

Monoclonal Gammopathy of Undetermined Significance

Natural History in 241 Cases

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Two hundred forty-one patients with a monoclonal protein in the serum but initially no evidence of multiple myeloma, macroglobulinemia, amyloidosis or lymphoma were followed up for more than five years. At the conclusion of the studies the patients were classified as follows: Group 1, patients without significant increase in monoclonal protein, 57 per cent; group 2, patients with more than 50 per cent increase in monoclonal serum protein or development of monoclonal urine protein, 9 per cent; group 3, patients who died without five-year serum studies, 23 per cent; and group 4, patients in whom myeloma, macroglobulinemia or amyloidosis developed, 11 per cent. Initially, the hemoglobin level, size of serum monoclonal protein peak, number of plasma cells in the bone marrow and levels of normal immunoglobulins were not significantly different among the four groups. The median interval from recognition of the monoclonal protein to diagnosis of multiple myeloma was 64 months, of macroglobulinemia 103 months and of amyloidosis 92 months. A significant increase of the monoclonal protein or development of myeloma, macroglobulinemia or amyloidosis occurred in 18 per cent of the patients with monoclonal immunoglobulin G (IgG), in 28 per cent with immunoglobulin A (IgA) and in 25 per cent with immunoglobulin M (IgM). Retrospective analysis of age, sex, presence of organomegaly, hemoglobin level, size and type of serum monoclonal protein peak, presence of small amounts of monoclonal light chain in the urine, serum albumin level, levels of uninvolved immunoglobulins, IgG subclass and level of plasma cells in the bone marrow did not show how to distinguish initially between stable benign disease and progressive disease. Therefore, periodic reexamination of patients with monoclonal gammopathy is essential.

The monoclonal gammopathies are a group of disorders characterized by proliferation of a single clone of plasma cells that produce a homogeneous, monoclonal (M) protein. A monoclonal immunoglobulin consists of two heavy polypeptide chains of a single class and subclass and two light polypeptide chains of a single type. The different kinds of monoclonal immunoglobulin are designated by capital letters that correspond to the class of their heavy chains, which are designated by Greek letters: γ (gamma) in IgG, α (alpha) in IgA, μ (mu) in IgM, δ (delta) in IgD and ϵ (epsilon) in IgE. Their light chain types are κ (kappa) and λ (lambda).

The term "benign monoclonal gammopathy" denotes the presence of a monoclonal protein in persons without evidence of myeloma, macroglobulinemia or other related diseases [1-5]. Since Waldenström's introduction of the term "essential hyperglobulinemia" in 1952,

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many modifications have appeared—including idiopathic, asymptomatic, benign, nonmyelomatous, discrete, cryptogenic and rudimentary monoclonal gammopathies; dysimmunoglobulinemia, lanthanic monoclonal gammopathy, idiopathic paraproteinemias and asymptomatic para-immunoglobulinemia. Waldenström [6] stressed the constancy of the size of the protein peak, contrasting it with the increasing quantity of the monoclonal protein in myeloma. However, "monoclonal gammopathy of undetermined significance" is a better term because one cannot tell whether the monoclonal protein will remain unchanged or whether the patient has an evolving myeloma or macroglobulinemia.

Monoclonal gammopathies have been found in approximately 3 per cent of patients beyond the age of 70 years in Sweden [1,7,8] and in the United States [9]. Data on long-term follow-up of patients with monoclonal gammopathies are limited. Among 62 patients who had monoclonal gammopathy without evident neoplastic disease, reexamination of 52 after two and a half years [10] and 39 after five and a half years [11] revealed no development of myeloma or macroglobulinemia. However, one cannot completely exclude the development of myeloma or macroglobulinemia among the 23 lost to follow-up. At 11 years myeloma had developed in two patients and lymphoma in one [12]. Of our 15 patients with a monoclonal protein in the serum, macroglobulinemia had developed in one but multiple myeloma had not developed in any of them at five years of follow-up [9]. Because monoclonal gammopathies of indeterminate significance are not uncommon and are of obvious importance to the patient and his physician, and because there has been no report of long-term follow-up of general medical patients with monoclonal gammopathy of undetermined significance, we have conducted such a study.

MATERIAL AND METHODS

We retrieved the records of all patients with a monoclonal gammopathy who were seen at the Mayo Clinic prior to January 1, 1971, a limiting date chosen to permit follow-up of at least five years. In all cases, data were abstracted on sheets suitable for key-punching. Maximum and minimum laboratory values and their dates were recorded. The data were tabulated and analyzed with a computer, which also screened for errors. (Examples of errors included the record of a urine protein peak on electrophoresis when there was no record of electrophoresis of the urine having been performed, a record of the cause of death or a death certificate if the patient were living and any printout showing an unlikely value, such as a hemoglobin level of 25 g or a leukocyte count of 100,000/mm³.) Distributions were made of the results of each laboratory test, showing the frequency of each value among the patients.

Follow-up letters were written to every patient and to the physician of each patient who had not been seen during the previous year. Letters were written to other contacts of the

patient, such as hospitals or other medical institutions where the patient had been. Death certificates were requested from the Department of Vital Statistics in the state of residence of the patient. Even when the date of death was not known, the death certificate was often obtainable when we suggested an interval of two or three years during which the patient probably had died. Retail credit searches produced follow-up information in some instances.

Patients who had not been to the Mayo Clinic recently were asked to send a sample of serum and also any laboratory data that had been obtained elsewhere. Patients in whom the monoclonal serum protein had increased were asked to send a 24-hour urine specimen for electrophoresis and immunoelectrophoresis.

Serum protein electrophoresis was performed on cellulose acetate membranes and stained with Ponceau S. Serums that gave a suggestion of a localized band were subjected to immunoelectrophoresis with monospecific antisera to α , γ , μ , κ and λ chains. All serums were screened by Ouchterlony immunodiffusion for excess of IgD or IgE. Quantitation of immunoglobulins was made with immunodiffusion plates or by nephelometry. Electrophoresis and immunoelectrophoresis were performed on urine concentrated by ultrafiltration [13]. Identification and quantitation of the IgG subclass was performed by a radioimmunoassay [14].

FINDINGS AT DIAGNOSIS

Of patients in whom a monoclonal protein in the serum was recognized during the study period, 253 remained after exclusion of those with an initial diagnosis of multiple myeloma, macroglobulinemia, amyloidosis or lymphoma. Four patients (1.5 per cent) could not be traced, and we were unable to obtain a serum specimen from six patients who were clinically well. The monoclonal protein had disappeared in two patients—of whom one had sarcoidosis and the other degenerative arthritis. These 12 patients will not be discussed further, and the remainder of the study will be limited to the 241 patients with adequate follow-up. At the conclusion of the study the patients were assigned to the following groups:

		Num- ber	Per Cent
Group 1:	No significant increase of monoclonal serum protein	137	(57)
Group 2:	More than 50 per cent increase of monoclonal serum protein from initial value, or appearance of monoclonal urine protein	22	(9)
Group 3:	Died without five-year serum study	55	(23)
Group 4:	Myeloma, macroglobulinemia or amyloidosis developed	27	(11)

TABLE I At Diagnosis: Age and Sex

	Group 1	Group 2	Group 3	Group 4
No. of patients studied	137	22	55	27
Age (yr)				
<40 (%)	5	5	0	4
≥70 (%)	30	18	51	19
Mean	62	59	70	62
Range	34–87	38–78	48–90	34–79
Sex				
Males (%)	53	45	69	67
Females (%)	47	55	31	33

Age and Sex Distribution. Four per cent of the patients were less than 40 years of age at the time of diagnosis. The patients in group 3 (who died) were older than those in the other groups, but the mean age of all patients with benign monoclonal gammopathy was similar to that of patients with multiple myeloma [15]. There were more males than females, except in group 2 (Table I)

History. Pain, when present, was due to a cause other than the monoclonal gammopathy. The incidence of bacterial infection was not increased. Herpes zoster had occurred in 1 per cent. Surprisingly, fever of undetermined origin was present intermittently in four patients—for 22 years in one of them

Malignancies were found in 31 first-degree relatives (siblings, parents or children) of the 241 patients. (This is almost twice the incidence among our 869 patients with multiple myeloma.) Among 10 of these relatives, the malignant conditions were lymphoma, leukemia or myeloma. It is interesting that in four families three first-degree relatives had a malignancy, in addition to the patient's monoclonal gammopathy. The lower incidence of malignancy among the patients in group 3 may reflect shorter follow-up because of the death of the patient.

Physical Examination. Physical findings among the patients were generally unremarkable. The liver was

palpable in 15 per cent of all patients. Congestive heart failure (in two patients), biliary cirrhosis, hemochromatosis and biopsy-proved fatty liver accounted for the five patients in whom the liver was palpable 5 cm or more below the right costal margin. Splenomegaly was found in 3 per cent of the patients and extended 5 cm or more below the left costal margin in six patients, of whom two had myelofibrosis with myeloid metaplasia, one lupus erythematosus, one an undifferentiated myeloproliferative process and one lymphoid hyperplasia of the spleen. In the sixth patient, the hepatosplenomegaly resolved without a diagnosis.

Blood Counts. Hemoglobin values are summarized in Table II. In no instance could the anemia be related directly to the monoclonal gammopathy. Anemia was caused by melena (two patients), myeloid metaplasia, myeloproliferative disease, Wegener's granulomatosis, hypoplasia of bone marrow and chronic cold agglutinin disease—and by hypernephroma in the eight patients with a hemoglobin level less than 10 g/dl. The mean value for hemoglobin was lower and the percentage of patients with a hemoglobin level less than 12 g/dl was greater in group 3 (patients who died) than in the other groups, but this may reflect the more advanced age and more severe illness of the patients in this group. The leukocyte count was less than 2,000/mm³ in only one patient (lupus erythematosus); and it exceeded 20,000/mm³ in two patients—one with an undifferentiated myeloproliferative disease and the other with myeloid metaplasia. Thrombocytopenia was uncommon; and in the five patients with counts less than 100,000/mm³, the causes were myeloid metaplasia, acute leukemia, idiopathic thrombocytopenic purpura, lupus erythematosus and hypoplasia of bone marrow. In only three patients were platelet counts greater than 500,000/mm³. These occurred with gastrointestinal bleeding, pneumonitis and hypernephroma. The sedimentation rate was normal in 20 per cent of the patients, but it was usually increased, exceeding 100 mm in 1 hour in 9 per cent of the patients. An increase in the erythrocyte sedimentation rate should always be investigated by serum protein electrophoresis.

Renal Function. Renal insufficiency was uncommon. The mean serum creatinine levels were within normal limits except in group 3, in which they were moderately elevated (Table III). One patient had nephrosclerosis and three others had modest renal insufficiency of indeterminate cause.

Uric Acid. Serum uric acid levels were generally within normal limits. Three women in group 3 had hyperuricemia (>11 mg/dl). This was associated with nephrosclerosis, acute leukemia and an episode of acute renal insufficiency.

Serum Calcium. In only two patients was the serum calcium more than 11 mg/dl, and both had hyperparathyroidism. Hypocalcemia was not seen.

TABLE II Hemoglobin, Leukocytes and Platelets at Diagnosis

	Group 1	Group 2	Group 3	Group 4
No. of patients studied	137	22	55	27
Hemoglobin (g/dl)				
Mean	13.3	13.4	12.8	13.4
Range	7.4–16.6	10.1–17.4	8.3–16.4	11.0–15.9
Leukocytes (10 ³ /mm ³)				
Mean	6.8	5.7	8.5	6.3
Range	1.5–18.0	3.0–10.3	3.4–58.0	3.4–11.5
Platelets (10 ³ /mm ³)				
Mean	245	239	180	256
Range	13–766	125–452	9–443	71–871

TABLE III Serum Creatinine at Diagnosis

	Group 1	Group 2	Group 3	Group 4
Males (no.)	69	10	26	17
Creatinine (mg/dl)				
Mean	1.1	1.1	1.4	1.16
Range	0.7–1.7	0.9–1.3	0.6–3.7	0.9–1.7
Females (no.)	60	11	13	8
Creatinine (mg/dl)				
Mean	0.9	0.85	1.35	0.86
Range	0.6–1.7	0.6–1.2	0.7–6.4	0.6–1.4

Serum Lipids. Serum cholesterol levels were usually within normal limits, and hypocholesterolemia—often present in multiple myeloma—was rarely seen. Serum triglyceride levels were generally normal. No significant difference in serum lipids was seen among the four groups.

Serum Electrophoresis and Immunoelectrophoresis. Electrophoresis of the serum was performed in all cases (Table IV). A peak of gamma mobility appeared in approximately 80 per cent of the cases except for group 2 in which gamma peaks were 55 per cent and the rest were beta. No reason is apparent for this, and it probably is unimportant. (It should be noted that six patients had a normal or broad-based band on the serum protein electrophoretic pattern, and a monoclonal protein would not have been detected if immunoelectrophoresis had not been performed.) The size of the serum globulin M peak was not greater in the patients in whom myeloma, macroglobulinemia or amyloidosis (group 4) subsequently developed; nor was it higher in the patients who subsequently had a significant increase in the size of the monoclonal (M) protein peak (group 2). Indeed, in no patient who was to experience either of these developments was the initial M peak greater than 2.5 g/dl.

Immunoelectrophoresis of the serum was performed in all cases (Table V). No difference among the four groups was apparent, except that 26 per cent of the monoclonal proteins in group 4 were IgM and 23 per

TABLE IV Size of Initial Serum Globulin M Peak

	Group 1	Group 2	Group 3	Group 4
No. of patients studied	137	22	55	27
Size (g/dl)				
≤1.5	30	45	27	26
1.6–2.0	44	37	53	48
2.1–2.5	21	18	15	26
≥2.6	5	0	5	0
Mean	1.8	1.6	1.8	1.8
Range	1.1–3.0	1.0–2.2	0.8–3.2	0.9–2.5

Note: Values indicate the per cent of subjects in whom these values were found.

cent of those in group 2 were IgA. Of the seven patients with monoclonal IgM protein in group 4, macroglobulinemia developed in four, amyloidosis in two and chronic lymphocytic leukemia in one. No difference in the $\kappa:\lambda$ ratio was seen in the four groups: about two thirds of the patients in each had κ light chains. The mobility of the monoclonal peak and its heavy or light chain type did not change in any instance. Five patients (four were in group 1) had a biclonal gammopathy, and these were classified according to the major monoclonal protein component.

Urinary Electrophoresis and Immunoelectrophoresis. Electrophoresis of the urine was performed in less than half of the cases. This is because electrophoresis usually was not ordered unless proteinuria was found on routine examination or a large serum peak suggested the possibility of myeloma or macroglobulinemia. Within each group, the mean protein excretion per 24 hours was less than 1 g. The increase of the quantity in group 4 was due to a nephrotic syndrome associated with amyloidosis (Table VI).

Group 1. Immunoelectrophoresis demonstrated a monoclonal light chain in the urine of 12 among 45 patients tested (Table VII). Among the six patients in whom it was discovered at the time when the serum monoclonal protein was detected, the monoclonal urine protein disappeared in one after removal of a parathyroid adenoma and remained stable in the other five. In the other six patients the urinary monoclonal protein

TABLE V Results of Immunoelectrophoresis of Serum

	Group 1		Group 2		Group 3		Group 4		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
No. of patients studied	137		22		55		27		241	
Heavy chain										
IgG (γ)	106	77	15	68	41	75	18	67	180	75
IgA (α)	13	10	5	23	5	9	2	7	25	10
IgM (μ)	18	13	2	9	9	16	7	26	36	15
Light chain										
κ	82	60	14	64	34	64	19	70	149	62
λ	55	40	8	36	19	36	8	30	90	38

TABLE VI Results of Electrophoresis of Urine

	Group 1	Group 2	Group 3	Group 4
No. of patients studied	58	20	21	12
Results (%)				
Normal	34	20	24	33
Albumin	47	55	48	50
Globulin	19	25	28	17
Total protein (g/24 hr)				
Mean	0.49	0.35	0.92	0.91

was discovered during the period of observation; but the monoclonal serum protein diminished in four, increased 0.1 g/dl in one, and remained the same in one. In eight of the 12 patients, the 24-hour urinary excretion was 0.5 g or less. In three of the remaining four, the amount of urinary light chain had remained stable for more than 10 years, and in the fourth it had disappeared after removal of a parathyroid adenoma.

Group 2. Of 17 urine specimens, eight contained a monoclonal light chain, although the amount exceeded 0.5 g/24 hours in only one. The urinary monoclonal protein was discovered at the same time as the serum monoclonal protein in two specimens; in one of these it increased during the observation period, whereas in the other seven specimens the serum monoclonal protein increased. Thus, either the urinary protein peak or the serum protein peak increased in all cases.

Group 3. Three of five urines contained a monoclonal light chain. All were recognized when the diagnosis of the serum monoclonal protein was made. None amounted to more than 1 g/24 hours, and no repeat determinations of it were made.

Group 4. Of seven patients tested, two had a urinary monoclonal light chain. In seven additional patients the monoclonal protein was not discovered until the diagnosis of multiple myeloma, amyloidosis or macroglobulinemia was made.

TABLE VII Results of Immunoelectrophoresis (IEP) of Urine

	Group 1 (no.)	Group 2 (no.)	Group 3 (no.)	Group 4 (no.)
IEP performed	45	17	5	7*
Light chain found				
κ	5	6	1	2
λ	7	2	2	0
Amount				
≤ 0.5 g/24 hr	8	7	1	1

* Seven cases not included because monoclonal protein was discovered at the time of diagnosis of myeloma or macroglobulinemia.

TABLE VIII Serum Albumin Values

	Group 1	Group 2	Group 3	Group 4
No. of patients studied	137	22	55	27
Albumin (g/dl)				
< 3.0	(29)*	(36)	(42)	(22)
Mean	3.3	3.2	3.0	3.3
Range	1.8–4.3	2.2–5.1	1.9–4.5	2.3–4.1

* Parentheses indicate the per cent of patients in whom these results were obtained.

Serum Albumin. Serum albumin values did not differ significantly among the four groups (Table VIII). The lower mean value in group 3 may reflect the greater age of its members. The value of 1.8 g/dl in group 1 was from a patient with a hypernephroma; it returned to normal after nephrectomy. The value of 1.9 g/dl in group 3 was from a patient with Wegener's granulomatosis. He died of his disease a few weeks later.

Quantitated Immunoglobulins. Measurements of immunoglobulins are recorded in Table IX. In some patients the quantity of normal (polyclonal, uninvolved) immunoglobulins was diminished, but the frequency of such diminution did not differ statistically between patients in whom the immunoglobulin status remained

TABLE IX Quantitated Immunoglobulins

	Group 1			Group 2			Group 3			Group 4		
	Meas*	Dim†	%	Meas	Dim	%	Meas	Dim	%	Meas	Dim	%
IgG												
No. patients	69	12	17	8	1	13	20	2	10	7	3	43
Mean (mg/ml)‡		19.8			23.9			23.2			28.3	
IgA												
No. patients	9	2	22	4	2	50	3	0	0	1	0	0
Mean (mg/ml)‡		10.3			8.2			12.8			4.8	
IgM												
No. of patients	15	6	40	1	0	0	5	2	40	2	0	0
Mean (mg/ml)‡		23.9						16.2			23.5	
Total	93	20	22	13	3	23	28	4	14	10	3	30

* Measured within one month of diagnosis.

† Diminished quantity of normal immunoglobulins.

‡ Normal and monoclonal proteins in all cases with quantitation.

TABLE X IgG Subclasses

IgG Subclass		Patients with IgG protein			
		Group 1 (86 patients)	Group 2 (10 patients)	Group 3 (21 patients)	Group 4 (13 patients)
Predominant Subclass Concentration					
IgG ₁ :	Patients (%)	86	80	96	87
	Median (mg/ml)	22.7	32.0	23.7	21.6
IgG ₂ :	Patients (%)	7	20	0	6.5
	Median (mg/ml)	1.3	2.1	0.93	0.69
IgG ₃ :	Patients (%)	3	0	0	6.5
	Median (mg/ml)	0.35	0.37	0.28	0.19
IgG ₄ :	Patients (%)	4	0	4	0
	Median (mg/ml)	0.14	0.18	0.10	0.06
Low Concentration Associated with IgG ₁ *					
IgG ₂ :	Patients (%)	67	70	86	77
IgG ₃ :	Patients (%)	66	70	76	69
IgG ₄ :	Patients (%)	69	80	95	92

* Per cent of all patients with IgG in each group

stable and those in whom the monoclonal protein increased or myeloma, macroglobulinemia or amyloidosis developed. The quantities of normal immunoglobulins in each class were low in the normal range or below normal in the majority of patients, without apparent difference among groups.

Subclasses of IgG. In each of the four groups, the IgG protein was of subclass IgG₁ in 80 per cent of instances or more. The proportion of subclass IgG₂ was less than expected (Table X). The median IgG₁ values were virtually identical in groups 1, 3, and 4; the slight increase

in group 2 is of questionable significance. The normal or uninvolved subclass immunoglobulins were diminished in more than two thirds of the patients. IgG₄ quantities were reduced in 95 per cent of group 3 patients but in only 69 per cent of group 1 patients (questionable significance). IgG₂ and IgG₃ concentrations were virtually identical in groups 1, 2 and 4.

Bone Marrow Aspirate. Findings from bone marrow aspirate are reported in Table XI. The means and ranges of the percentages of plasma cells are virtually the same among all four groups. Groups 2 and 4 had fewer patients with less than 4 per cent plasma cells, but this is of questionable significance.

TABLE XI Plasma Cells in Initial Bone Marrow Aspirate

	Group 1	Group 2	Group 3	Group 4
No. of patients studied	96	18	34	22*
Plasma cells (%)				
Mean	3.0	4.0	3.4	3.6
Range	1-7	1-7	1-10	1-7

* Five cases not included, because bone marrow aspirate was obtained at time myeloma was diagnosed.

TABLE XII Survival

	Group 1 (%)	Group 2 (%)	Group 3 (%)	Group 4 (%)
No. of patients studied	137	22	55	27
Died at				
≤2 yr	..	.	42	0
3-5 yr	.	.	34	11
6-10 yr	4	4	20	18
>10 yr	..	.	4	15
Alive at				
<5 yr	..	.	.	8
6-10 yr	83	82	.	33
>10 yr	13	14	.	15
Total	100	100	100	100

COURSE AND FOLLOW-UP

Group 1. Of these 137 patients known not to have had increase of monoclonal protein during survival of five

TABLE XIII Serum Globulin M-Peak Increase (Group 2)

Data	Result
Patients studied (no.)	18
Interval to significant protein increase (mo.)	
Median	73
Range	35-187
Patients studied (no.)	18
Size of M-protein increase (g/dl)	
Median	1.35
Range	0.9-2.2
Patients studied (no.)	22
Total follow-up (mo.)	
Median	90
Range	64-193
Serum protein determinations (no.)	
Median	5
Range	2-17

TABLE XIV Monoclonal Gammopathies: Transition To Multiple Myeloma or Macroglobulinemia

Case No.	Hemo- globin, (g/dl)	M Peak (g/dl)	Marrow (% plasma cells)	Duration Till Diagnosis (mo.)	Hemoglobin, (g/dl)		M peak (g/dl)		Marrow (% plasma cells)	Bone Roentgenograms
					At Diagnosis	Minimum	At Diagnosis	Maximum		
Initial					Multiple Myeloma					
1	12.5	1.7	..	116	5.3	5.3	2.8	4.4	85	Lytic
2	13.7	0.9	7	23	10.2	6.7	3.6	3.6	45	Negative
3	12.8	1.7	6	31	11.6	11.6	3.7	3.7	17	Negative
4	11.8	1.8	.	86	10.2	10.2	2.0	2.1	25	Lytic
5	15.0	2.0	4	59	12.4	12.4	3.3	3.3	21	Negative
6	13.7	1.0	5	136	10.1	10.1	1.7	1.8	23	Lytic + pathologic fracture
7	13.4	2.2	2	86	7.1	5.9	8.1	10.9	80	Negative
8	11.0	2.1	...	54	10.5	7.6	3.4	6.0	90	Lytic
9	14.3	2.2	7	60	12.9	7.0	3.6	6.0	66	Extradural plasma-cytoma
10	13.9	1.1	.	125	11.1	9.3	1.8	3.8	90	Lytic
11	13.8	1.7	4	35	10.8	8.0	2.7	2.7	65	Lytic
12	12.6	1.7	3	110	11.2	8.2	2.6	2.6	39	Porosis & compression fracture
13*	11.3	1.7	5	41	8.1	5.0				Lytic
14†	13.5	1.5	..	68	8.9	8.9				Lytic
15	14.7	2.0	2	72	10.7	10.0	4.5	4.5	16	Lytic, porosis and compression fracture
16	15.1	1.7	5	40	6.4	6.4	5.8	5.9	90	Lytic
17	13.8	2.4	3	96	10.7	10.7	4.9	4.9	16	Negative
18	14.5	1.6	7	76	8.3	8.3	3.1	5.0	40	Lytic
Initial					Macroglobulinemia					
19	15.9	2.2		163	9.4	5.0	5.6	8.5	‡	Lytic
20	12.8	1.9	2	47	6.2	6.2	5.1	5.1	‡	Negative
21	12.1	2.1	2	82	12.1	9.4	6.7	6.7	‡	Porosis
22	14.2	1.3	2	124	11.7	9.7	3.3	3.3	‡	Porosis with compression fracture

* Diagnosed as multiple myeloma at home hospital on basis of anemia, for which patient was given transfusions, and lytic bone lesions. Given radiation therapy and cyclophosphamide. Myeloma on death certificate

† Diagnosed as multiple myeloma at university hospital on basis of severe anemia, lytic bone lesions and multiple collapsed vertebrae, hypercalcemia and renal insufficiency, large IgG λ spike in serum and monoclonal spike in urine with 11 g protein/24 hours. Patient treated with melphalan and cyclophosphamide

‡ All bone marrows were hypercellular and infiltrated with lymphocytes and plasma cells

years or more (Table XII), two are still alive after 15 years, without evidence of multiple myeloma, macroglobulinemia or amyloidosis. Five patients died between five and 10 years of heart disease (two patients), carcinoma of the ovary (one patient), infection (one patient) and malnutrition at the age of 92 (one patient).

Group 2. In the 22 patients in this group the monoclonal gammopathy progressed as evidenced by an increase of 50 per cent or more in the size of the monoclonal (M) serum protein (18 patients; median increase = 1.35 g/dl) or by the appearance of a monoclonal (M) protein in the urine (four patients). The median interval from diagnosis to 50 per cent increase of the M peak was 73 months (Table XIII), and the patients in this subgroup have been followed up for periods averaging nearly eight years (median 90 months). Among

the 10 patients who had five or more serum protein determinations, the increase was gradual in eight and rather abrupt in two. It must be emphasized that the size of the monoclonal protein peak may fluctuate considerably. Over a period of nine and a half years one patient had 17 serum protein determinations, of which the first value was 1.4 g/dl and the last 2.2 g/dl, but the value fluctuated from 1 to 3.5 g/dl without specific therapy. One patient in group 2 died of long-standing biliary cirrhosis in the ninth year of observation; the remaining 21 are being followed up.

Group 3. All 55 patients in this group have died; but none had evidence of multiple myeloma, macroglobulinemia or amyloidosis, or a significant increase in the monoclonal serum protein or appearance of a monoclonal light chain in the urine. Thirteen patients, although

they survived five or more years, did not have serum protein electrophoresis five years after the recognition of a monoclonal protein and therefore were not placed in group 1. Some of these patients could have had a significant increase in the monoclonal serum protein or begun to excrete a monoclonal protein in the urine, or perhaps even myeloma or macroglobulinemia or amyloidosis developed; but for lack of evidence that they did so, all were put in group 3. Causes of death included cardiac disease (20 patients), cerebrovascular disease (eight patients), infection (six patients), other malignancy (four patients, three with carcinoma and one with acute leukemia), miscellaneous (nine patients) and unknown (eight patients).

Group 4. Of the 27 patients in this group, multiple myeloma developed in 18 (67 per cent) (Table XIV). All patients had more than 15 per cent abnormal plasma cells in their bone marrow aspirates. All patients had a monoclonal protein in their serum, and it was >3.0 g/dl in 14 of them. A monoclonal spike was present in the urine of nine patients, and anemia developed in all patients. Lytic bone lesions were recognized in eleven patients; osteoporosis and compression fractures in one patient; and a large extradural plasmacytoma producing paralysis in one patient. These findings easily fulfill the criteria for the diagnosis of multiple myeloma [16]. The median interval before the diagnosis of multiple myeloma was 64 months, with a range of 23 to 136 months (Table XV); and the median survival after diagnosis was 22 1/2 months. Among the eight patients who had enough serum protein determinations to show a trend, the onset of myeloma was gradual in four and rather abrupt in the other four. The increase in the size of the monoclonal peaks of two representative patients is shown in Figure 1. Electrophoretic tracings of the serum of two other patients are depicted in Figure 2.

Macroglobulinemia of Waldenstrom developed in four patients. All had a monoclonal IgM κ protein in the serum which ranged from 3.3 to 8.5 g/dl during the course of the disease. All patients had significant anemia, and their bone marrow aspirate and biopsy or autopsy specimens showed increased numbers of lymphocytes and plasma cells. The number of serum protein determinations during the development of macroglobulinemia was not sufficient to show whether the onset of the disease was gradual or abrupt.

Amyloidosis was found in four patients, five to 13 years after the recognition of a monoclonal protein in their serum. Histologic evidence of amyloidosis was found on renal biopsy in two patients and by autopsy in two others.

In one patient chronic lymphocytic leukemia developed after 56 months of observation, but the size of her monoclonal IgM protein did not increase with this change. Initially, her leukocyte count was $5,700/\text{mm}^3$

TABLE XV Observations in Group 4

	Multiple Myeloma	Macroglobulinemia	Amyloidosis
No. of patients studied	18	4	4
Interval to diagnosis (mo)			
Median	64	103	92
Range	23–136	47–163	67–162

NOTE: Chronic lymphocytic leukemia developed in one patient 56 months after the monoclonal protein was recognized

with neutrophils 62 per cent, lymphocytes 29 per cent, monocytes 8 per cent and eosinophils 1 per cent; at the diagnosis of chronic lymphocytic leukemia, the leukocyte count was $27,500/\text{mm}^3$ with neutrophils 18 per cent, lymphocytes 81 per cent, monocytes 0.5 per cent and eosinophils 0.5 per cent. At examination 15 months later, the hemoglobin level had decreased to 10.8 g/dl and leukocytes had increased to $79,000/\text{mm}^3$ with neutrophils 7 per cent, lymphocytes 88.5 per cent, monocytes 2 per cent, eosinophils 2 per cent and basophils 0.5 per cent. The monoclonal protein was essentially unchanged.

Analysis by Immunoglobulin Group. Altogether, 20 per cent of the 241 patients showed an increase of monoclonal protein (group 2) or progression to multiple

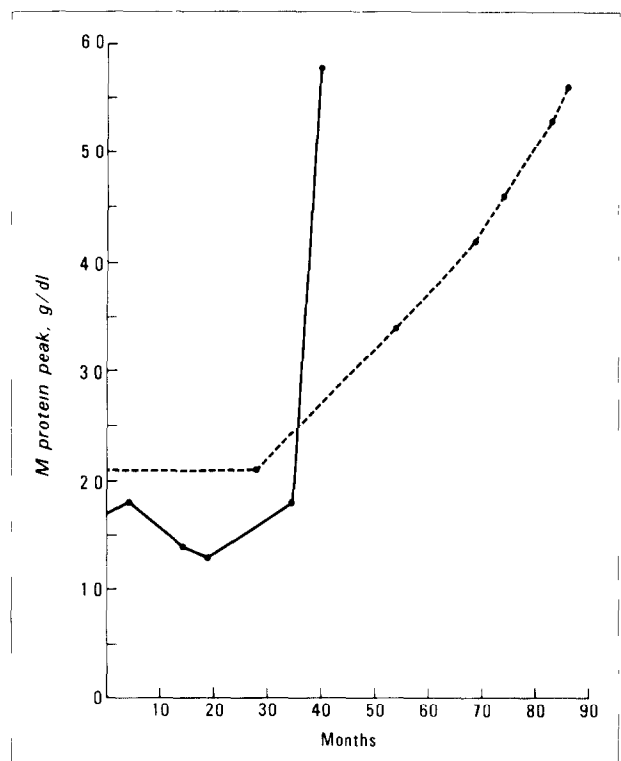


Figure 1. Rate of M-protein increase during development of myeloma

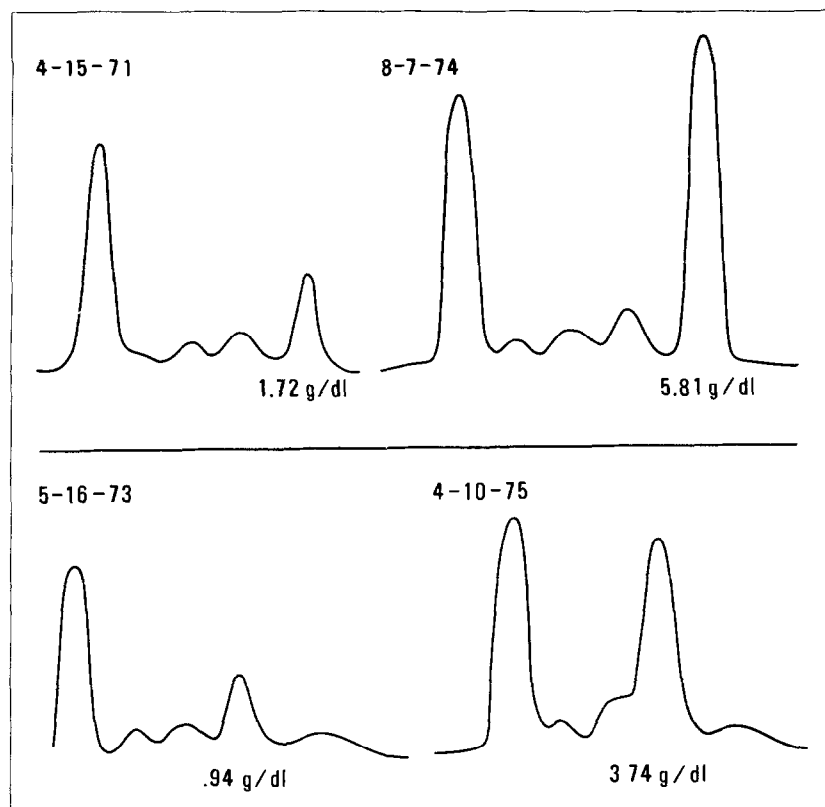


Figure 2. Serum protein electrophoretic pattern prior to multiple myeloma and after diagnosis of disease (anode on left) in two patients.

myeloma, macroglobulinemia, amyloidosis or chronic lymphocytic leukemia (group 4). Among those whose monoclonal proteins were IgG, IgA and IgM, respectively, the proportions were 18 per cent of 180 patients, 28 per cent of 25 patients and 25 per cent of 36 patients (Table XVI). Worth noting is the observation that the IgM monoclonal protein peak did not increase in three patients (in two of whom amyloidosis developed and in the one with chronic lymphocytic leukemia).

ASSOCIATED DISEASES

The diseases present at the discovery of the monoclonal protein are listed in Table XVII. Of the 241 patients, 26 per cent came to the Mayo Clinic for general examination and had no detectable abnormalities other than the monoclonal gammopathy. Cardiovascular or cerebrovascular disease was present in 13 per cent. Included in the inflammatory group were four patients who had fever of undetermined origin (which had been present intermittently for four to 22 years), three with recurrent phlebitis, two with chronic inflammatory bowel disease and one with sprue. Malignancy was noted in 16 patients (7 per cent), of whom one had acute leukemia and another Kaposi's sarcoma. Fourteen patients (6 per cent) had rheumatoid arthritis, ankylosing spondylitis, lupus erythematosus, scleroderma or undifferentiated connective tissue diseases. Among the 15

patients in the group with neurologic disorders, five had carpal tunnel syndrome without recognition of amyloidosis and one had Guillain-Barré disease. The benign tumors included thyroid nodules and polyps of the colon. Hematologic diseases comprised myelofibrosis with myeloid metaplasia (two patients), idiopathic thrombocytopenic purpura (two patients), and one patient each with von Willebrand's disease, hypoplastic anemia, aregenerative anemia (red cell aplasia), undifferentiated myeloproliferative disease and idiopathic neutropenia. The patients with endocrine disorders included three with hyperparathyroidism, three with idiopathic osteoporosis, and one each with Cushing's disease, Turner's syndrome and acquired Fanconi's syndrome. Among those with miscellaneous disorders were patients with psychoneurosis, hyperventilation syndrome, duodenal ulcer, melena, pruritus, diabetes, Peyronie's disease and plane xanthoma.

COMMENTS

Monoclonal gammopathies are being discovered much more commonly than in the past. At present, we screen more than 40,000 serum protein electrophoretic strips each year, and immunoelectrophoresis of the serums of patients with a suspected band on the cellulose acetate tracing permits us to identify about 400 instances of monoclonal protein annually. Approximately one third

of the patients have multiple myeloma, amyloidosis or macroglobulinemia; but monoclonal gammopathies of undetermined significance remain after a complete medical work-up.

Monoclonal gammopathies are found in approximately 3 per cent of patients past the age of 70 years in Sweden [1,7,8] and in the United States [9]. In 6,995 normal Swedish subjects beyond the age of 25, the over-all occurrence of monoclonal proteins was about 1 per cent [7]; in our series of 1,200 persons aged 50 years or older who were residents of a small Minnesota community, 1.25 per cent had a monoclonal protein [9].

The common occurrence of a monoclonal serum protein adds weight to the desirability of determining whether the abnormal state will remain stable and benign or progress to multiple myeloma, macroglobulinemia, lymphoma or amyloidosis. Many criteria have been proposed to aid in the differentiation of stable and advancing disease, but none has been satisfactory.

The amount of monoclonal protein present is of some help. Bachmann [17] reported that 78 per cent of the patients with more than 2 g/dl of IgG monoclonal protein and 82 per cent of those with more than 1 g/dl of IgA monoclonal protein had myeloma, and that 67 per cent of the patients with more than 2 g/dl of IgM monoclonal protein had macroglobulinemia. Spiegelberg et al. [18] concurred that monoclonal proteins are most likely to be malignant if the IgG, IgA and IgM concentrations are greater than 2.0, 1.0 or 2.0 g/dl, respectively. Ritzmann et al. [3] believed that 3.0 g/dl of IgG, IgA or IgM monoclonal protein was the upper limit for benign monoclonal gammopathy.

Concentrations of immunoglobulin classes not associated with the monoclonal protein (normal polyclonal immunoglobulins) are frequently decreased in multiple myeloma. From study of 223 patients with malignant plasma cell or lymphocytic disease, Hobbs [19] reported that only five had normal levels of normal immunoglobulins. And among patients with benign monoclonal gammopathy, Williams et al. [20] found that the concentrations of normal immunoglobulins were lower than normal when the serum monoclonal protein was 2.0 g/dl or greater. We found that the normal immunoglobulins were reduced almost as frequently in our group with a stable disorder as in those who had an increase of monoclonal protein or in whom myeloma or macroglobulinemia developed. Study of normal immunoglobulins did not enable us to distinguish our patients in whom other diseases developed (group 4) from those whose condition remained stable (group 1).

The association of Bence Jones proteinuria with a monoclonal serum protein usually indicates a neoplastic process. Waldenstrom [21] stated that the excretion

TABLE XVI Progression of monoclonal Gammopathy

Immuno- globulin	Total (no.)	Group 2 (no.)	Group 4 (no.)	Total	
				No.	Per Cent
IgG	180	15	18	33	18
IgA	25	5	2	7	28
IgM	36	2	7	9	25
Totals	241	22	27	49	

of a demonstrable amount of Bence Jones protein in the urine of a patient with a monoclonal serum protein was strong evidence of malignancy. Hobbs [19] said that Bence Jones proteinuria of more than 1.0 mg/dl (10 mg/liter) was of "sinister significance" and suggestive of malignant plasmacytic disease. Seligmann and Basch [22] noted that a Bence Jones protein level of 30 mg/100 dl (300 mg/liter) or more in a patient with pathologic serum immunoglobulins and decreased normal immunoglobulins strongly suggested malignant proliferation. Dammacco and Waldenstrom [23], from a study of 42 patients with benign monoclonal gammopathy, reported weakly positive results of the heat test for Bence Jones protein in one patient and small amounts of light chains in 10. None of these patients had more than 60 mg/liter of Bence Jones protein. In another series, 59 of 65 cases of monoclonal gammopathy with Bence Jones proteinuria were malignant [24].

However, Bence Jones proteinuria with apparently benign monoclonal gammopathy has been reported. In these instances the amount of Bence Jones protein has been negligible, the absence of myeloma has not been assured or the follow-up has been too short to establish that the condition was benign [25-31]. However, we have followed up periodically two patients who have maintained a stable amount of monoclonal serum protein and excreted 0.8 g or more of Bence Jones protein

TABLE XVII Diseases Associated with Monoclonal Protein

Disease	Total	
	No.	Per Cent
None	62	26
Cardiac and cerebrovascular	31	13
Inflammatory	26	11
Malignant	16	7
Connective tissue	14	6
Neurologic	15	6
Benign tumor	8	3
Hematologic	9	3.5
Endocrine	9	3.5
Miscellaneous	51	21
Totals	241	100

daily for more than 10 years without evidence of the development of myeloma, amyloidosis or similar malignant disease [32]. Recently, Ameis et al. [33] reported that Bence Jones proteins were detected in the urine of 28 of 301 patients with various benign diseases. This is in keeping with the presence of monoclonal light chains in the urine of 12 of our patients in group 1.

The presence of more than 5 per cent plasma cells in the bone marrow suggests myeloma, but the condition of patients with greater plasmacytosis has remained stable for long periods; and conversely, patients with overt myeloma may have fewer than 5 per cent plasma cells in single bone marrow specimens because the disease may be spotty. Morphologic abnormalities of the plasma cells are not sufficient to differentiate a benign from a malignant process. In each of our four groups, the plasma cells in bone marrow ranged from 1 to 10 per cent and averaged 3 to 4 per cent.

The presence of osteolytic lesions is very suggestive of multiple myeloma, but metastatic carcinoma may produce lytic changes and plasmacytosis. We have seen a number of patients who had modest amounts of serum monoclonal protein, plasmacytosis and lytic lesions secondary to a metastatic carcinoma. Lytic bone lesions were not seen before the diagnosis of myeloma in any patient in the series reported here. Osteoporosis with compression fractures of thoracic or lumbar vertebrae occurred in some of our patients, but it was thought to be postmenopausal or idiopathic.

Other tests and criteria, including the presence or absence of chromosomal abnormalities, ABO blood group profiles, phytohemagglutinin stimulation of lymphocytes, mixed lymphocyte culture reactions and delayed skin hypersensitivity studies, have not proved to be adequate for distinguishing between benign monoclonal gammopathy and multiple myeloma [3].

In our current series of 241 patients with monoclonal gammopathy of indeterminate significance, the age and sex did not differ significantly in the four groups. Hepatosplenomegaly was uncommon and usually of moderate degree when present. Causes other than the monoclonal gammopathy were responsible for the organomegaly. The incidence of another malignancy in the patient was the same as among our 869 patients with multiple myeloma. Incidence of malignancy in first-degree relatives was higher in this series as a whole than in the series of patients with multiple myeloma. In four instances, three other first-degree relatives in the family had a malignancy. The hemoglobin value was slightly less in group 3, but the members of that group were older and had other illnesses that may have caused the anemia. Leukocyte and platelet counts did not differ significantly among the groups. Increases in the sedimentation rate were common in all four groups and reflect the increase in monoclonal protein. Hyper-

calcemia was not a feature of the monoclonal gammopathy; it indicated hyperparathyroidism.

Immunoelectrophoresis of serum revealed IgG in 75 per cent of cases, IgA in 10 per cent and IgM in 15 per cent, with κ light chains in 62 per cent and λ in 38 per cent. There was no significant difference among the four groups. The incidence of κ and λ light chains was very similar to that in multiple myeloma. The 10 per cent incidence of monoclonal IgA proteins was less than in multiple myeloma but not so striking as the 4 per cent found in 68 cases of benign monoclonal gammopathy by Fine and Lambin [34]. Creyssel et al. [35], in 27 cases of benign monoclonal gammopathy, found three of the IgA class.

Many investigators have thought that an IgM monoclonal protein rarely represents a benign process and usually develops into macroglobulinemia or related diseases. However, only one fourth of the patients with IgM monoclonal protein either had an increase in the size of the protein peak or the development of another disease.

The size of the initial serum globulin peak was virtually identical among all four of our groups. In fact, the upper limit in groups 2 and 4 was 2.5 g/dl. In group 1 it was 3.0 g/dl, but that was not exceeded later. In each of the four groups the incidence of IgG₁ subclass was greater than reported in multiple myeloma. Incidence of IgG₂ and IgG₃ was less than in multiple myeloma [36], but there was no significant difference among our four groups. The mean value for IgG₁ was higher in group 2 than in the others, but the importance of this difference is indeterminate. The serum albumin levels did not differentiate the four groups.

At the conclusion of the study, follow-up information and serum samples were obtained in all patients in groups 1, 2, and 4. All patients in group 1 had been followed up for more than five years, and 13 per cent were alive and being followed up after 10 years. Although three fourths of the patients in group 3 were dead at five years, no data suggested that they had had myeloma, macroglobulinemia or amyloidosis, or an increase in their monoclonal serum protein or the development of a monoclonal urine protein.

It is important that patients with monoclonal gammopathies be followed up for many years. Multiple myeloma has developed and patients have died of it at intervals ranging from 15 to 24 years after the initial demonstration of a monoclonal protein [37]. We have seen one patient in whom classic multiple myeloma developed 16 years after the demonstration of monoclonal hyperglobulinemia [38]. The interval from discovery of the monoclonal protein to a 50 per cent increase in our patients ranged from 35 to 187 months, with a median greater than six years. The increase of monoclonal protein appeared to be gradual in eight in-

stances and abrupt in two others. Among the 18 patients in group 4 in whom multiple myeloma developed, the median interval was 64 months and the range 23 to 136 months. This is very similar to the five year interval for the development of multiple myeloma as postulated by Hobbs [39]. The size of the monoclonal peak increased gradually in four of our eight patients; and in four it remained stable for several years, then increased rather rapidly, along with symptoms and findings of multiple myeloma. Macroglobulinemia developed in four patients after a median interval of more than eight years. In these cases the number of interim determinations of serum protein was insufficient to determine whether the increase was gradual or sudden. Amyloidosis was recognized after a median interval of almost eight years. This again shows that the potentiality of serious disease requires observation over many years.

Although benign monoclonal gammopathy frequently exists without other abnormalities, sometimes certain diseases are associated with it—as would be expected in an older population. Therefore, it is essential to have a control group when considering the validity of such an association to show whether it is meaningful or only coincidental.

CONCLUSION

We have been unsuccessful in determining which cases of monoclonal gammopathy without multiple myeloma, macroglobulinemia, or amyloidosis will remain stable and which will progress eventually to one of these diseases. Even retrospective analysis of age, sex, presence of organomegaly, hemoglobin level, size and type of serum monoclonal protein, presence of small amounts of monoclonal light chain in the urine, serum albumin level, levels of normal or polyclonal immunoglobulins, IgG subclass and level of plasma cells in the bone marrow did not permit us to distinguish initially between patients with stable benign disease and those with progressive disease. At present, periodic reexamination of patients with monoclonal gammopathy is the only certain way of determining whether the disorder is incipient myeloma, macroglobulinemia, amyloidosis or a true benign monoclonal gammopathy.

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