

# Detection by Immunofixation of M Proteins in Hypogammaglobulinemic Patients With Normal Serum Protein Electrophoresis Results

Renuka Lakshminarayanan, MD,<sup>1</sup> Yueju Li, MA,<sup>2</sup> Kim Janatpour, MD,<sup>1</sup> Laurel Beckett, PhD,<sup>2</sup> and Ishwarlal Jialal, MD, PhD, FRC Path<sup>1</sup>

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## Abstract

*Serum protein electrophoresis (SPE) demonstrates a monoclonal protein as an M spike in the majority of patients with monoclonal gammopathies. However, in patients with an apparently normal SPE pattern or hypogammaglobulinemia, immunofixation electrophoresis (IFE) can reveal an M protein. We undertook this study to determine the yield of reflex IFE testing in patients with hypogammaglobulinemia and to identify any laboratory or biochemical parameters that would predict a positive IFE result. We evaluated 380 patients with hypogammaglobulinemia and a normal SPE pattern. Of 380, 37 (9.7%) had a positive IFE result in serum, urine, or both. Of the other laboratory values evaluated, a high  $\alpha_2$ -globulin level with an increased  $\alpha_2$ -globulin/ $\alpha_1$ -globulin ratio, a low hemoglobin level, and an elevated creatinine level predicted a positive IFE result. There was a 2-fold increase in the odds ratio for a positive IFE result when the  $\alpha_2$ -globulin/ $\alpha_1$ -globulin ratio was elevated. We recommend reflex IFE testing in patients with hypogammaglobulinemia with a normal SPE pattern if any of the following are present: elevated  $\alpha_2$ -globulin/ $\alpha_1$ -globulin ratio, low hemoglobin level, and elevated creatinine level.*

Serum protein electrophoresis (SPE) is the mainstay laboratory test for the detection of abnormal monoclonal proteins. The presence of abnormal monoclonal proteins, which is referred to as monoclonal gammopathy, is a frequent, characteristic feature of plasma cell dyscrasias. Monoclonal gammopathy is defined as the electrophoretically and antigenically homogeneous protein product of a single clone of B lymphocytes or plasma cells. The monoclonal protein is usually detected as a discrete band in the  $\gamma$  or  $\beta$  region in serum or urine protein electrophoresis (M spike). The nature of the monoclonal protein is then characterized and confirmed by an immunofixation electrophoresis (IFE). An abnormal M spike is seen in serum or urine protein electrophoresis in more than 90% of patients with multiple myeloma. Hypogammaglobulinemia is seen in 10%, and 10% have a normal electrophoretic pattern.<sup>1</sup> Narayan et al<sup>2</sup> reported that despite a normal SPE pattern, patients with increased  $\beta_1$ -globulin and especially  $\beta_2$ -globulin levels can have an M protein masked in these bands.

In plasma cell dyscrasias and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), there is a concomitant suppression of normal immunoglobulins leading to hypogammaglobulinemia. Hypogammaglobulinemia can occur as an isolated abnormality in multiple myeloma, including light chain disease, CLL/SLL, immunodeficiency, AL amyloidosis, and chemotherapy.<sup>3</sup> In older people, hypogammaglobulinemia may indicate light chain disease or a B-cell neoplastic process. Reflex serum and or urine IFE is performed in patients with marked hypogammaglobulinemia, without an obvious M spike, or any other abnormal bands on SPE. When gammaglobulin levels are mild to moderately decreased ( $\gamma$ -globulin level, <0.7 g/dL [7 g/L]) with a normal SPE pattern, an IFE is usually recommended. Urine studies

(urine protein electrophoresis [UPE]) to rule out monoclonal free light chains<sup>4</sup> may also be advised.

The purposes of this study were to determine the yield of this reflex IFE testing in hypogammaglobulinemic patients with a normal SPE pattern and to identify any routine laboratory parameters that might prove helpful in predicting a positive IFE result in patients with hypogammaglobulinemia and no obvious M spike or any abnormal band on SPE.

## Materials and Methods

We evaluated 380 consecutive patients with hypogammaglobulinemia ( $\gamma$ -globulin level,  $<0.7$  g/dL [7 g/L]) and a normal initial SPE pattern with no obvious M spike on SPE. The serum protein fractions analyzed included total protein, albumin,  $\alpha_1$ -globulin,  $\alpha_2$ -globulin,  $\beta_1$ -globulin,  $\beta_2$ -globulin, and  $\gamma$ -globulin. Laboratory parameters evaluated included hemoglobin, serum calcium, creatinine, and lactate dehydrogenase levels and the erythrocyte sedimentation rate. The presence of reflex serum and/or urine IFE testing and the results of the same were also noted for every patient when available. Of the 380 cases, 155 had IFE performed. All test results that were evaluated were available for 136 cases. These patients were separated into 2 groups: 1, patients with a normal SPE pattern, no M protein, and a positive IFE result ( $n = 37$ ); and 2, patients with a normal SPE pattern, no M protein, and negative IFE results ( $n = 99$ ).

SPE was performed with a Sebia-hydrasys automated electrophoresis system (Sebia, Norcross, GA). The same system was used for IFE with polyclonal antihuman serum for identifying immunoglobulin light and heavy chains. UPE and IFE were performed in 24-hour samples that were concentrated 100-fold. For all patients, serum chemistry panels and CBC counts were performed by standard laboratory techniques.

## Statistical Analysis

Logistic regression models were used to assess the degree to which age, sex, and laboratory results correlated with a positive IFE result with no M band on SPE (compared with a negative IFE result with no M band). We began with univariate summaries of all potential predictors, including mean, SD, stem-and-leaf display, and diagnostics for outliers and nonnormality. We compared distributions of age and laboratory values between groups 1 and 2 by using a Wilcoxon rank sum test, to address possible nonnormality of the laboratory values. Next, each predictor that had a significant difference in rank order between groups 1 and 2 was examined in a single-variable logistic regression model, followed by multiple variable logistic regression. All tests were 2-sided at an  $\alpha$  level of .05, and all analyses were carried out in SAS, version 9.1 (SAS Institute, Cary, NC).

Follow-up of the 37 hypogammaglobulinemic patients with no M spike and positive IFE results was by examining the medical records and pathology files for bone marrow biopsy and repeated SPE, UPE, and/or IFE. The follow-up period ranged from 6 to 48 months.

## Results

Of 380 patients with hypogammaglobulinemia and a normal SPE pattern with no obvious M spike, 37 had a positive monoclonal protein as detected by IFE, for a yield of 9.7%. The specific monoclonal components in the serum and urine and their distribution in the 37 patients are outlined in **Table 1**. Representative cases of SPE- and IFE+ (serum) and SPE- but UPE+ and IFE+ (urine) cases are shown in **Figure 1** and **Figure 2**.

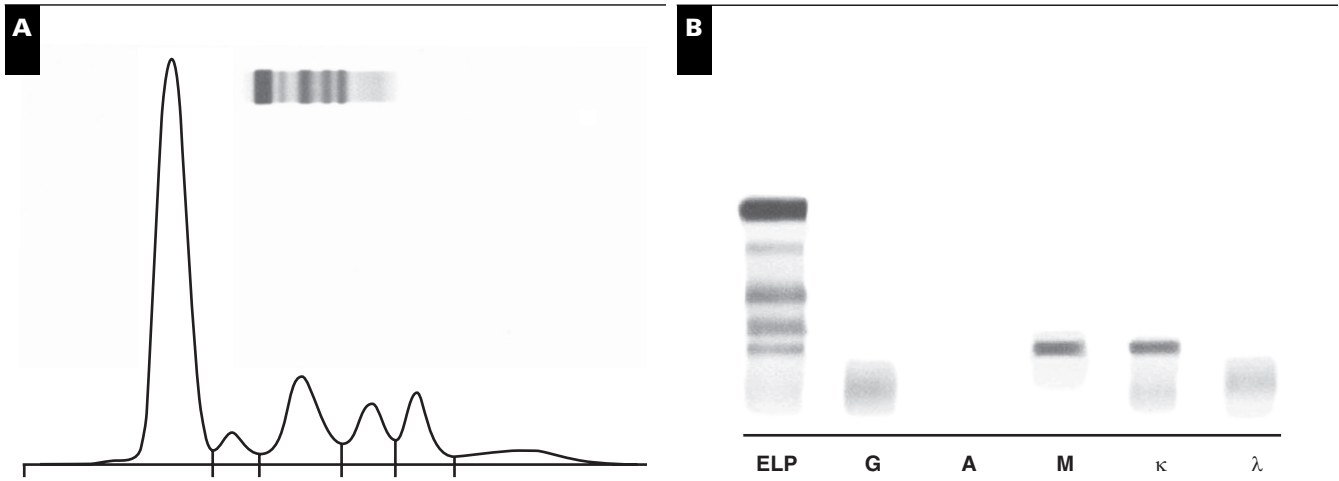
Laboratory test results, including hematology and serum chemistry panels, and demographic data for the 136 patients were analyzed. Demographics were similar between groups, with similar age and sex frequencies. In unadjusted univariate comparisons based on Wilcoxon rank sum tests, patients with a positive IFE result were likely to have had higher  $\alpha_2$ -globulin, lower  $\alpha_1$ -globulin and hemoglobin, and higher creatinine levels **Table 2**.

We then examined the degree to which individual laboratory results or combinations of laboratory results might predict a positive IFE result with no obvious M spike on SPE, using logistic regression analysis **Table 3**. In univariate analyses, hemoglobin was significantly predictive of a positive IFE result; every unit decrease in the hemoglobin level was associated with a 21% increase in the odds of a positive IFE result ( $P = .03$ ). A lower  $\alpha_1$ -globulin level was associated with a nearly 5-fold decrease in the odds of a positive IFE result ( $P = .03$ ), whereas a higher  $\alpha_2$ -globulin level was associated with a more than 2-fold increase in the odds of a positive IFE result ( $P = .03$ ). The creatinine level

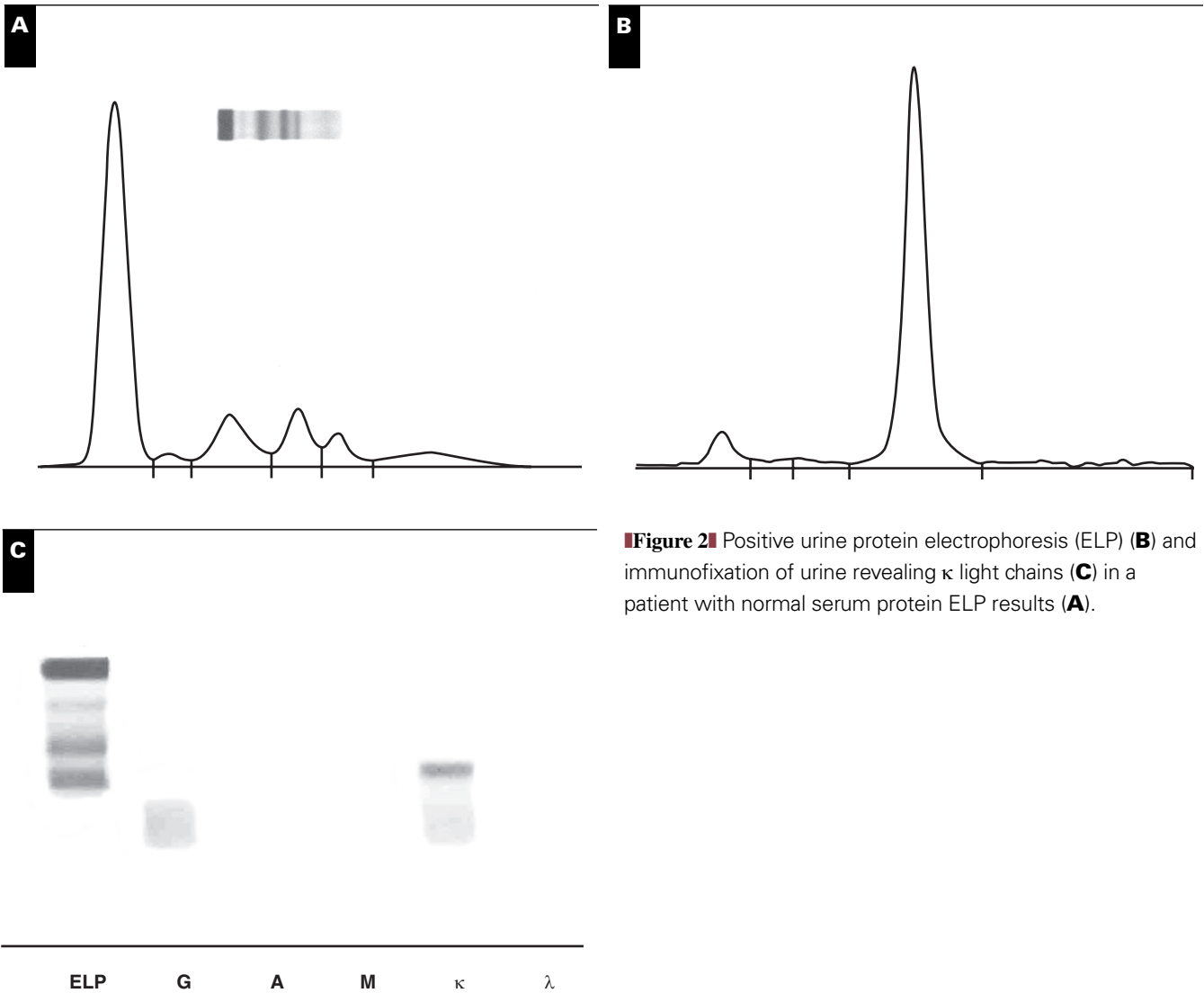
**Table 1**  
Monoclonal Components in Serum and Urine in Serum Protein Electrophoresis–Negative Immunofixation Electrophoresis–Positive Patients

Type of M Protein*	No. of Cases
Serum	
IgG ( $\kappa$ , 8; $\lambda$ , 2)	10
IgA ( $\kappa$ , 2; $\lambda$ , 4)	6
IgM ( $\kappa$ , 6)	6
$\lambda$ Light chain	5
$\kappa$ Light chain	3
Urine only	
$\kappa$ Light chain	6
$\lambda$ Light chain	1

\* The numbers of cases for serum M components include patients who had serum M protein only or serum and urine M protein. The 7 patients included in the "Urine only" section had only urinary M protein.



**Figure 1** Positive immunofixation electrophoresis (ELP) test result demonstrating IgM  $\kappa$  (B) in a patient with normal serum protein ELP results (A).



**Figure 2** Positive urine protein electrophoresis (ELP) (B) and immunofixation of urine revealing  $\kappa$  light chains (C) in a patient with normal serum protein ELP results (A).

**Table 2**  
Salient Clinical Characteristics and Routine Laboratory Test Results for 136 Patients With Hypogammaglobulinemia\*

Variable	Positive Group (n = 37)	Negative Group (n = 99)	P†
Age (y)	67.3 (14.1)	65.1 (15.5)	.55
Total protein (g/dL)	5.84 (0.74)	5.87 (0.78)	.46
Albumin (g/dL)	3.56 (0.61)	3.66 (0.80)	.11
$\alpha_1$ -Globulin (g/dL)	0.24 (0.10)	0.28 (0.11)	.02
$\alpha_2$ -Globulin (g/dL)	0.73 (0.16)	0.65 (0.20)	.01
$\beta$ -Globulin (g/dL)	0.85 (0.20)	0.77 (0.14)	.054
$\gamma$ -Globulin (g/dL)	0.47 (0.15)	0.51 (0.11)	.12
Hemoglobin (g/dL)	11.19 (1.63)	12.09 (2.13)	.01
Ca 2+ (mg/dL)	8.62 (1.44)	8.93 (0.79)	.12
Creatinine (mg/dL)	1.72 (1.49)	1.41 (1.60)	.01
Lactate dehydrogenase (U/L)	231.32 (99.14)	190.47 (61.69)	.10
Erythrocyte sedimentation rate (s)	23.65 (23.57)	25.06 (27.30)	.81

\* Data are given as mean (SD) in conventional units; conversions to Système International units are as follows:  $\alpha_1$  and  $\alpha_2$  (g/L), multiply by 10.0; albumin (g/L), multiply by 10;  $\beta$  (g/L), multiply by 10.0; Ca 2+ (mmol/L), multiply by 0.25; creatinine ( $\mu$ mol/L), multiply by 88.4;  $\gamma$  (g/L), multiply by 10.0; and hemoglobin (g/L), multiply by 10.0.

† Wilcoxon test.

**Table 3**  
Logistic Regression Results for the Degree to Which Individual or Combinations of Laboratory Results Predict a Positive Immunofixation Electrophoresis With No Obvious M Spike on Serum Protein Electrophoresis in 136 Cases of Hypogammaglobulinemia

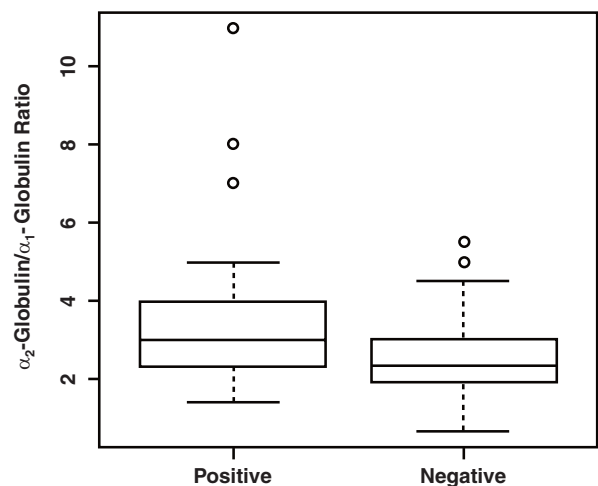
Variable	Estimate (P)	Odds Ratio (95% Confidence Interval)
Univariate logistic regression		
$\alpha_1$ -Globulin	-4.84 (.03)	0.01 (0-0.64)
$\alpha_2$ -Globulin	2.21 (.03)	9.15 (1.19-70.59)
Hemoglobin	-0.22 (.03)	0.80 (0.66-0.97)
Creatinine	0.11 (.33)	1.12 (0.89-1.40)
$\alpha_2$ -Globulin/ $\alpha_1$ -globulin	0.75 (<.001)	2.11 (1.42-3.15)
Multivariate logistic regression		
$\alpha_1$ -Globulin	-9.40 (<.001)	<0.001 (<0.001-0.01)
$\alpha_2$ -Globulin	4.07 (.003)	58.36 (4.15-821.59)
Hemoglobin	-0.36 (.005)	0.70 (0.54-0.89)
Creatinine	-0.15 (.33)	0.86 (0.64-1.16)

was not significantly associated with a change in risk. These results were supported in multivariate analysis. The  $\alpha_1$ -globulin,  $\alpha_2$ -globulin, and hemoglobin levels all continued to predict significantly and with similar magnitudes of effect on risk.

We also looked at the predictive value of the  $\alpha_2$ -globulin/ $\alpha_1$ -globulin ratio in the 2 groups. A higher  $\alpha_2$ -globulin/ $\alpha_1$ -globulin ratio was associated with a 2-fold increase in the odds of a positive IFE result ( $P < .001$ ). A box plot (Figure 3) comparing the  $\alpha_2$ -globulin/ $\alpha_1$ -globulin ratio in both groups shows a definite upward shift in the group with a positive IFE result, indicating that this ratio is a better predictor than a higher  $\alpha_2$ -globulin or a lower  $\alpha_1$ -globulin value alone.

## Discussion

The prevalence of monoclonal proteins as detected by IFE in hypogammaglobulinemia in the absence of an obvious



**Figure 3**  $\alpha_2$ -Globulin/ $\alpha_1$ -globulin ratio in patient groups with positive and negative immunofixation electrophoresis results.

M spike or an abnormal band on SPE is 9.7% (37 of 380 cases). Monoclonal proteins can migrate anywhere from the  $\gamma$  region up to the  $\alpha$  region.<sup>5</sup> High-resolution SPE techniques can detect small M proteins that may migrate anywhere between the  $\alpha_2$  and  $\gamma$  regions.<sup>4,6</sup> Still, with the wide range of migration of the M proteins in SPE, a significant proportion of them can be missed. Hence, a much more sensitive test such as IFE<sup>6</sup> is recommended, especially when there is a high clinical suspicion. According to the guidelines for clinical and laboratory evaluation of patients with monoclonal gammopathies,<sup>4</sup> IFE is useful even when the results of high-resolution SPE are negative and there is a clinical suspicion of a plasma cell dyscrasia.

Hypogammaglobulinemia in the appropriate clinical setting can indicate a covert monoclonal protein, and hence, serum IFE is recommended in such situations. A urine study is recommended to rule out monoclonal proteins if a tiny restriction is

present in the  $\alpha_1$  region, especially when associated with a low  $\gamma$ -globulin level.<sup>6</sup>

Of the laboratory tests evaluated in the 2 groups of patients, low hemoglobin, high creatinine, low  $\alpha_1$ -globulin, and high  $\alpha_2$ -globulin levels had a predictive effect on a positive IFE result by Wilcoxon rank sum test. Low  $\alpha_1$ -globulin, low hemoglobin, and high  $\alpha_2$ -globulin levels and a high  $\alpha_2$ -globulin/ $\alpha_1$ -globulin ratio predicted a positive IFE result by logistic regression analysis. A high  $\alpha_2$ -globulin/ $\alpha_1$ -globulin ratio in hypogammaglobulinemic patients increased the odds of a positive IFE result by 2 ( $P < .001$ ).

In group 1, none of the patients had a high  $\alpha_2$ -globulin value. None had M protein in the  $\alpha_2$  region. No increase in the  $\beta$  region (lipoproteins) was noted in the positive group, and it was not a significant predictor. It should be noted that patients with an M spike in the  $\beta$  region ( $\beta_1$  or  $\beta_2$  band with high-resolution SPE) were not included in the study.

In addition to the M protein being the likely reason for an elevated  $\alpha_2$ -globulin/ $\alpha_1$ -globulin ratio, an increase or a decrease in other protein components that migrate in the  $\alpha_1$  and  $\alpha_2$  regions may also be of relevance in patients with a positive IFE result but no M protein on SPE.

An increased  $\alpha_2$ -globulin level is commonly observed in nephrotic syndrome with an associated elevation in  $\beta$ -region lipoproteins.  $\alpha_2$ -Globulins consist mainly of  $\alpha_2$ -macroglobulin, ceruloplasmin, and haptoglobin.  $\alpha_2$ -Macroglobulin is increased in nephrotic syndrome with selective glomerular leakage. Haptoglobin can form complexes with hemoglobin, which may produce a peak in the  $\alpha_2$  region suggestive of an M protein.<sup>7</sup> None of our patients with a positive IFE result had clinical or laboratory evidence of hemolysis. Haptoglobin, in addition to being increased in acute inflammatory responses, is also synthesized more in response to interleukin-6 (IL-6)<sup>3</sup> and so is ceruloplasmin. The IL-6 level is also increased in plasma cell dyscrasias in addition to in acute inflammation.<sup>8</sup> It is possible that elevated  $\alpha_2$ -macroglobulin, ceruloplasmin, and haptoglobin levels (produced in response to IL-6 in B-cell and plasma cell dyscrasias) underlies the high  $\alpha_2$ -globulin/ $\alpha_1$ -globulin ratio in the positive group.

Of the 37 patients, 27 had been tested for urine free light chains. Of the 27 cases, 10 (37%) had urine monoclonal free  $\kappa$  or  $\lambda$  light chains (monoclonal free light chains), including 7 cases in which the urine monoclonal free light chain was the sole abnormal protein (Table 1). Of the 37 patients, 34 were tested for proteinuria. Of these 34 patients, 24 (71%) had positive results for proteinuria; 7 (29%) of the 24 patients had nephrotic range proteinuria ( $>3$  g/d). The nephrotic pattern in SPE seen in patients in group 1 could be attributed to monoclonal immunoglobulin deposition disease and AL amyloidosis.

Anemia, an important clinical sign in plasma cell dyscrasias, predicted a positive IFE result. The odds of a positive IFE result increased by 21% for every unit of decrease in

hemoglobin value. Anemia can be due to bone marrow involvement by a lymphoproliferative process or plasma cell dyscrasia or to low erythropoietin levels as a result of renal insufficiency.

Of the 37 group 1 patients, multiple myeloma, B-cell CLL/SLL, and amyloidosis developed; 16 patients had no evidence of a monoclonal lymphoproliferative process or a plasma cell dyscrasia (possible monoclonal gammopathy of unknown significance [MGUS]) and 2 had other diagnoses (post-lung transplant with no overt evidence of a lymphoproliferative process and peripheral neuropathy) (Table 4). Of the 16 patients with presumed MGUS, 5 underwent bone marrow biopsy 10 months to 2 years after a positive IFE result; 1 had increased plasma cells (10%), myeloma (bone marrow plasma cells  $>30\%$ ) developed in 1, and in the other 3 patients, bone marrow did not show any evidence of a lymphoproliferative process or increased plasma cells. Of the 14 patients with presumed MGUS (excluding the 2 patients with myeloma and CLL), 7 had a follow-up SPE and/or IFE performed. In 4 patients, the monoclonal protein persisted as evidenced by a positive IFE result. In 3 patients, the M protein was not detected by IFE. Seven patients did not have follow-up SPE and/or IFE (Table 5).

Highly sensitive, recently introduced automated immunoassays for monitoring free light chains in urine and serum use turbidimetric methods that are more sensitive than

**Table 4**  
Outcome for 37 Patients With Positive Immunofixation Electrophoresis and Normal Serum Protein Electrophoresis Results

Outcome	No. (%) of Cases
Myeloma	15 (41)
B-cell neoplasia	3 (8)
Amyloidosis	1 (3)
Other (post-lung transplantation and peripheral neuropathy)	2 (5)
Possible monoclonal gammopathy of unknown significance	16 (43)

**Table 5**  
Follow-up of Patients With Presumed Monoclonal Gammopathy of Unknown Significance

Bone Marrow or Peripheral Blood or Tissue Diagnosis	No. of Patients	Follow-up SPE and IFE
Plasma cells, 30% in bone marrow	1	+
CLL (peripheral blood)	1	+
Plasma cells, 10% in bone marrow	1	+
Bone marrow, nondiagnostic	3	+, 1; -, 2
No bone marrow or tissue diagnosis	10	+, 2; -, 1; not done, 7

CLL, chronic lymphocytic leukemia; IFE, immunofixation electrophoresis; SPE, serum protein electrophoresis; +, positive; -, negative.



SPE or UPE.<sup>9</sup> These assays have detection limits more than 50-fold lower than SPE and UPE and more than 20-fold lower than IFE and, hence, could prove useful for monitoring patients with light chain disease. Katzmman<sup>10</sup> recently provided an editorial on the quantification of serum and urine free light chains; he stated that this assay has increased diagnostic sensitivity and may also lead to increased false-positive results. The International Myeloma Working Group stated that serum free light chain assays are solely for patients with disease whose M protein is not measurable with current methods.<sup>11</sup> This assay might prove to be an effective method for monitoring patients with B-cell dyscrasias and may also be incorporated as an additional diagnostic test in monoclonal gammopathies.

## Conclusions

Although this study may be limited by numbers in the positive group (positive IFE and no M band on SPE), it is evident that patients with hypogammaglobulinemia in the appropriate clinical setting should undergo further examination, ie, IFE. A 9.7% yield for a positive IFE result in hypogammaglobulinemic subjects supports this conclusion. We recommend IFE, especially in the presence of anemia, high or borderline creatinine levels, and a high  $\alpha_2$ -globulin/ $\alpha_1$ -globulin ratio associated with hypogammaglobulinemia ( $\gamma$ -globulin, <0.7 g/dL [7 g/L]). An elevated  $\alpha_2$ -globulin/ $\alpha_1$ -globulin ratio increases the odds of a positive IFE result in hypogammaglobulinemic patients with anemia, an increased creatinine level, and no obvious M protein or other abnormal bands on SPE. A study in a larger reference laboratory could confirm our findings and provide cutoffs for  $\alpha_2$ -globulin/ $\alpha_1$ -globulin ratios that could be useful as a cost-effective measure in dictating which patients should undergo IFE testing.

From the <sup>1</sup>Department of Pathology and Laboratory Medicine, University of California, Davis, School of Medicine; and the

<sup>2</sup>Division of Biostatistics and Public Health Sciences, University of California, Davis.

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Address reprint requests to Dr Jialal: 4635 2nd Ave, Research I #3000, Sacramento, CA 95817.

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