full records, laboratory findings including interpretation of bone marrow examination and follow-up were

MGUS = monoclonal gammopathy of undetermined significance
Ig = immunoglobulin
M = monoclonal

available. For patients who were followed by their family physicians (group 2) we had access only to their electronic files. The files included laboratory results, new diagnoses and summaries of hospital admissions. Demographic, clinical and laboratory parameters as well as the clinical course of both groups were evaluated as indicated. The study was approved by the Meir Medical Center ethics committee.

Statistical analysis

The comparison of demographic and clinical characteristics between the patient groups was assessed by the chi-square test for categorical variables and the Student *t*-test for continuous variables.

Results

Altogether, 521 patients in whom M protein was detected in the serum between 1 January 2001 and 31 December 2002 were screened for this study. Excluded were 166 because they had been previously diagnosed with plasma cell dyscrasias or had clinical or laboratory characteristics that were incompatible with MGUS. An additional 43 patients were lost to follow-up. The remaining 312 patients were divided into two groups: 57 who were referred to the hematology clinic in Meir Hospital for evaluation and follow-up (group 1) and 255 patients who were followed by their primary physicians (group 2l). Both groups had similar demographic, laboratory and clinical characteristics [Table 1]. Although the differences in creatinine levels and in the presence of urine Bence-Jones protein were statistically significant, they were clinically meaningless

Bone marrow examination was performed in 30 of the 57 patients (group 1) following the decision of a senior hematologist. There were no significant differences between patients who had or had not undergone the examination by demographic, laboratory and clinical parameters [Table 2]. Sixteen of the bone marrow examinations were normal, 8 had an excess of normal plasma cells (5–10%), and 6 had an excess of pathologic plasma cells. However, only two of the six last patients had ≥ 10% pathologic plasma cells in the bone marrow and the diagnosis of multiple myeloma could be established. These two patients had clinical characteristics similar to the other four and required no treatment.

After a mean follow-up of 22 ± 11 months, only two patients developed overt multiple myeloma (one of them had an initial bone marrow examination with 10% pathologic plasma cells). Of the 255 patients who were followed by their primary physicians during the same period, 9 were referred to other hospitals: 6 were diagnosed as multiple myeloma and 3 as MGUS. The rest had a stable course with no records of plasma or lymphoproliferative disorders or significant changes in their laboratory values.

Table 1. Demographic and clinical parameters of the studied patients

	Group 1 (n=57)	Group 2 (n=255)	*P*
Female/Male	29/28	140/115	0.370
Mean age (yrs)	70 ± 12	72 ± 15	0.201
Hemoglobin (g/dl)	12.2 ± 1.8	12.0 ± 2.0	0.467
Serum creatinine (mg/dl)	1.0 ± 0.2	1.3 ± 0.8	0.0001
Serum calcium (mg/dl)	9.2 ± 0.6	9.3 ± 0.7	0.706
M protein: % (mg/dl)			
IgGκ	50% (1678 ± 564)	47% (1661 ± 795)	0.900
IgGλ	25% (1643 ± 372)	33% (1633 ± 815)	0.940
IgAκ	7% (1097 ± 534)	4% (816 ± 504)	0.409
IgAλ	7% (1283 ± 720	2% (650 ± 246)	0.177
IgM	11% (629 ± 267)	14% (862 ± 579)	0.724
No. of patients with urine Bence-Jones protein	12 (n=48)	3 (n=67)	0.004

Table 2. Demographic and clinical parameters of group 1 patients, according to bone marrow examinations data

	Bone marrow examination		
	Done (n=30)	Not done (n=27)	*P*
Female/Male	13/17	15/12	0.357
Mean age (yrs)	68 ± 10	71 ± 13	0.484
Hemoglobin (g/dl)	12.3 ± 2.0	12.0 ± 1.6	0.595
Serum creatinine (mg/dl)	1.1 ± 0.2	1.0 ± 0.2	0.795
Serum calcium (mg/dl)	9.1 ± 0.6	9.3 ± 0.5	0.108
M protein: % (mg/dl)			
IgGκ	50% (1540 ± 463)	52% (1816 ± 636)	0.201
IgGλ	18% (1584 ± 423)	30% (1680 ± 361)	0.670
IgAκ	10% (1244 ± 554)	4% (657)	0.456
IgAλ	12% (1283 ± 720)	–	
IgM	10% (863 ± 40)	4% (512 ± 252)	0.137
No. of patients with urine Bence-Jones protein	8 (n=48)	4 (n=24)	0.182

Discussion

MGUS should be differentiated from multiple myeloma, the malignant spectrum of plasma cell dyscrasias. According to the findings of the current study, two diagnostic criteria of MGUS are sufficient for this purpose: low M protein level and normal laboratory findings and skeletal X-ray survey. Bone marrow examination did not modify therapeutic decisions in any patient and did not predict clinical behavior. Thus, this invasive and painful procedure does not have a role in the initial diagnostic workup of MGUS.

Bone marrow histology is considered important to differentiate MGUS from multiple myeloma and also helps to assess the risk of MGUS progression to multiple myeloma. Riccardi and coauthors [7] reported that changes in bone marrow composition from MGUS to early myeloma and to an advanced stage follow a precise pattern. It includes an increased percentage of bone marrow plasma cells, a shift from plasmocytic to plasmoblastic cytology, an increase in bone marrow cellularity and fibrosis, a change in bone marrow infiltration (diffuse rather than interstitial), a decrease in residual hematopoiesis, and an increase in osteoclasts. Bone marrow angiogenesis was found to increase progressively along the spectrum of plasma cell disorders from the more benign MGUS stage to advanced myeloma, indicating that angiogenesis may be related to disease progression [8].

In addition, the Plasma Cell Labeling Index, which measures the synthesis of DNA, is a most useful tool for differentiating MGUS or smoldering myeloma from overt myeloma. It is acceptable that in patients with MGUS the labeling index is always < 1%, whereas it is > 1% in patients with multiple myeloma [9]. Finally, bone marrow plasma cells < 5% and M protein ≤ 1.5 g/dl predict a stable course, while detectable Bence-Jones proteinuria, polyclonal serum immunoglobulin reduction and high erythrocyte sedimentation rate predict MGUS transformation to myeloma [10,11]. Based on these findings, bone marrow evaluation became a routine examination in most patients with paraprotein in the blood or urine. Indeed, most textbooks and guidelines recommend its performance at the initial evaluation of such patients [1,4,5].

Only a few studies claimed that bone marrow examination is not essential for the diagnosis of MGUS and its differentiation from multiple myeloma. In an earlier study about one-third of the patients had a normal bone marrow [12], compared to a median percentage of bone marrow plasma cells of 3% (range 0–10%) [2,3]. Kyle et al. concluded that the concentration and type of M proteins were the only independent predictors of disease progression, while the following variables including age, gender, hepatosplenomegaly, hemoglobin, serum creatinine or albumin levels, as well as the presence, type and amount of monoclonal urinary light chain and reduction of uninvolved immunoglobulins were not. Of note, bone marrow findings were not predictive of malignant transformation [2,3]. However, in these studies only 109 of 241 patients [2] and 160 of 1384 [3] had bone marrow examination. Other studies examined the role of biological parameters while assessing the significance of bone marrow examination. Approximately 40% of asymptomatic myeloma patients had a normal labeling index value.

In recent years several genetic and cytogenetic abnormalities have been described in plasma cell neoplasms. Among them are hyperdiploidy and chromosome translocations involving the immunoglobulin heavy-chain locus, deletion and monosomy of chromosome 13, and abnormalities of chromosome 1. However, many of the translocations observed in multiple myeloma are also seen in MGUS, even in individuals without progression to full malignant disease for many years [13]. Furthermore, karyotyping is often of no value in determining the risk of progression because cells in metaphase are rare in MGUS [8]. Recent guidelines on the diagnosis and management of myeloma stated that skeletal survey and bone marrow examination are not mandatory to make a diagnosis of MGUS in the absence of relevant clinical symptoms. They are recommended in younger patients and may be considered for older patients with M-protein levels above 2.0 g/dl [14].

The current study is retrospective and may have the inherent bias of its nature. However, it was carefully designed, unselected and included follow-up data. The hospital records were available in all group 1 patients and the electronic files of group 2 subjects were automatically updated.

In conclusion, bone marrow examination is not contributive in patients who fulfill strict criteria of MGUS. Careful follow-up and clinical monitoring are probably sufficient to detect progression to multiple myeloma.

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